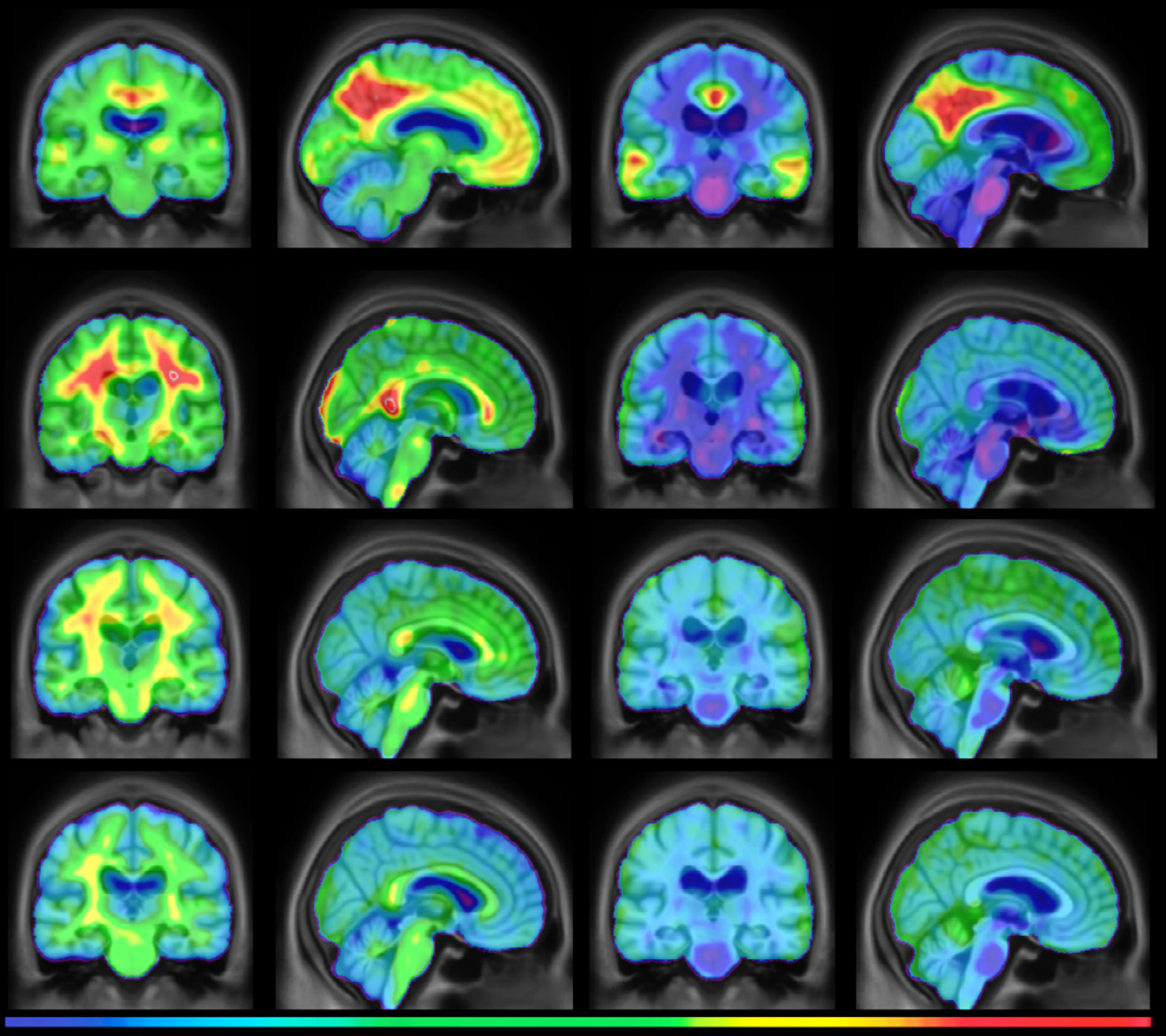
Alzheimer's Disease International

The global voice on dementia

World Alzheimer Report 2021

Journey through the diagnosis of dementia



Alzheimer's Disease International

The global voice on dementia

World Alzheimer Report 2021

Journey through the diagnosis of dementia

Authors

Professor Serge Gauthier

Professor Emeritus in Neurology and Psychiatry/Academic Co-Lead, Dementia Education Program, McGill University

Professor Pedro Rosa-Neto

Director of the McGill University Research Centre for Studies in Aging/Professor, Departments of Neurology and Neurosurgery and Psychiatry, McGill University

Professor José A. Morais

Director, Division of Geriatric Medicine/Academic Lead, Dementia Education Program, McGill University

Claire Webster

Founder and Ambassador, Dementia Education Program, McGill University/Founder and President of Caregiver Crosswalk Inc.

ADI would like to thank our corporate partners and donors:

Anonymous Trust
Biogen
Eisai
Eli Lilly
Janssen
Novo Nordisk
Otsuka America Pharmaceutical, Inc.
Roche
The Mary Oakley Foundation
The Van Otterloo Family

Published by Alzheimer's Disease International.
September 2021

Suggested citation:
Gauthier S, Rosa-Neto P, Morais JA, & Webster C. 2021. World Alzheimer Report 2021: *Journey through the diagnosis of dementia*. London, England: Alzheimer's Disease International.

About the authors

Serge Gauthier

Serge Gauthier is a clinical neurologist specialising in the development of new tools for diagnosis and treatments for people living with Alzheimer's disease. He was the Director of the McGill University Research Centre for Studies in Aging from 1986 to 1997, and became a senior scientist of the CIHR-Rx&D program (Canadian Institutes of Health Research and Canada's Research-Based Pharmaceutical Companies) in 1997. Dr. Gauthier is the Academic Co-Lead for the Dementia Education Program and Professor Emeritus, Neurology and Psychiatry at McGill University. His accomplishments led to him being appointed to the Order of Canada in 2014 and the National Order of Québec in 2017.

Pedro Rosa-Neto

Pedro Rosa-Neto is a clinical neurologist with expertise in the quantification of dementia pathophysiology and preclinical diagnosis of Alzheimer's disease using biomarkers. He is affiliated with the Douglas Research Institute; le Centre intégré universitaire de santé et de services sociaux (CIUSSS) de l'Ouest-de-l'Île-de-Montréal; and the Departments of Neurology and Neurosurgery, Psychiatry and Pharmacology and Therapeutics at McGill University. He was appointed Director of the McGill University Research Centre for Studies in Aging in 2017. This was soon followed by a Professor position in Neurology at McGill University in 2019.

José A. Morais

José A. Morais is Professor of Medicine at McGill University. He is a senior scientist at the Research Institute of the McGill University Health Centre (RI-MUHC) in the Metabolic Disorders and Complications axis. In 2009, he became Director of the Division of Geriatric Medicine, McGill University, as well as of the MUHC and Jewish General Hospital. He is also Co-Director of the Quebec Network for Research on Aging and is the Academic Lead of the Dementia Education Program of the McGill Faculty of Medicine and Health Sciences. He was the Founder and first Director of the Centre of Excellence on Aging and Chronic Disease of the RUISSS McGill from 2012–2015.

Claire Webster

Claire Webster is a Certified Dementia Care Consultant (PAC), Certified Professional Consultant on Aging (CPCA), as well as a conference speaker and educator in the field of caring for an individual with dementia. She is Founder and President of Caregiver Crosswalk Inc., a consulting firm that provides education and support services to help individuals navigate the journey of Alzheimer's disease and/or dementia related illnesses. Claire works in collaboration with McGill University's Faculty of Medicine and Health Sciences and the Division of Geriatric Medicine. She is the Founder and Ambassador of the McGill Dementia Education Program and 'McGill Cares,' a weekly webcast series designed to support family care partners.

Acknowledgements

ADI and the report authors would like to extend thanks to the contributors of essays and testimonies included in this report. We would like to thank the people not mentioned by name elsewhere who gave generously of their time and expertise in preparation of the report. They are: Carol Servaes, Diane Lynn Weidner, Mona Atallah, Maria Vincelli, Stijn Servaes, Tamara Ellen Carver and Zeina Zeinab Salameh. Special thanks go to Roger Marple and an anonymous individual with dementia, who read early drafts of this report and provided invaluable feedback.

Contributing authors

Authors	Affiliation
Akinyemi, Rufus	Neuroscience and Ageing Research Unit, Institute for Advanced Medical Research and Training, College of Medicine, University of Ibadan, NIGERIA
Al Sinawi, Hamed	Department of Behavioral Medicine, Sultan Qaboos University, OMAN
Alladi, Suvarna	National Institute of Mental Health and Neurosciences (NIMHANS), INDIA
Ashton, Nicholas J.	Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, SWEDEN
Au, Lisa W.C.	Division of Neurology, Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, CHINA
Aventurato, Ítalo Karmann	Department of Neurology, University of Campinas, BRAZIL
Azizi, Mahsa	University of Saskatchewan, CANADA
Bacsu, Juanita-Dawne	University of Saskatchewan, CANADA
Balthazar, Marcio	Department of Neurology, University of Campinas, BRAZIL
Benedet, Andréa L.	Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, SWEDEN
Black, Sandra E.	Departments of Neurology, and Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, CANADA
Blennow, Kaj	Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, SWEDEN
Brucki, Sonia Maria Dozzi	Department of Neurology, Hospital Santa Marcelina, São Paulo, BRAZIL
Bruser, Gabrielle	Laurentian University, Ontario, CANADA
Camargos, Sarah Teixeira	School of Medicine, The Federal University of Minas Gerais, Belo Horizonte; Movement Disorders Unit, Neurology Service, The Federal University of Minas Gerais, Belo Horizonte, BRAZIL
Camicioli, Richard	Neuroscience and Mental Health Institute and Department of Medicine, Division of Neurology, University of Alberta, CANADA
Cammer, Allison	University of Saskatchewan, CANADA
Campo, Laura	Eli Lilly and Company, UNITED STATES
Canevelli, Marco	National Center for Disease Prevention and Health Promotion, Instituto Superiore di Sanita, Rome, ITALY
Caramelli, Paulo	• Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, BRAZIL • School of Medicine, The Federal University of Minas Gerais, Belo Horizonte; Movement Disorders Unit, Neurology Service, The Federal University of Minas Gerais, Belo Horizonte, BRAZIL • Cognitive and Behavioral Neurology Group, Neurology Service, The Federal University of Minas Gerais, Belo Horizonte, MG, BRAZIL
Cardoso, Francisco	School of Medicine, The Federal University of Minas Gerais, Belo Horizonte, MG, BRAZIL
Chadha, Antonella Santuccione	Women's Brain Project, SWITZERLAND
Cheewakriengkrai, Laksanun	Phramongkutklao Hospital, Bangkok, Thailand
Cohen, Annie	Department of Psychiatry, University of Pittsburgh, PA, UNITED STATES
Crowshoe, Lynden (Lindsay)	University of Calgary, Alberta, CANADA

Authors	Affiliation
Cruz de Souza, Leonardo	School of Medicine, The Federal University of Minas Gerais, Belo Horizonte, BRAZIL
Cui, Yue	Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, CHINA
Cullum, C. Munro	Division of Psychology, Department of Psychiatry, O'Donnell Brain Institute, University of Texas Southwestern Medical Center, UNITED STATES
Dimech, Annemarie Schumacher	Women's Brain Project, SWITZERLAND
Farina, Nicolas	Brighton and Sussex Medical School, UNITED KINGDOM
Ferretti, Maria	Women's Brain Project, SWITZERLAND
Ferri, Cleusa P.	Universidade Federalde Sao Paulo, BRAZIL
Fisk, John D.	• Division of Geriatric Medicine, Department of Medicine, Dalhousie University, Halifax, CANADA • Department of Psychology and Neuroscience, Dalhousie University, CANADA
Fortea, Juan	Sant Pau Memory Unit, Neurology Department, Hospital de la Santa Creu i Sant Pau – Biomedical Research Institute Sant Pau – Universitat Autònoma de Barcelona, Barcelona, SPAIN
Gambier-Ross, Katie	Edinburgh Centre for Research on the Experience of Dementia, University of Edinburgh, SCOTLAND
Gauthier, Serge	McGill Centre for Studies in Aging, Faculty of Medicine, McGill University & Department of Neurology & Neurosurgery & Department of Psychiatry, McGill University, CANADA
Geddes, Maiya R	Department of Neurology and Neurosurgery, McGill University, CANADA
Gélinas, Isabelle	McGill University, School of Physical & Occupational Therapy, CANADA
Gowda-Sookochoff, Rory	University of Saskatchewan, CANADA
Green, Robert C.	Mass General Brigham and Harvard Medical School, UNITED STATES
Green, Shoshana	University of Saskatchewan, CANADA
Grewal, Karl	University of Saskatchewan, CANADA
Hampel, Harald	Sorbonne University, GRC n° 21, Alzheimer Precision Medicine (APM), AP-HP, Pitié-Salpêtrière Hospital, Boulevard de l'hôpital, F-75013, Paris, FRANCE
Hrincu, Viorica	Division of Neurology, Department of Medicine, University of British Columbia, Vancouver, CANADA
Iroanyah, Ngozi	Alzheimer Society of Canada, CANADA
Ismail, Zahinoor	Departments of Psychiatry, Clinical Neurosciences, and Community Health Sciences, Cumming School of Medicine, University of Calgary, CANADA
Iulita, Maria	Women's Brain Project, SWITZERLAND
Jack, Clifford R.	Mayo Clinic, Rochester, MN, UNITED STATES
Kalaria, Raj N	Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UNITED KINGDOM
Kandiah, Nagaendran	Department of Neurology, National Neuroscience Institute, Singapore, SINGAPORE
Karam, George E.	Department of Psychiatry and Clinical Psychology, St Georges Hospital University Medical Center/Balamand University, Beirut, LEBANON
Karikari, Thomas K.	Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, SWEDEN
Kinnaird, Lindsay	Alzheimer Scotland Dementia Research Centre, University of Edinburgh, SCOTLAND
Koh, Wilbur	Department of Neurology, National Neuroscience Institute, Singapore, SINGAPORE
Kuo, Phillip H.	Departments of Medical Imaging, Medicine, and Biomedical Engineering, University of Arizona, UNITED STATES

Authors	Affiliation
Lagarde, Julien	Department of Neurology of Memory and Language, GHU Paris Psychiatry and Neurosciences, Hôpital Sainte Anne, F-75014, Paris, Université de Paris, F-75006 Paris, FRANCE
Largent, Emily A.	Department of Medical Ethics and Health Policy, University of Pennsylvania Perelman School of Medicine, UNITED STATES
Li, Xiaofeng	Department of Neurology, The second affiliated hospital of Chongqing Medical University, Chongqing, CHINA
Liu, Li	Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, CHINA
Malpetti, Maura	Department of Clinical Neurosciences, University of Cambridge, Cambridge, UNITED KINGDOM
Martinkova, Julie	Department of Neurology, Charles University, Second Faculty of Medicine and Motol University Hospital, CZECH REPUBLIC
Masellis, Mario	University of Toronto and Sunnybrook Health Sciences Centre, CANADA
Mathotaarachchi, Sulantha	Enigma Biomedical Group, CANADA
Mok, Vincent C.T.	Division of Neurology, Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, CHINA
Morais, José A.	Division of Geriatric Medicine/Academic Lead, Dementia Education Program, McGill University, CANADA
Mundadan, Reanne G.	Faculty of Health Sciences, Western University, CANADA
Munro, Denise	Alzheimer Scotland Dementia Research Centre, University of Edinburgh, SCOTLAND
Ng, Kok Pin	Department of Neurology, National Neuroscience Institute, Singapore, SINGAPORE
Nitrini, Ricardo	Department of Neurology, Faculdade de Medicina, Universidade de São Paulo, São Paulo, BRAZIL
O'Connell, Megan E.	Department of Psychology, University of Saskatchewan, CANADA
Oguntiloye, Olabode O	Department of Neurology, University College Hospital, Ibadan, NIGERIA
Olivieri, Pauline	Department of Neurology of Memory and Language, GHU Paris Psychiatry and Neurosciences, Hôpital Sainte Anne, F-75014, Paris, Université de Paris, F-75006 Paris, FRANCE
Ouaijan, Christelle N.	Department of Clinical Nutrition, St Georges Hospital University Medical Center, Beirut, LEBANON
Pascoal, Tharick A.	Department of Psychiatry, University of Pittsburgh, PA, UNITED STATES
Poole, Lisa	Dementia Advocacy Canada, CANADA
Possin, Katherine L.	• Department of Neurology, Memory and Aging Center, University of California San Francisco, San Francisco, California, UNITED STATES • Global Brain Health Institute, University of California San Francisco, San Francisco, California, UNITED STATES
Rabinovici, Gil	Memory & Aging Center, Departments of Neurology, Radiology and Biomedical Imaging, Weill Institute for Neuroscience, UCSF, UNITED STATES
Rajagopalan, Jayeeta	Strengthening Responses to Dementia in Developing Countries (STRiDE); National Institute of Mental Health and Neurosciences (NIMHANS), INDIA
Rao, Bharat R.	Enigma Biomedical Group, UNITED STATES
Reitermann, Michael	Enigma Biomedical Group, UNITED STATES
Roberts, J. Scott	Department of Health Behavior & Health Education, University of Michigan School of Public Health, Ann Arbor, Michigan, UNITED STATES
Robillard, Julie	Division of Neurology, Department of Medicine, University of British Columbia, Vancouver, CANADA
Robinson, Dame Louise	Newcastle University, UNITED KINGDOM

Authors	Affiliation
Rosa-Neto, Pedro	McConnell Brain Imaging Centre, Montreal Neurological Institute, Montreal and McGill Center for Studies in Aging, CANADA
Rowat, Julia	Laurentian University, Ontario, CANADA
Russ, Tom	Alzheimer Scotland Dementia Research Centre, University of Edinburgh, SCOTLAND
Sachdev, Perminder S.	Centre for Healthy Brain Agein (CHeBA), School of Psychiatry, University of New South Wales, Sydney 2052, AUSTRALIA
Sarazin, Marie	Department of Neurology of Memory and Language, GHU Paris Psychiatry and Neurosciences, Hôpital Sainte Anne, F-75014, Paris, Université de Paris, F-75006 Paris, FRANCE
Savundranayagam, Marie	Faculty of Health Sciences, Western University, CANADA
Schilling, Lucos Porcello	Brain Institute of Rio Grande do Sul (BraIns), Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, BRAZIL
Servaes, Stijn	McGill Centre for Studies in Aging, Faculty of Medicine, McGill University, CANADA
Sivananthan, Saskia	Faculty of Health Sciences, Western University, CANADA
Soucy, Jean-Paul	McConnell Brain Imaging Centre, Montreal Neurological Institute, CANADA
Spiteri, Raymond J.	University of Saskatchewan, CANADA
Strydom, André	Institute of Psychology, Psychiatry and Neuroscience, King's College London, London, UNITED KINGDOM
Therriault, Joseph	McGill Centre for Studies in Aging, Faculty of Medicine, McGill University, CANADA
Tsoy, Elena	Department of Neurology, Memory and Aging Center, University of California San Francisco, San Francisco, California, UNITED STATES
Vanacore, Nicola	National Center for Disease Prevention and Health Promotion, Istituto Superiore di Sanità, Rome, Italy.
Villemagne, Victor L	Department of Psychiatry, University of Pittsburgh, PA, UNITED STATES
Vincent, Rose	Edinburgh Centre for Research on the Experience of Dementia, University of Edinburgh, SCOTLAND
Vitali, Paulo	McGill University Research Centre for Studies in Aging, CANADA
Walker, Jennifer D.	McMaster University, Ontario, CANADA
Wallon, David	Normandie Univ, UNIROUEN, Inserm U1245, Department of Neurology and CNR-MAJ, CHU Rouen, Normandy Center for Genomic and Personalized Medicine, Rouen, FRANCE Rouen, FRANCE
Wang, Huali	Dementia Care and Research Center, Peking University Instittute of Mental Health, Beijing, CHINA
Webster, Claire	Certified Dementia Care Consultant, Founder Caregiver Crosswalk Inc and Founder, McGill University Dementia Education Program, CANADA
Wighton, Mary Beth	Dementia Advocacy Canada, CANADA
Wilkinson, Heather	Edinburgh Centre for Research on the Experience of Dementia, University of Edinburgh, SCOTLAND
Wimo, Anders	Department of NVS, Centre of Alzheimer research, Section of Neurogeriatrics, Karolinska Institutet, SWEDEN
Wu, Liyong	Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, CHINA
Yatawara, Chathuri Yatawara	Department of Neurology, National Neuroscience Institute, Singapore, SINGAPORE
Zetterberg, Henrik	Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, SWEDEN
Zimmer, Eduardo	Department of Biochemistry, Federal university of Rio Grande do Sul, BRAZIL
Zukotynski, Katherine A.	Departments of Radiology and Medicine, McMaster University, Hamilton, CANADA

Contents

Glossary of terms

Activities of daily living – the activities we do every day including tasks such as planning an outing, paying bills, taking medication, calling family and friends as well as basic tasks like dressing, eating and using the bathroom.

Agnosia – the inability to recognise people, objects, sounds, shapes or smells. This disorder is not the result of any vision or hearing impairment.

AI (artificial intelligence) – the ability of computers to simulate intelligent human behaviour.

Alzheimer's disease – Alzheimer's disease is the most common and well-known form of dementia, accounting for 60–80% of all cases. Brain cells and nerves are blocked by abnormal proteins, resulting in the disruption of the transmitters which carry messages in the brain, particularly those responsible for storing memories.

Alpha-synuclein – a protein present in the normal brain responsible for synaptic function. In people with Lewy body dementia and Parkinson's disease, abnormal alpha-synuclein clumps within the cells and form Lewy bodies. We call synucleinopathies the diseases characterised by accumulates of abnormal alpha-synuclein.

Amyloid – see Beta-amyloid

Amyloid scan – a type of positron emission tomography (PET) imaging. An amyloid scan enables in vivo detection of brain Aβ deposition, one of the neuropathological hallmarks of Alzheimer's disease.

Anosognosia – a lack of self-awareness about having a disability. This condition is very common in dementia as it is linked to Alzheimer's disease pathophysiology in vulnerable structures.

Aphasia – the inability to comprehend or formulate language due to damage to specific regions of the brain. It can be acute such as after a stroke, or progressive, like in some types of dementia including Alzheimer's disease and Fronto-Temporal Dementia.

APOE4 gene – this allele is present in approximately 15% of people and increases the risk for Alzheimer's disease and lowers the age of onset. Having this gene is a risk factor for dementia but does not mean that Alzheimer's disease is inevitable. Some people have two copies of the e4 gene (homozygotes or APOE4), or more commonly, one copy (heterozygotes).

Atypical dementia – this term designates the clinical diagnosis of individuals with a progressive cognitive and functional decline dominated by non-amnestic symptoms or/and young-onset (<65 years old).

Beta-amyloid – a peptide that is derived from a larger precursor protein and is the primary component of plaques characteristic of Alzheimer's disease.

Biomarkers – short for biological markers, are measurable indicators of normal biological processes (such as blood sugar), pathological processes (such as protein tau fragments in spinal fluid) or responses to an intervention.

Cardiovascular disease – a group of disorders of the heart and blood vessels including coronary heart disease, cerebrovascular disease, deep vein thrombosis and pulmonary embolism. Cardiovascular diseases are usually associated with a build-up of fatty deposits inside the arteries – known as atherosclerosis – and an increased risk of blood clots.

Cerebrovascular disease – disease of the blood vessels including the arteries that supply the brain.

Cholesterol – a compound of the sterol type found in most body tissues. Cholesterol and its derivatives are important constituents of cell membranes and precursors of other steroid compounds, but a high proportion in the blood of low-density lipoprotein (which transports cholesterol to the tissues) is associated with an increased risk of coronary heart disease.

Cognition – mental processes involved in gaining or using knowledge and comprehension. These processes include thinking, knowing, remembering, judging and problem-solving. Some dementias have more impact on some aspects of cognition (such as remembering recent events) than others.

Corticobasal syndrome – is a condition characterised by a progressive cognitive and asymmetric motor degeneration characterised by various combinations of akinesia, rigidity, dystonia, focal myoclonus, ideomotor apraxia, and alien-limb phenomena. Alzheimer's disease and aggregates of 4R-tau protein are frequently causes of this syndrome.

Creutzfeldt-Jakob disease – this is a rapidly progressive dementia caused by a build-up of proteins called prions, usually associated with abnormal motor movements, impaired gait, and severe neurological impairment.

CT (computerised tomography) scan – a type of scan that uses X-rays and a computer to create detailed images of the inside of the body.

Dopamine transporter (DAT) scan – DAT scan is a type of single photon emission computed tomography (SPECT). This imaging test reveals levels of dopamine transporter in the brain. It is a valuable tool to help differentiate dementia with Lewy bodies from Alzheimer's disease.

Dementia – a condition that groups symptoms of impaired memory, thinking, behaviour and emotional control problems resulting in a loss of autonomy. There are many classifications of dementia.

Dominantly Inherited Alzheimer Network – enables researchers around the world to monitor and identify changes in individuals who carry one of the gene mutations (Presenilin1, Presenilin2 or APP) known to cause dominantly inherited Alzheimer's disease.

Early-/young-onset – any dementia beginning before the age of 65. These terms are used interchangeably by report contributors.

Fluodeoxyglucose (FDG) scan – It is a type of positron emission tomography (PET) imaging. A FDG scan enables in vivo detection of brain glucose metabolism. Reduced glucose metabolism one of the hallmarks of Alzheimer's disease.

Frontotemporal lobar degeneration – a group of disorders within the larger frontotemporal lobar degeneration (FTLD) family characterised by the loss of nerve cells in the frontal and temporal lobes. They typically develop at an earlier age than Alzheimer's disease, usually in a person in their forties or fifties. Three distinct types of FTLD have been described: (1) behavioural-variant frontotemporal dementia, characterised by changes in behaviour and personality (2) semantic dementia, a progressive syndrome affecting factual knowledge about words and objects and (3) progressive non-fluent aphasia, characterised by significant effort in language output, loss of grammar and motor speech deficits.

Frontotemporal dementia – one of the subgroups of the larger frontotemporal lobar degeneration family, it accounts for approximately 10% of dementia cases. Its symptoms include changes in speech, personality, behaviour, poor impulse control and coordination.

Geriatrician – a medical doctor who specialises in the care of older adults.

High-income countries – a country with over US$12,696 Gross National Income per capita, according to the World Bank 2020 classification.

Hypertension – a condition in which the blood vessels have persistently raised pressure. Also known as high or raised blood pressure.

Incidence – the measurable rate or probability of an occurrence, such as a disease, in a defined population within a specific timeframe. In other words, the number of new cases of a disease diagnosed within a population.

Korsakoff's syndrome – an irreversible loss of memory due to an acute deficiency of vitamin B1 (thiamine). This can be associated with alcohol abuse as well as with severe nutritional deficits. This is not the same as alcohol-induced dementia which predominantly affects the brain's frontal lobe.

Lewy body dementia – or dementia with Lewy bodies, designates dementias characterised by the neuronal accumulation of abnormal alpha-synuclein, in the form of Lewy bodies. Dementia with Lewy bodies and Parkinson's disease dementia are examples of Lewy body dementias. Half or more of people with Lewy body disease also develop signs and symptoms of Parkinson's disease.

Low-income countries – a country with less than US$1,045 Gross National Income per capita, according to the World Bank 2020 classification.

Lumbar puncture – also called a spinal tap, this is the procedure of removing cerebrospinal fluid in the lower back region through a hollow needle, usually done for diagnostic purposes.

Middle-income countries – a country with between US$1,045 to $12,695 Gross National Income per capita, according to the World Bank 2020 classification.

Mild Cognitive Impairment– the stage between the expected cognitive decline of normal aging and the more serious decline of dementia.

Mixed dementia – Mixed dementia refers to the condition where abnormalities characteristic of more than one type of dementia occur simultaneously. For example, individuals can have both Alzheimer's disease and Vascular dementia together.

Monoclonal antibodies – an antibody produced by a single clone of cells or cell line and consisting of identical antibody molecules.

Magnetic resonance imaging (MR) – a type of diagnostic scan that uses magnetic fields, radio waves and a computer to produce detailed images from inside the body.

Neurodegeneration – degeneration of the neurons in the brain. Many neurodegenerative diseases – including Alzheimer's disease, Parkinson's disease and Huntington's disease – occur as a result of neurodegenerative processes.

Neurology – the branch of medicine or biology that deals with the anatomy, functions, and organic disorders of nerves and the nervous system.

Neuropathologist – a medical doctor who specialises in the diagnosis of diseases of the brain and nervous system by microscopic examination of the tissue and other means.

Oxidative stress – an imbalance between free radicals and antioxidants in the body.

Positron emission tomography (PET) – a type of non-invasive diagnostic scan. Once a short-lived positron-emitting radioactive tracer has been injected in the body, cameras and computer analysis can produce detailed images of the body.

Phosphorylated Tau (p-tau) –a biochemical modification in tau protein characteristic of Alzheimer's disease. The presence of elevated p-tau in the cerebrospinal fluid and plasma indicates the biological presence of Alzheimer's disease.

Prevalence – the measurable proportion of an occurrence, such as a disease, within a defined population and within a specific timeframe. In other words, the percentage of cases of a disease diagnosed within a population.

Prodromal – an early warning sign or symptom(s), which may indicate the onset of a disease.

Progressive supranuclear palsy (PSP) – a brain disorder mainly characterised by impaired balance affecting body movement, walking (falls), and uncontrolled eye movements. It results from damage to the brain's nerve cells that control thinking and mobility. These motor-based symptoms are frequently accompanied by memory and thinking problems.

Psychosocial – the combined influence that psychological factors and the surrounding social environment have on individual's physical and mental wellness and their ability to function.

Risk factors – health conditions or characteristics associated to the development of a condition, often linked to lifestyle, age and family history.

Spinal fluid – also called cerebrospinal fluid (CSF), is a fluid that is continuously produced, absorbed and circulated in the brain's ventricles, around the surface of the brain and spinal cord. The primary function of spinal fluid is to act as a protective cushion for the brain within the skull and be a shock absorber for the central nervous system. It also circulates nutrients and chemicals filtered from the blood and removes waste products from the brain.

Sporadic disease – a disease that occurs infrequently and irregularly and that is not inherited from parents.

Stroke – a medical condition that occurs when the blood supply to part of the brain is cut off.

Tau – proteins that stabilise microtubules. Hyperphosphorylated tau may accumulate in neurons, forming neurofibrillary tangles, leading to degeneration in a wide variety of disorders including Alzheimer's disease.

Total Tau (t-tau) – a protein responsible for keeping the shape of a cell stable. The presence of elevated total-tau in the cerebrospinal fluid is assumed be due to brain damage.

Tau scan – It is a type of positron emission tomography (PET) imaging. A tau scan enables in vivo detection of brain neurofibrillary deposition, one of the neuropathological hallmarks of Alzheimer's disease.

Transient ischemic attack (TIA) – temporary (less than 24 hours but usually less than five minutes) symptoms similar to a stroke, due to a temporary blockage of blood flow to a region of the brain.

Typical dementia –the clinical diagnosis of individuals who are 65 years old and older with a progressive cognitive and functional decline dominated by amnestic symptoms.

Vascular dementia – vascular disease occurs when blood vessels are damaged, blocked or weakened and therefore prevent the adequate supply of oxygen and nutrients. When the blood flow is disrupted and results in an insufficient oxygen supply to the brain, cells are likely to die. This may lead to a series of mini strokes (infarcts) and possible vascular dementia. Vascular dementia alone or in combination with Alzheimer's disease accounts for 20%-30% of all cases of dementia.

World Health Organization (WHO) – the United Nations health agency responsible for directing and coordinating matters relating to and promoting international public health, including non-communicable chronic diseases and syndromes such as dementia.

Foreword

Paola Barbarino, Chief Executive Officer, Alzheimer's Disease International

In 2018 I was invited to a meeting of the Innovative Medicines Initiative of the European Commission to talk about innovation in diagnostics. It was then, while studying wearables to detect early symptoms of Alzheimer's disease and big data, that I came across some really fascinating studies. These were signposted to me by the omniscient Serge Gauthier, then Chair of our Medical and Scientific Advisory Panel. They talked about people who suspected they had dementia and were desperate for a diagnosis, but too ashamed or scared to go to the doctor, were using bogus Internet sites promising equally bogus treatments or cures.

As Hrincu, Fisk and Robillard state in this report '*Ease of information-sharing via websites and social media can perpetuate misinformation, which can undermine the relationship between people living with dementia and their healthcare providers. These issues stemming from an unregulated online environment are particularly troubling for vulnerable individuals, as some sites promote non evidence-based treatments that may lead to financial loss and negative health outcomes*. [Page 39]'.

As Alzheimer's Disease International (ADI) is an organisation first and foremost about protecting vulnerable people, this troubled me a lot. Why aren't governments providing reliable online resources or redirections to Alzheimer's and dementia associations as a first port of call? Why aren't there trustworthy online tests provided by national healthcare systems to give worried individuals a sense of whether they should go to see their doctor or not? Can we not create the equivalent of an online BMI (Body Mass Index) to test for dementia? Can we overcome any technical, ethical and cultural challenges?

As I shared some of these questions with Serge, I realised the diagnostic issue really is at the core of everything we do. Healthcare professionals themselves need to believe that Alzheimer's (and related dementias), is a disease and that it is their job to diagnose it. As Louise Robinson puts so eloquently in the report '*Healthcare professionals can be reluctant to speak openly and honestly about dementia, especially with the person concerned, with some reluctant to use the actual 'D' word*'. [Page 36]

> **There is a perfect storm gathering on the horizon and governments all over the world should get to grips with it.**

Diagnosis and stigma go hand in hand. There is a direct link between our 2019 World Alzheimer's Report on stigma and this report.

Dementia is now the 7th leading cause of mortality globally and, as we know from previous World Alzheimer Reports, one of those with the highest cost to society. There are 55 million people living with dementia as we speak, and as this report indicates, probably less than 25% globally are actually diagnosed. In lower income countries this percentage may be as low as 10%.

There is a perfect storm gathering on the horizon and governments all over the world should get to grips with it.

New therapeutic breakthroughs are starting to appear on the market. These require a confirmatory diagnosis of Alzheimer's or dementia to be prescribed. At the same time, there seems to be a link between COVID-19 and the development or acceleration of cognitive deterioration. There is also, at last, a concrete possibility of a plasma biomarker that would make diagnosing Alzheimer's much easier and quicker. Last, but not least, the number of those who sadly develop dementia is growing, with age being the biggest risk factor and globally ageing populations.

On the other side of the scale (and you will see this clearly in the report) there are still too few primary healthcare practitioners able, willing or with the means to perform all the tests required to ascertain whether a person has dementia. This is not just in lower income countries but all over the world. In some countries there are no scanners, or professionals who can perform cerebrospinal fluid tests, or specialists to interpret the results.

This report is complex because diagnosing dementia is difficult. There are many grey areas and the report does not shy away from them. It aims to intersect race, gender, social, scientific, technological, economic and geopolitical issues with layers of medical information.

It also tackles complex areas, for example the fact that diagnosis is still a hit or miss affair. The report explains that up to 30% of people are actually misdiagnosed. This is why we urgently need better diagnostic systems, as in the case of the biomarkers mentioned earlier.

Healthcare practitioners need to be better educated to understand what is expected of them. In the words of Emily A. Largent '*Regrettably, older adults are often inadequately assessed for cognitive decline during primary care visits due to limitations on clinician time as well as lack of clinician expertise*'. [Page 143]

The report also tackles the issue of disclosure of the diagnosis and why this is such a difficult area for doctors. In the words of Serge Gauthier, '*[…] many people with dementia due to Alzheimer's disease, have a lack of awareness regarding their cognitive and functional decline (this phenomenon is called 'anosognosia') that makes them uninterested in the diagnosis and its likely causes. On the other end of the spectrum are those people who are so anxious about their diagnosis that a catastrophic reaction such as severe depression, and even suicidal thoughts are possible*'. [Page 176]

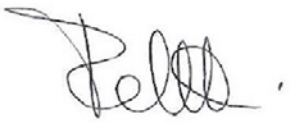
For those who are still wondering why diagnosing dementia is important even if there is no cure yet (a belief sadly shared by 33% of clinicians responding to our questionnaire), I suggest they read the words of Jose Antonio Garcia, a person living with dementia, '*Early diagnosis is very important because at this age, we still have responsibilities to our children and our elders. Our capabilities must be kept intact so that we can maintain our independence for as long as possible. Both our healthcare professionals and society in general need to provide us with maximum knowledge of the disease and with the means to improve it.*' [Page 154]

In the words of a former carer, and one of this report's authors, Claire Webster, '*Only by learning to adapt to all the cognitive and physical changes brought on by this condition will a carer be able to manage effectively*'. [Page 191]

People have a right to know, to learn, to understand, to make their own choices. Presuming otherwise is condescending and wrong.

In conclusion, I think the world is still in denial about diagnosing dementia. We cannot ignore the problem in the hope that it will go away. The phrase 'conspiracy of silence' might sound a tad melodramatic, but I have often felt like this when speaking to Health Ministries worldwide. Dementia is everywhere in the world and the case for the cost effectiveness of diagnosis versus not doing anything is clear, as Anders Wimo and Serge Gauthier articulate so cogently at the end of the report.

This work aimed to bring out into the open every little myth around diagnosis and I feel strongly it has succeeded. We hope it will offer people living with dementia, carers, researchers, physicians and policymakers a solid foundation for their journey or their practice. We also hope it will also act as a call to action to those governments that are yet to embrace the realities of what is coming. You can all help by making sure this report lands where it is needed. If you have read this far, please help us by sharing and disseminating this important piece of work into the right hands across all corners of the globe. As ever, we count on you.



Paola Barbarino
CEO, Alzheimer's Disease International
London 2021

Executive summary

ADI estimates that globally 75% of people with dementia are not diagnosed; this may be as high as 90% in some low- and middle-income countries, where stigma and lack of awareness of dementia remain major barriers to diagnosis.

Over 55 million people live with dementia worldwide. This is a staggering figure, made all the more striking as it rises on a daily basis, with forecasts reaching 78 million by 2030. The World Health Organization (WHO) Global action plan on the public health response to dementia targets at least 50% of countries to diagnose 50% of the estimated number of people with dementia by 2025. As most countries enforced lockdown measures to contain the spread of COVID-19 during 2020–2021, movement restriction cut off much access to healthcare services for people with dementia symptoms; the full impact of this disruption to diagnosis of dementia is yet to be seen.

Survey results

Online surveys from a total of 3,542 clinicians, people with dementia and carers, completed as part of the 2021 World Alzheimer's Report, plus personal testimonies of people with dementia in all WHO regions suggest that:

- Just 45% of people with dementia and carers felt they were given adequate information at the point of diagnosis, identifying a major gap in clinician signposting.
- Conversely, clinicians do have a source to refer to as 98% of 101 Alzheimer's and dementia associations stated that they maintain and update information on diagnosis on their webpages.
- Key barriers to diagnosis identified by people with dementia and carers included lack of access to trained clinicians (47%), fear of diagnosis (46%) and cost (34%).
- Key barriers to diagnosis identified by clinicians included lack of access to specialised diagnostic tests (38%), lack of knowledge in making a diagnosis (37%) and the belief that nothing could be done, thus making a diagnosis futile (33%).
- 75% of clinicians ranked the increasing number of people seeking a diagnosis as a major challenge in the future, followed by people seeking diagnosis due to self-testing (with the proliferation of online and at home tests), and an increase in disease-modifying treatments.
- 77% of clinicians in the survey said they would be interested to use a new blood test to increase diagnostic precision of the cause of dementia (those that didn't cited cost barriers, belief they would need further validation, or time pressures with extra time required to explain results).
- 83% of clinicians maintain that the COVID-19 pandemic delayed access of people with cognitive decline for assessment.
- Personal testimonies from people with dementia and carers consistently indicate the lengthy time taken before being given a diagnosis, as well as a lack of information at the point of diagnosis about specific types of dementia, progression and available support.

Stigma remains a major barrier to diagnosis, including healthcare practitioner stigma, with 33% of clinicians surveyed believing nothing can be done. Self-stigma and societal stigma hamper the diagnosis pathway with expert essays in this report showing that in Africa, a belief that dementia is 'a curse of god or the ancestors, a curse from the devil', amongst other supernatural concepts, fuels stigma. In rural China, cultural values of hardiness and independence add up to a two year delay prior to people seeking out help. In the Arabic speaking world, there are drives to change the use of the word *kharaf*, which means 'the one who has lost his mind'.

Expert essays collected from leading clinicians and practitioners are summarised thematically throughout the report: clinical assessment, laboratory tests, formulation of diagnosis, particular circumstances and the future of dementia diagnosis.

Clinical assessment

- ADI calls for governments to adopt a standardised approach to online cognitive assessment tools which are often unregulated, do not adhere to ethical standards and need government level control for best practice.
- Specialised assessment and advanced biomarker studies should be conducted where possible in individuals with atypical, early-onset and rapidly progressive dementias.
- Questions about changes in daily life may be more reliably answered by a family member, close friend or co-worker, especially if there is suspected anosognosia (someone who is unaware of their condition).
- Psychological symptoms associated with cognitive decline may be part of the disease process but may also be reactions to what is happening.
- Behavioural symptoms associated with dementia have a significant healthcare impact on carer fatigue, depression and possible burnout.

Laboratory tests

- ADI maintains that best practice is a combination of cognitive testing with confirmatory scan/cerebrospinal fluid (CSF), plus emerging biomarkers. Access to scanner technology and training for specialists is essential.
- Research has shown up to a 30% misdiagnosis rate post-mortem and 25% adjustment in Alzheimer's disease diagnosis following a PET scan, emphasising both the complexity of diagnosis and the need for the robust combination of laboratory and cognitive assessment.
- The performance of general blood tests is an important step in the diagnostic process to rule out other causes of cognitive changes.
- Head magnetic resonance imaging (MRI) or computed tomography (CT) should be considered as part of the initial laboratory evaluation of dementia.
- In complex cases, neuroimaging using PET or SPECT increases the diagnostic accuracy of Alzheimer's disease or of dementia with Lewy bodies.
- Under appropriate use criteria, neuroimaging using PET or SPECT may improve the diagnosis and care pathway of individuals by revealing the specific brain diseases underlying their dementia.
- Lumbar puncture (cerebrospinal fluid) is a safe and acceptable procedure aimed at a specific diagnosis in people with dementia of undefined aetiology, but use is not currently widely adopted globally.
- Cerebrospinal fluid analysis biomarkers (phosphorylated tau (P-tau) and amyloid beta (Aβ42 and Aβ42/40 ratio) constitute an affordable alternative to imaging biomarkers, with excellent diagnostic properties.
- There is a need for cerebrospinal fluid biomarkers specific for dementias with causes other than Alzheimer's disease.
- Blood biomarkers now show diagnostic promise given their practical, scalable, and economic advantages.
- A structured genetic assessment is required if there is a suspicion of familial type of dementia.
- Although APOE4 is the major genetic risk factor for Alzheimer's disease, APOE4 genotyping is not currently recommended in routine clinical practice.

Formulation of diagnosis

- ADI calls on governments globally to more accurately measure and record diagnosis rates not just in line with the WHO Global action plan on the public health response to dementia but universally – to enable better planning, treatment, care and support.
- As disease-specific blood biomarkers become available and machine learning is being developed to support clinical diagnosis, early identification of Alzheimer's disease will facilitate access to secondary prevention and disease-modifying therapies.
- Clinicians should promote informed decision-making, employ proven health communication techniques and provide guidance on appropriate next steps.
- Long-term follow-up of people with dementia is needed as new symptoms and physical signs may appear and lead to a change in diagnosis.
- As research is progressing on the biological definition of Alzheimer's disease, similar efforts are needed for non-Alzheimer dementias.

Particular circumstances

- ADI calls for the development of culturally appropriate cognitive assessment tools and awareness campaigns in order to improve diagnosis rates and to improve access to treatment and trials. In particular, there is an urgent need for cognitive assessment scales to be better translated and validated.
- Low- and middle-income countries face a greater challenge making the diagnosis of dementia in a timely fashion due to human and technological restrictions.
- Commitment to the development of national dementia plans, supported by robust health and care system policies is needed to improve the diagnostic pathway, leading to more comprehensive post diagnosis support.
- A modified, patient-centric approach is needed in the assessment of dementia for low-educated individuals.
- Women living with Alzheimer's disease face a 'triple jeopardy' of barriers from stigma related to age, cognitive decline, and gender stereotypes and bias.
- People with young-onset dementia, including people with Down syndrome, require careful evaluation to rule out treatable conditions that may be mistaken for dementia.

The future of the diagnosis of dementia

- ADI calls on governments to deliver national awareness raising campaigns around the warning signs of dementia and timely diagnosis, in line with action area 2 of the WHO Global action plan on the public health response to dementia.
- The first point of contact for people experiencing symptoms that make them question whether they have an emerging dementia disorder is, in most cases, a primary care physician, (GP, family practitioner/physician). As global populations age and as new diagnostic and treatment breakthrough emerge, there is an urgent need to prepare healthcare systems globally to cope with an increase of demand at primary care level.
- The diagnostic infrastructure, particularly in a primary care setting, is not prepared for a large increase in the demand for pre-dementia (and early-onset dementia) Alzheimer's disease diagnostics.
- The emerging risk from COVID-19 must be recognised. This means paying close attention to symptomatic warning signs following a diagnosis of COVID-19.

- The development of plasma Alzheimer's disease biomarkers has ushered in a new age in which a biologically-based diagnosis of Alzheimer's disease may be generally available non-invasively and inexpensively, and may be implemented for both research and clinical diagnostic purposes.
- With the approval by the United States Federal Drug Administration (FDA) of the first disease-modifying treatment for Alzheimer's disease, Aduhelm (aducanumab), it may soon be possible to treat earlier stages of the disease. However, further studies are warranted to prove clinical benefit.
- As disease-modifying treatments emerge, healthcare practitioner stigma should decrease.
- The new technologies, medications, and tools that are currently being researched and introduced into the clinical landscape, as well as the perspectives of people with dementia themselves, shine a light on the existing socio-economic imbalances and act as important catalysts to propel progress forward. This adds one more element to the mix… a measure of hope.

Recommendations

- Healthcare systems globally should introduce annual brain health check-ups for people over 50, facilitated by evolution in biomarkers science, along with the opportunity to promote risk reduction strategies.
- Governments globally must urgently start to measure and record diagnosis more accurately. Accurate measurement of diagnosis rates is the key to treatment, care and support, to healthcare system preparedness, and to challenging stigma.
- Governments must prepare for a tsunami of demand for healthcare services as a result of global ageing populations, improved diagnostics, including biomarkers, and emerging pharmacological treatments.
- Improved dementia training and education, plus increased time allocation for diagnosis in primary healthcare. This is with the intention of combatting a lack of skills and confidence and to remove the counter-productive time pressure on primary care doctors when dealing with a complex and sensitive diagnosis and disclosure.
- Healthcare systems must invest in, and improve, diagnostic capabilities, moving towards precision diagnosis, to eradicate high levels of misdiagnosis.
- Improved disclosure training required for clinicians to communicate a diagnosis transparently and sensitively, providing information on next steps, clinical follow up, condition evolution, treatment options and importantly direction to post diagnosis support options.
- Governments globally must recognise the right to a timely clinical diagnosis and put in place the capacity to deliver this, to enable better planning, treatment, care and support, in line with action area four of the World Health Organization (WHO) Global action plan on dementia.
- Healthcare systems must make culturally appropriate, translated and validated cognitive assessment tools available to increase diagnosis rates. This is with the aim of better information provision and planning, plus increased access to treatments, trials and support.
- A call for standardised, online, ethical, government adopted, cognitive assessment tools, to enable people to take initial and informed steps and to mitigate against dangerous misinformation.
- National awareness raising campaigns must address the stigma surrounding dementia, especially in some low-income countries where up to 90% of cases go undiagnosed as well as actively promote awareness of the warning signs, in line with action area two of the WHO Global action plan on dementia.
- Best practice in assessment must be recognised as a combination of cognitive testing, backed up by scan and/or cerebrospinal fluid (CSF) testing, plus preparedness and readiness to embrace emerging biomarkers.
- Improved access to scanner technology required for confirmatory diagnosis, for access to emerging treatments and ongoing monitoring, with equivalent specialist training.
- Long-term clinical follow-up for people living with dementia, as part of a holistic, post diagnosis support package, to encompass disease progression and changes in diagnosis. This includes treatment monitoring and evaluation in an era where new disease-modifying treatments are becoming available.
- As two-thirds of people with Alzheimer's disease are women, more research must be funded into precision medicine focusing on evidence-based, sex-specific measures for cognitive, clinical and biomarker testing.
- A call to educate healthcare professionals and the general public about the role of cerebrospinal fluid testing and a repositioning of this misunderstood diagnostic tool, in line with similar perspectives on epidurals.
- Clinicians must become aware and better informed about information, support and planning available via national Alzheimer and dementia associations, and the vital role they play in pre and post diagnosis support.
- Build on the innovative, often technology-based, approaches including telemedicine, which evolved rapidly during the COVID-19 pandemic. Research how these might best supplement, but not replace, future cognitive assessment, while acknowledging the benefits for remote or rural communities or for those unable to travel safely.
- Governments must prepare now for future pandemics to ensure that the diagnostic and treatment pathways are not disrupted at the levels experienced during COVID-19.

Methodology

In compliance with the standards and principles stipulated by the McGill Research Ethics board, the team set out to create a comprehensive and multi-pronged report that brought together the different voices impacted by a dementia diagnosis. The list is a long one – individuals with dementia, their friends, families and carers, advocates, laboratory researchers, professors, general practitioners and specialists – and collectively, they create an inclusive account of the journey that is dementia.

Target population

As dementia speaks to everyone, this report attempts to do the same. That is why some sections were designed to be easily accessible to everyone. The fact is that every group listed above will converge at some point during the diagnostic process, thus it seemed sensible that this report be addressed to a multitude of audiences. This not only includes healthcare and long-term care professionals, but also those apprehensive people contemplating an assessment or concerned family and friends who may have witnessed changed behaviour or symptoms and may want to investigate and learn. Two people in Canada with a diagnosis of dementia reviewed the report for accuracy and authenticity.

Report design

The report consists primarily of online survey results and expert essays about the journey to a diagnosis of dementia. Analysis of the surveys was conducted using Python 3.8 (1) implemented in the Anaconda Software Distribution, version 4.10.3 (2).[i,ii]

Surveys: Three online surveys targeted different groups interested in the diagnosis of dementia, namely clinicians, people with a diagnosis of dementia and carers, as well as the national Alzheimer and dementia associations represented by ADI. The three surveys were conducted concurrently between March and June 2021.

Expert essays: To encapsulate a broad range of knowledge, healthcare professionals were invited to submit essays within their field of expertise. The choice of experts was based on the principles of equity, diversity and inclusion, as well as a variety of geographic locations for global representation and range of country income status.

This report builds on, but does not revisit or replicate, the content and focus of the 2011 ADI report 'Early diagnosis and intervention'. No systematic literature search was performed for this report, but some of the most recent publications containing significant epidemiologic, clinical or methodological information were added as references at the end of each chapter, up to and including August 9th, 2021.

Case studies: Individual case studies were requested from people living with dementia and eight are included covering all WHO regions. Reproduced using their own words, they are at the heart of this report, taking us along the dementia journey from the clinical world and theoretical concepts to real-life transformative situations and genuine experiences.

Summary of the contributions received

The quantitative and qualitative responses featured in this report were obtained from 1,111 multidisciplinary clinicians in 108 countries, 205 people with dementia and 2,122 carers in 83 countries, and 101 ADI member associations. 62% of clinicians who responded were from high income countries, 38% were from low- and middle-income countries.

Many of the survey findings are represented in charts and figures throughout the report. Commentary and discussion points were provided by the McGill University team to frame and provide context for each chapter. We received fifty-one invited expert essays that were edited for style, taking into consideration the mixed readership, and allocated to the relevant chapters.

i Van Rossum G, Drake FL. Python 3 Reference Manual. Scotts Valley, CA: CreateSpace; 2009.
ii Anaconda Software Distribution. Anaconda Documentation. Anaconda Inc.; 2021. https://docs.anaconda.com/

Chapter 1
What is dementia, why make a diagnosis and what are the current roadblocks?

Claire Webster

Key points

- The term dementia is used to describe a group of symptoms affecting thinking, mood and behaviour severe enough to interfere with daily life.
- Most countries encourage individuals to visit their primary care physician (family doctor) as a first step towards a diagnosis of dementia.
- A significant roadblock to obtaining a diagnosis is a lack of knowledge and awareness about the disease by the general public.

What is dementia?

The term 'dementia', otherwise known as 'major neurocognitive disorder', is not one specific disease but rather a group of symptoms that happen because of a disease. It impacts memory, behaviour, thinking and social abilities severely enough to interfere with one's activities of daily living and social autonomy. While Alzheimer's disease is the most common cause of dementia in people over the age of 65, it is not the only one. Most people over the age of 80 have more than one cause to account for their dementia, such as small strokes or Parkinson's disease. In this report, we discuss differential diagnostic issues once the presence of dementia has been established by a clinical assessment supported by appropriate laboratory tests and brain imaging.

Many of the diseases that cause dementia exhibit similar symptoms, including memory loss, disorientation, confrontational behaviour, language problems, and a variety of physical issues altering vision and mobility. For each disease, and each person affected, these symptoms can present in different ways.

Alzheimer's disease: The distinguishing feature of Alzheimer's disease is the presence of beta-amyloid and tau proteins that build up in the brain to the point that they obstruct normal cognitive functions. This usually manifests with changes in memory, abstract thinking, judgement, behaviour, mood and emotions, and ultimately interferes with physical control over the body.

Vascular dementia: This is the second most common form of dementia. It occurs when the brain is deprived of vital nutrients and oxygen from the blood flowing through the brain. This can happen after one stroke in a strategic brain area, or a series of small strokes. Other factors that can contribute to the development of vascular dementia include a history of heart attack, irregular or unusually rapid heartbeat (atrial fibrillation), hardened arteries that restrict blood flow (atherosclerosis), high blood pressure, diabetes, high cholesterol, obesity and smoking.

Dementia with Lewy bodies: This type of dementia combines the cognitive impairments of Alzheimer's disease with the diminished motor skills associated with Parkinson's disease. This can make diagnosis especially challenging. Dementia with Lewy bodies is characterised by the presence of alpha-synuclein proteins that form clusters in brain cells. These invasive structures then interfere with normal brain functioning. While also encompassing the more common symptoms of dementia, dementia with Lewy bodies is differentiated by recurring visual hallucinations, fluctuations in attention

and alertness, and declining cognitive abilities such as problem solving, and increased visuospatial problems that make it difficult to interpret what is seen. Individuals with dementia with Lewy bodies may have more nocturnal sleep disturbance than people with Alzheimer's disease.

Frontotemporal dementia: The frontal and temporal cortexes atrophy (shrink) as neurons in those parts of the brain die. Early signs of frontotemporal dementia usually include changes in speech, personality, behaviour, impulse control, and coordination. Frontotemporal dementia tends to occur at a younger age.

Young-onset dementia: This rare form of dementia, accounting for approximately 3% of cases, may be caused by any of the above-described diseases, be it Alzheimer's disease, vascular, Lewy bodies or frontotemporal dementia. The only difference is that it occurs in people under the age of 65. In many cases, there is a delay in obtaining an accurate diagnosis as dementia is often overlooked as a possibility in a younger person.

Although this report's primary focus is dementia, we can, in some circumstances, diagnose conditions such as Alzheimer's disease in its pre-dementia symptomatic stage, designated as mild cognitive impairment (MCI) and mild behaviour impairment (MBI) due to Alzheimer's disease or prodromal Alzheimer's disease. This diagnosis does however require laboratory-measured biomarkers. These are not yet available for use in a primary care setting. This report provides an update about the current science and research relating to these biomarkers and Alzheimer's Disease International will be monitoring their validity and use in the future. It should be noted that mild cognitive impairment may be reversible or non-progressive over time and may be the best opportunity for secondary prevention against dementia.

Seeking a diagnosis for cognitive complaints

There are many reasons one might encourage a loved one family member to consult a healthcare professional for a cognitive assessment. Perhaps there is a family history of dementia, or awareness that a friend or relative seems 'off' – they are uncharacteristically forgetful, anxious, or depressed. It is often difficult for many family and informal carers to convince someone they care about to seek medical advice. Some people deny having a problem with their cognition for various reasons. Changes in the brain associated with dementia can interfere with the ability to recognise differences in memory and/or behaviour, as well as in the ability to perform daily tasks (the medical term for this is anosognosia). 'Why bother getting a diagnosis of dementia if there is no cure, and they will take my driver's licence away?' is a common belief. Fear of losing control of one's independence once a disease is officially diagnosed may also be a concern.

Although a progressive decline in memory regarding recent events is one the most common symptoms of dementia, there may be other types of early warning signs such as searching for words, errors with directions, not recognising familiar faces, hesitation in making decisions and a significant change in mood and behaviour. There are often psychological symptoms associated with cognitive decline, such as anxiety, social withdrawal, irritability, and depressive feelings. They can be part of the disease process but may also be adverse reactions to what is happening. Since there are many reversible or controllable causes of cognitive decline, it is very important to seek medical attention and obtain a proper assessment.

The diagnostic journey for a person with cognitive complaints may differ around the world; however, most countries encourage individuals to visit their primary care physician (family doctor) as a first step. In many cases, they will be assisted by a nurse who may record some medical history ahead of the visit, and/or administer some of the memory screening tests over the phone, by email or in person. For those individuals who do not have a primary care physician, it is recommended that they visit a public healthcare clinic with multiple primary care doctors or other healthcare professionals who may have the expertise to perform the assessment and diagnosis of dementia.

It is important to the diagnostic process that any information about the signs and symptoms of concern from the person experiencing cognitive complaints, or from their family and friends, be shared with the healthcare professional. Some screening scales have been developed to get a general measure of their cognitive abilities; the score is then compared to that of an average person in the same age group and level of education. These scales are often repeated at each subsequent visit to assess whether the person is improving, stable or declining. The initial cognitive tests will focus on the warning signs of dementia, such as problems with language, disorientation, misplacing items and other signs highlighted by ADI as part of global awareness raising. See Figure 1 for information about warning signs of dementia.

Other scales have been designed to assess more specific difficulties with speech production (such as naming words from a letter) or understanding, writing, reading or identifying faces or objects. These scales usually require a separate assessment by a healthcare professional who has been specially trained to administer these tests.

While a healthcare professional may be able to confirm evidence of cognitive and functional decline, it is rarely feasible to give an accurate diagnosis of dementia and its causes after only one visit based solely on medical history and basic cognitive testing. Where possible, the complete diagnostic process will include a series of additional tests, such as basic blood tests and brain scans, and occasionally, brain scans using radioactive substances and/or a lumbar puncture to measure proteins in the cerebrospinal fluid. These tests, combined with accumulating information gained from observing the progression of signs and symptoms, lead to a diagnosis of the cause of the dementia – such as Alzheimer's disease, vascular dementia, dementia with Lewy bodies, frontotemporal dementia or mixed dementia (attributed to more than one cause).

Making an accurate and timely diagnosis is the first step in a long process that can last years. Support for the person living with dementia as well as their family and friends is crucial. Physicians have a role to play in assisting people with dementia and their carers to navigate this journey. From the moment an individual is diagnosed, early intervention of a multidisciplinary team of healthcare professionals, along with legal advice, can have a positive effect on care. This report brings together leaders in the global medical community to provide the latest information regarding the diagnosis of dementia. The aim is multi-pronged: to provide an arena where knowledge and research is shared, to facilitate dementia understanding for the person living with cognitive decline, as well as their family members and friends who may act as carers, and finally, to influence policymakers who can advocate for continued support for the advancement of research, science and innovative strategies.

Figure 1. ADI 10 warning signs of dementia.[i]

i ADI 10 warning signs of dementia infographic is available to download at https://www.alzint.org/resource/warning-signs-of-dementia-infographic/

Roadblocks to a timely diagnosis

Never before has there been so much attention focused on Alzheimer's disease and/or dementia-related illnesses. According to the World Health Organization[ii] (2020), Alzheimer's disease and other dementias are the seventh leading cause of death and there are more than 55 million people worldwide who have been diagnosed, with countless others unaccounted for due to lack of awareness about the signs and symptoms of the disease, cultural or geographical biases, inaccessible resources and lack of trained professionals.

As our population ages, Alzheimer's disease, as well as other forms of dementia and major neurocognitive disorders, are on the rise. Dementia affects people of every gender, culture, ethnicity, religion, citizenship, sexual orientation and ability. While the number of people being diagnosed with dementia increases, so does the number of people finding themselves in the role of carer without the knowledge or training to manage the condition and properly care for the person living with dementia.

One of the most significant roadblocks to obtaining a diagnosis of dementia is a lack of knowledge and awareness about the disease by the general public. Despite the increased media attention over the past several years, including being featured in several compelling Hollywood movies, very few countries have public awareness campaigns that provide information about the signs and symptoms of the condition. As a result, progressive cognitive decline and/or changes in behaviour are often thought to be associated with normal ageing or depression or mistaken for other mental illnesses.

Once the symptoms progress to the point that medical intervention is needed, the person with dementia and their carer who are seeking a diagnosis may well be confronted with several obstacles. These include limited access to healthcare due to confusion about which healthcare professional to consult; remote geographical locations; transportation restrictions and language barriers. It may also be because of a shortage of specialised healthcare care experts and accompanying diagnostic tools; an absence of health insurance coverage; or a lack of access to free public healthcare and/or limited finances.

Depending on the type and nature of the symptoms, some people assume that a psychiatrist is required while others make an appointment with a family doctor. Stigma and negative stereotypes associated with dementia prevent many individuals, families and carers from seeking the help and support they need.

As the survey results suggest, the most significant roadblock regarding dementia care management after diagnosis is the absence of a 'Prescription of Care' (a term used by the McGill University Dementia Education Program) for what may lie ahead. A dementia diagnosis often leaves the individual and their family carers devoid of information, specifically about how it may progress, and how to manage its related everyday challenges. Other than prescribing an initial round of medication which may or may not help symptoms, the medical community does not always provide crucial educational material, nor does it refer to support services in the community.

ii For WHO dementia-related information please see https://www.who.int/health-topics/dementia#tab=tab_1

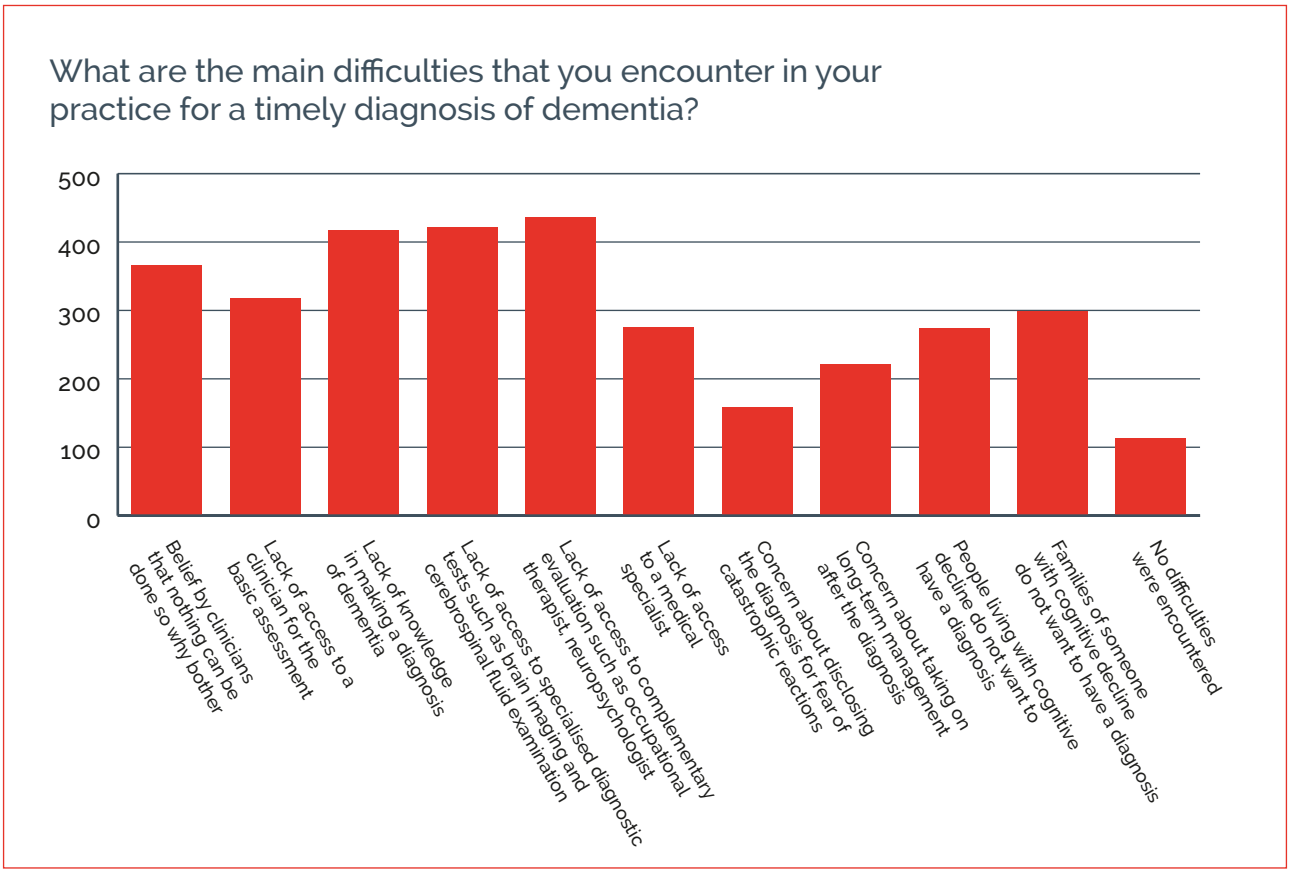


Chart 1. Clinician responses (multiple answers selected).

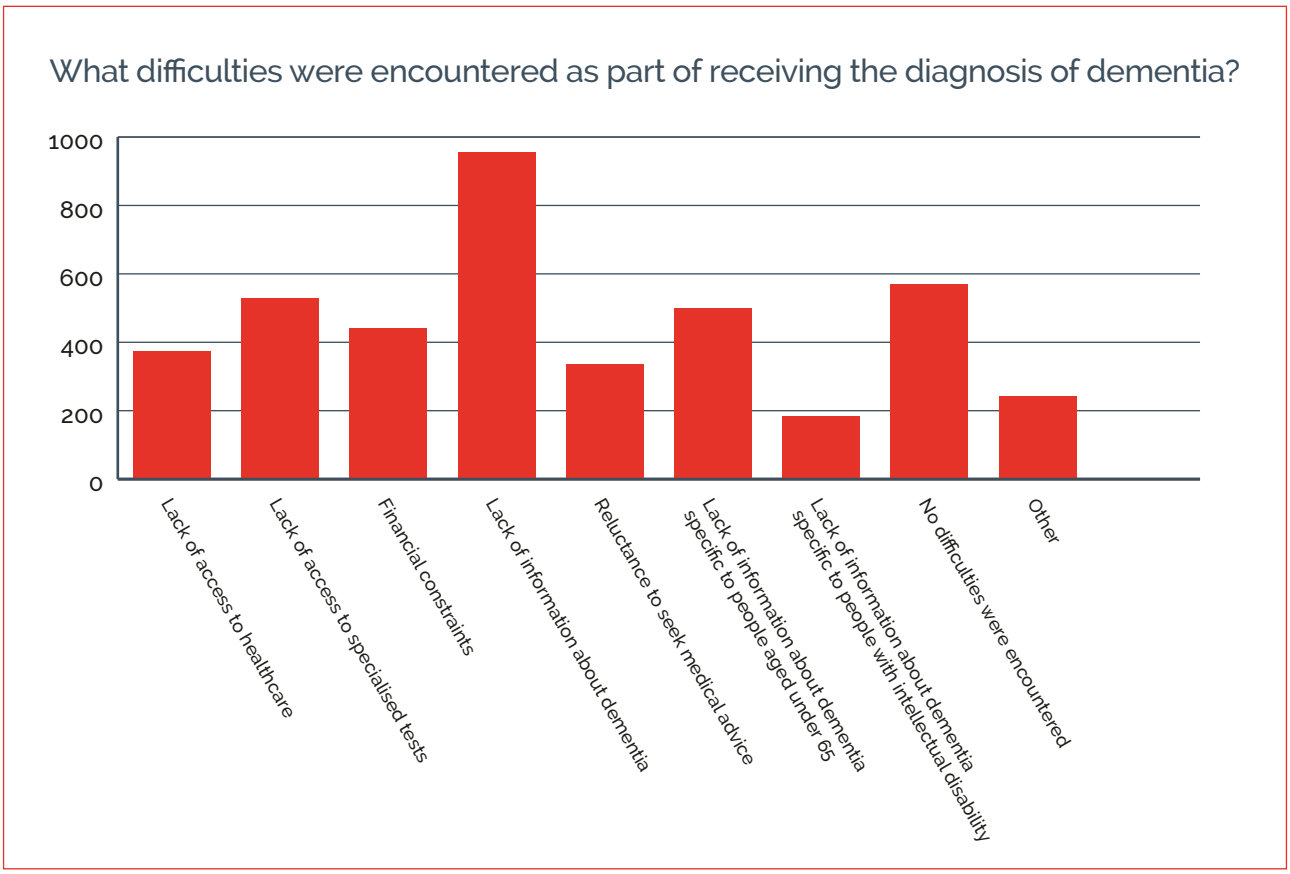


Chart 2. People with dementia and carer responses (multiple answers selected).

Conclusions

The journey through a diagnosis of dementia is a complex one. It is a multiple step process that begins by understanding the early signs and symptoms of an illness that is still plagued by an overall lack of social awareness. A shift in focus is needed, one that makes research, education, advocacy, and most importantly, universal access to an informed and knowledgeable healthcare system a priority. From there, it is a matter of creating a support system that prioritises the needs of the person living with dementia alongside the needs of their carer.

There is still much to learn and do about dementia and a united front is needed – one that reduces stigma, that increases awareness and that heralds change and scientific advances. ADI calls for governments to lead the way in providing a standardised and ethical online assessment option. Aligning a dementia-centric approach on all fronts is paramount.

Part I
Clinical assessment

Chapter 2
Who makes the diagnosis of dementia and how do you prepare for the assessment?

Serge Gauthier

Key points

- Primary care provides a more familiar, person-centred environment for the initial assessment.
- Referral to a specialist such as a geriatrician, neurologist, psychiatrist or neuropsychologist may be required for more complex cases of dementia.
- The online environment offers a wide range of resources for people seeking information about dementia although the quality of online resources varies greatly.
- To promote the benefits of the online environment while minimising harm, resources for dementia should be developed following established ethical guidelines.

General background

Whether it is you as a person with cognitive decline or a concerned family member or friend who initiates a search for diagnosis, the question is how to go about it. Most people these days go online using key search words such as 'memory, dementia or Alzheimer.' While there are websites with credible information, usually those hosted by Alzheimer or dementia organisations, specialist charities, or universities, there are some that feature questionable material or commercially oriented intentions. Some sites provide screening questions about the symptoms associated with dementia, while other sites include self-assessments tests. This type of search may be a good first step, but these sites are no substitute for an in-person clinical assessment by a healthcare professional.

Most countries encourage that initial visit be to your regular primary care physician. If you do not have one, a visit to a clinic with several primary care physicians may be advantageous; one may have an existing interest and experience in the diagnosis of dementia. Often, this is complemented with support by other healthcare professionals such as a nurse. They may take some preliminary patient history ahead of your visit, and/or complete some of the memory screening tests online or in person. Referral to a memory clinic or other specialised health professionals may be required after this preliminary assessment but is not always necessary.

Survey results

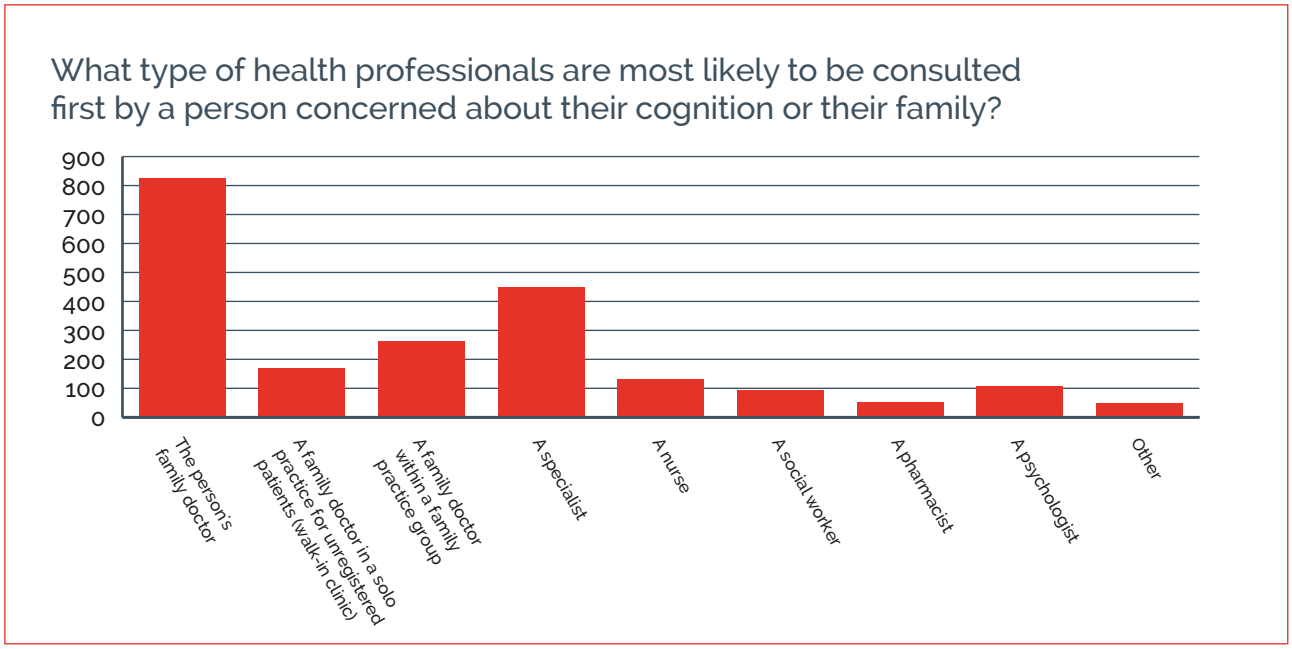


Chart 1. Clinician responses.

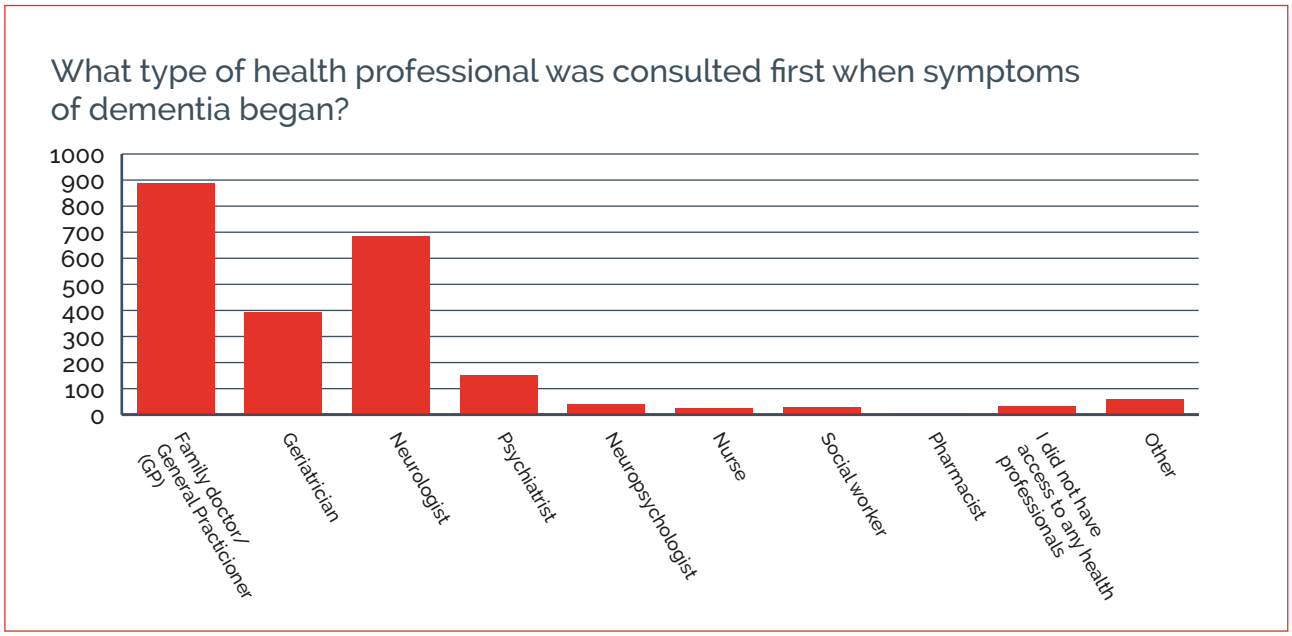


Chart 2. People with dementia and carer responses.

A total of 1,111 multidisciplinary clinicians responded to this survey and provided the anticipated response, namely that most people seeking a diagnostic opinion saw their family doctor as a first step (74%).

A total of 2,327 people with dementia and carers who completed the survey indicated that while most people saw their family doctor first (39%), specialists also played a major role in the diagnosis (neurologists, 29%; geriatricians, 17%; psychogeriatricians, 6%). Interestingly, many sought out information from the Internet before (29%), during (38%) and after (36%) the diagnostic assessment. The Alzheimer associations surveyed showed that access for all people in need of diagnostic assessment was only readily available in 36% countries represented. This was confirmed in the survey aimed at clinicians which identified the key limiting factors as being a lack of specialised tests, high costs, a lack of trained clinicians and fear of the diagnosis of dementia. The early warning signs of dementia are highlighted on nearly all Alzheimer associations websites (97%), specific information about diagnosis is given on 64% and updates about diagnosis on 42%.

Expert essay

21st century dementia care: the role of primary care

Dame Louise Robinson

Newcastle University, UNITED KINGDOM

Dementia is one of the costliest long-term illnesses to society, with 85% of costs related to family or social care (1), and is a significant contributor to loss of independence, disability and care home placement (2). Secondary care services have traditionally been the mainstay for the diagnosis and management of dementia. However, with increasing emphasis on timely diagnosis, to enable people with dementia and their family's earlier access to cost effective interventions to slow cognitive loss and improve quality of life, global policy has recommended primary care to have a greater role in both pre-diagnostic assessment and the long-term management of dementia (3). Such a policy shift has naturally occurred as 'market demand', our rapidly ageing populations and rising numbers of people living with dementia, outstrip healthcare resources, especially in lower- and middle-income countries (LMICs) where specialist services are often limited or even absent.

In Europe and the United Kingdom (UK), family physicians, or general practitioners (GPs) as they are also known, were hesitant about such a shift in care, largely due to concerns over lack of time and the appropriate knowledge and skills; however, this appears to be changing for the better (4). In 2017, a survey of 445 primary care providers across 25 European countries found the majority involved in dementia investigations and assessment. Notwithstanding there was considerable diversity in their responsibilities for post diagnosis care; such variation was explained through policy differences, for example the presence or absence of national dementia plans, and clinical practice, that is, the existence of clinical guidelines. This essay presents a case study from the UK, on the role and responsibilities of a primary care physician in dementia assessment and diagnosis, where national evidence-based, clinical guidelines have recently been critically reviewed and updated (5).

The role of primary care in dementia diagnosis: evidence-based clinical recommendations from the UK

Primary care and secondary care physicians play complementary roles in dementia diagnosis with updated, evidence-based guidance available to inform practice (5,6). Secondary care services have an important role in defining the dementia subtype, dealing with the management of more complex cases and stratifying which individuals with mild cognitive impairment are at greatest risk of developing a future dementia and most in need of follow up. In the UK, where primary care acts as the gatekeeper to other specialist healthcare services, the family physician/GP is usually the first point of contact for people experiencing cognitive difficulties, or their families who are worried their relatives may have dementia; they should have a low threshold for referring someone with suspicious symptoms for specialist assessment (7).

The role of primary care is to (7):

- Explore the patient's ideas and concerns around their symptoms.
- Exclude a potentially treatable illness or reversible cause of the possible dementia, for example drug-related, depression, vitamin B12 deficiency and thyroid disturbance (5).
- Refer more urgently for specialist assessment those with unusual symptoms (neurological, psychiatric, or behavioural changes) or those at significant risk (psychosocial issues, harm to self or others).
- Discuss and explain the possible investigations to be conducted in secondary care in order to reduce patient and family anxiety and uncertainty (8) and;
- Ensure individuals with mild cognitive impairment are followed up and, if their symptoms become more severe, refer for specialist assessment.

Primary care clinicians need to be aware of the diversity of presenting symptoms of a possible dementia illness ranging from the more usual memory loss and difficulty in finding words or making decisions to personality and/or mood changes. Changes in cognition and functioning are obviously influenced by a person's cultural and educational background. Increased frequency of patient visits to the family physician or local pharmacist, missed healthcare appointments or confusion

over medication may also be warning signs (7). Family concern is of particular importance especially as an individual may compensate, or deny, their issues in the early stages.

In terms of reversible causes of cognitive decline, occasional lapses of memory are common as people get older, especially in the presence of stress, depression and acute physical illness. In such cases, the family physician is well placed to review the patient over the following months, after appropriate treatment has been given, before deciding on specialist referral (7). Evidence from large cohort studies has shown that certain drugs, those with high anticholinergic burden, can cause cognitive impairment, thus aggravating dementia or causing a false positive diagnosis: simple, validated tools, such as the Anticholinergic Cognitive Burden Scale, allow the family physician to identify potential medications to be stopped before referral to secondary care (6).

Initial assessment in primary care should include a careful history from both the person with dementia and their main carer, with particular emphasis on disturbance of cognitive function, activities of daily living and carer concerns. A physical examination should be undertaken to determine any focal neurological signs and exclude visual or auditory problems. Before referral to secondary care, the family physician should undertake baseline investigations (bloods tests and potentially a chest X-ray and ECG) and a brief cognitive assessment using tools such as: 10-point cognitive screener (10-CS); General Practitioner Assessment of Cognition (GPCOG); 6 item Cognitive Impairment Test (6CIT); Mini-Cog Assessment Instrument or Memory Impairment Screen (MIS) (5). The updated UK dementia guidelines found most brief cognitive assessment tools to be broadly similar in their properties and thus do not recommend one test above another. They equally found no evidence to justify the use in primary care of more time-consuming tests such as the MoCA or the MMSE, which also has copyright restrictions limiting its use in practice (5). It is important to note, however, that such tests have usually been developed in countries where English is the first language and may be unsuitable, and culturally inappropriate even when translated into the country's native language, for use in lower income countries (LICs) (9).

Primary care provides a familiar, person-centred environment for the individual with cognitive issues, and/or their families, to discuss their worries and concerns at both the pre diagnosis stage, where a potential dementia diagnosis may be sensitively raised, and post diagnosis to review how they are coping with the new diagnosis. Healthcare professionals can be reluctant to speak openly and honestly about dementia, especially with the person concerned, with some

Primary care provides a familiar, person-centred environment for the individual with cognitive issues, and/or their families, to discuss their worries and concerns at both the pre diagnosis stage, where a potential dementia diagnosis may be sensitively raised, and post diagnosis to review how they are coping with the new diagnosis.

reluctant to use the actual 'D' word. Although initially discussing the diagnosis may be distressing, evidence suggests most people prefer to know if they have dementia to access appropriate support and treatment and to plan ahead for the future. It also allows documentation of the person's family and informal support networks; the main family carer(s) of a person with dementia may also be patients of the family physician and require assessment and support (7).

In addition, with evidence demonstrating a preventative aspect to around 40% of dementias worldwide and the recent identification of 12 modifiable risk factors (10), primary healthcare affords an excellent opportunity for case finding. Case finding comprises proactively screening specific sub-groups who are at higher future risk of developing dementia (5); these include: people aged over 75 years; those with high vascular risk and past history of stroke disease and those with Parkinson's disease and learning disabilities. However, there is little evidence to date that case findings initiatives are cost effective and importantly do not cause more distress or harm to people than the benefits of earlier identification (5,7).

Unfortunately, even with the luxury of revised, evidence-based guidelines, dementia diagnostic rates in the UK, where there is a well-established, free to all, primary healthcare service, were still less than 70% prior to the corona virus pandemic. During 2020 and early 2021, these figures have fallen considerably due to national lockdowns and service disruption. Globally more considerable challenges exist. Currently over 60% of people with dementia live in LMICs, countries with the least capacity to cope with rising numbers of people with dementia due to a range of issues including: lack of public and professional awareness about dementia; culturally appropriate cognitive assessment tests, access to affordable primary care services and limited availability of specialist services and evidence-based therapies (3).

References

1. Alzheimer's Disease International. World Alzheimer's Report 2015: The Global Impact of Dementia. London, UK; 2015.
2. International AD. World Alzheimer's Report 2013: An analysis of long term care for dementia [Internet]. 2013 [cited 2021 Jul 1]. https://www.alz.co.uk/research/WorldAlzheimerReport2013.pdf
3. Alzheimer's Disease International. World Alzheimer Report 2016. Improving healthcare for people with dementia. London, UK; 2016.
4. Petrazzuoli F, Vinker S, Koskela TH, Frese T, Buono N, Soler JK, et al. Exploring dementia management attitudes in primary care: a key informant survey to primary care physicians in 25 European countries. Int Psychogeriatrics [Internet]. 2017 Sep 1 [cited 2021 Jul 8];29(9):1413–23. https://www.cambridge.org/core/journals/international-psychogeriatrics/article/abs/exploring-dementia-management-attitudes-in-primary-care-a-key-informant-survey-to-primary-care-physicians-in-25-european-countries/E54D88FF4E68B95036688FC56C40FC23
5. Care NI for H and. Dementia: assessment, management and support for people living with dementia and their carers. 2018.
6. Pink J, O'Brien J, Robinson L, Longson D. Dementia: assessment, management and support: summary of updated NICE guidance. BMJ [Internet]. 2018 Jun 20 [cited 2021 Jul 8];361. https://www.bmj.com/content/361/bmj.k2438
7. Robinson L, Tang E, Taylor J-P. Dementia: timely diagnosis and early intervention. BMJ [Internet]. 2015 Jun 16 [cited 2021 Jul 8];350. https://www.bmj.com/content/350/bmj.h3029
8. Samsi K, Abley C, Campbell S, Keady J, Manthorpe J, Robinson L, et al. Negotiating a Labyrinth: experiences of assessment and diagnostic journey in cognitive impairment and dementia. Int J Geriatr Psychiatry [Internet]. 2014 Jan 1 [cited 2021 Jul 8];29(1):58–67. https://onlinelibrary.wiley.com/doi/full/10.1002/gps.3969
9. Magklara E, Stephan BCM, Robinson L. Current approaches to dementia screening and case finding in low- and middle-income countries: Research update and recommendations. Vol. 34, International Journal of Geriatric Psychiatry. John Wiley and Sons Ltd; 2019. p. 3–7.
10. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Vol. 396, The Lancet. Lancet Publishing Group; 2020. p. 413–46.

Expert essay

Online resources about dementia: finding the balance between benefits and harms

Viorica Hrincu,[1] John D. Fisk,[2] Julie M. Robillard[1]

[1] Division of Neurology, Department of Medicine, University of British Columbia, Vancouver, CANADA
[2] Division of Geriatric Medicine, Department of Psychiatry, Dalhousie University, Halifax, CANADA

Internet use by older adults is growing worldwide. Although access inequalities persist (1), the 'digital divide' is narrowing between younger and older adults. The online environment offers a wide range of resources for older adults seeking information specifically about dementia. Dementia topics of interest include information about prevention and treatment, interactive self-assessments, and opportunities to connect with peers through social networks. However, the quality of information of these resources, and extent to which its presentation is based on an ethical foundation, vary greatly. The result is that those consulting online health information or engaging with interactive content regarding dementia may experience both benefits and harm. Critical evaluation of online dementia resources is vital to the promotion of individual and community well-being.

Online health information

A recent scoping review outlined the reported information needs of people living with dementia and their informal carers. Electronic sources, internet, mass media, and smartphones, were the preferred method of gathering information on the disease, patient care provision, healthcare services, and carer self-care (2). Information about stages of dementia, treatment options, prevention strategies, and caregiving considerations, among other topics, is available from websites of wide-ranging types of organisations such as advocacy, government, academic, and industry. These resources are typically freely accessible, easy to consume and share, and can help address the information needs of people at different stages of the dementia journey.

However, there are potential harms associated with online dementia information-seeking via websites. Accessibility can be challenging due to readability and demographics factors, such as disability and socioeconomic status (1,3). Website quality ranges from high to low, with substantive differences in content (4). Discerning credible, high-quality content can be difficult for non-experts, and this ambiguity is exploited by predatory or fraudulent sources (5). Conflicts of interest are not always immediately apparent or disclosed (4). Ease of information-sharing via websites and social media can perpetuate misinformation, which can undermine the relationship between people living with dementia and their healthcare providers. These issues stemming from an unregulated online environment are particularly troubling for vulnerable individuals, as some sites promote non-evidence-based treatments that may lead to financial loss or negative health outcomes (5,6).

Interactive content

Dementia information resources on the internet also exist in forms of dynamic multimedia, interactive assessment tools, and online communities. Benefits of interactive online spaces include up-to-date information presented in lay language, current or real-time opportunities to engage with services and research, and the ability to develop a network of peers to exchange information and advice. These benefits must be weighed against potential risks, which vary based on the affordances and context of the specific resource type.

Free online tests claiming to allow for the self-diagnosis of mild cognitive impairment, Alzheimer's disease, and unspecified dementias can be readily accessed (7). These tools may lead to feelings of empowerment or increased motivation to seek medical advice (7). However, expert analysis revealed that many of these online tests do not adhere to ethical standards regarding such matters as privacy, confidentiality or conflicts of interest and can provide clinically inaccurate results (7).

Social media is a popular platform for information exchange, where dementia experts and non-experts alike can interact in online networks (8). Online content creation platforms provide other methods of information presentation and incorporate social network elements for community-building. However, the lack of built-in verification methods for individual and organisational claims of expertise or legitimacy in the dementia field may contribute to the spread of misinformation or predatory content.

This is particularly true when individualised content curation creates information 'bubbles' that limit exposure to valid content sources.

Moving forward

To promote the benefits of the online environment while minimising harms to older adults, resources and tools for dementia should be developed following established ethical guidelines (9). Some researchers have proposed ethical strategies to adopt Internet and tech-based innovations in dementia and health research (9,10). One example in social media is Bender et al.'s principle-based framework to provide guidance on ethical issues that arise in health research recruitment (10). Although frameworks like this provide substantive clarity for online concerns like privacy, there remains a dearth of practical guidance for users in the social media space.

A principled approach to online dementia information may encourage the creation of higher quality resources, but that alone will not prevent the spread of misinformation or fraudulent claims. It is imperative that older Internet users become fully aware of its potential benefits and risks, and that they become able to make sound decisions about their information consumption, both from static resources such as health information sites, and from interactive resources such as social media. Health agencies and advocacy groups must take on the challenge of developing and promoting educational strategies to equip people living with dementia and their carers with the knowledge they require to safely navigate and use online resources about dementia.

Establishing beneficial standards for the development and implementation of online resources and for eHealth literacy programmes requires the engagement of members of the dementia community; particularly those with lived experience of dementia and their carers. Applying participatory design methods encourages action, critical reflection, and the empowerment of community members to collaboratively voice their needs and generate solutions (9). Patient-oriented research engages people with dementia as partners throughout the research process to identify priorities and strategies to improve health outcomes. Other methods for eliciting community knowledge and perspectives include public consultations, workshops for the co-creation of knowledge, qualitative and quantitative consensus-building, and creative visualisation such as digital storytelling and participatory video. Engagement of the broad dementia community will encourage the design of online resources that work best for members while acknowledging the rights and responsibilities of the individuals affected by this complex technology.

Only by taking a participatory approach to the development and evaluation of online resources, will we be able to create an online environment that ethically addresses the needs of the rapidly growing number of older people seeking knowledge and support resources regarding dementia.

Figure 1. Mind map of the factors affecting the reliability of online dementia information. The medium-sized boxes represent the major ethical factors. The smaller boxes are the aspects of each factor that can be used to assess the relevant risks and benefits.

References

1. Hargittai E, Piper AM, Morris MR. From internet access to internet skills: digital inequality among older adults. Univers Access Inf Soc 2018 184. 2018 May;18(4):881–90.
2. Soong A, Au ST, Kyaw BM, Theng YL, Tudor Car L. Information needs and information seeking behaviour of people with dementia and their non-professional caregivers: A scoping review. BMC Geriatr. 2020 Feb;20(1).
3. Robillard JM, Sporn AB. Static versus interactive online resources about dementia: A comparison of readability scores. Gerontechnology. 2018 Mar;17(1):29–37.
4. Robillard JM, Feng TL. Health advice in a digital world: Quality and content of online information about the prevention of Alzheimer's disease. J Alzheimer's Dis. 2016;55(1):219–29.
5. Robillard JM. The Online Environment: A Key Variable in the Ethical Response to Complementary and Alternative Medicine for Alzheimer's Disease. J Alzheimer's Dis. 2016 Feb;51(1):11–3.
6. Robillard JM, Feng TL. When Patient Engagement and Research Ethics Collide: Lessons from a Dementia Forum. J Alzheimer's Dis. 2017;59(1):1–10.
7. Robillard JM, Illes J, Arcand M, Beattie BL, Hayden S, Lawrence P, et al. Scientific and ethical features of English-language online tests for Alzheimer's disease. Alzheimer's Dement Diagnosis, Assess Dis Monit. 2015 Sep;1(3):281–8.
8. Robillard JM, Johnson TW, Hennessey C, Beattie BL, Illes J. Aging 2.0: Health Information about Dementia on Twitter. PLoS One. 2013 Jul;8(7).
9. Robillard JM, Cleland I, Hoey J, Nugent C. Ethical adoption: A new imperative in the development of technology for dementia. Alzheimer's Dement. 2018 Sep;14(9):1104–13.
10. Bender JL, Cyr AB, Arbuckle L, Ferris LE. Ethics and Privacy Implications of Using the Internet and Social Media to Recruit Participants for Health Research: A Privacy-by-Design Framework for Online Recruitment. J Med Internet Res. 2017 Apr;19(4).

Conclusions

The Internet has become a wide-ranging source of information for people who have access to it. When first faced with concerns regarding their cognitive decline, most individuals, or their family and friends, will naturally search the Internet for information as it offers a wide range of material about the condition.

While there are many credible sites, especially those affiliated with universities or national dementia organisations, caution must be exercised as other websites may spread misinformation, fail to respect privacy policies, or have fraudulent intentions.

However, this online exploration does not, nor should it, replace an in-person assessment by a healthcare professional. The family physician is overwhelmingly the first point of contact for someone, or their family and friends, questioning changes to their cognitive condition, though consultation may also involve nurses and specialists.

Chapter 3
Medical history and physical examination

Serge Gauthier

Key points

- The healthcare professional performing the diagnostic assessment needs information about the earliest symptoms and their progression over time.
- A complete physical examination is conducted with emphasis on signs of cardiovascular health and a neurologic examination including balance and gait.

General background

When assessing dementia, a progressive decline in memory regarding recent events is the most common clinical presentation. However, there may also be other early signs present such as searching for one's words (dysphasia), misjudging distances or directions (spatial disorientation), failure to recognise familiar faces (prosopagnosia), difficulty managing finances and uncertainty making decisions (executive impairment). A crucial step in the diagnostic process is providing the healthcare professional with as much information as possible, whether it be from the person experiencing cognitive changes or their family and friends. This includes when the initial symptoms became apparent. Keeping a written record of these as well as their frequency and duration is a useful tool to share during the medical visit.

The potential impact of cognitive decline on activities of daily living is an essential part of the history taking needed for a dementia diagnosis. For instance, memory decline may lead to missed appointments, forgetting a grandchild's birthday or leaving a water tap running. The healthcare professional may use a semi-structured interview approach or a task checklist encompassing leisure activities (such as playing cards), instrumental tasks such as meal preparation, using the telephone, housework, managing finances and correspondence, going on an outing, keeping to a medication schedule, and basic activities such as dressing, personal hygiene, continence and eating. All of these are markers about whether a person can safely remain at home. This information must be substantiated by family and friends as human nature often dictates that we downplay our own difficulties. At times, an activities of daily living checklist is completed while in the healthcare professional's waiting room, at home or online prior to the visit (1,2).

BOX 1: Important issues to address with a doctor during consultation

1. Bring a partner, friend or family member for support and to provide needed information.
2. Recount all instances of memory, thinking and behavioural changes that has been noted in the last few years.
3. Inform the doctor when these changes started.
4. Describe how these changes progress – slowly, quickly and stepwise decline.
5. Inform the doctor about any medical circumstances surrounding these changes including health conditions, current or new medications and family history.

Anxiety, social withdrawal, irritability and depressive feelings are some of the psychological symptoms associated with cognitive decline. These may be attributed to the changes in the brain as the dementia progresses, emotional reactions that speak to the uneasiness and confusion about what is happening, or a combination of both. Thus, questions about such symptoms during the history taking are to be expected. As a fuller picture of daily life will best serve the needs of a person with dementia, expect that the accompanying family member or friend also be questioned. This is not meant to offend, simply to obtain as much information as possible. Occasionally, a checklist is completed ahead of the visit (2).

When seeing someone for the first time, the healthcare professional will typically review past medical history and medications. It would be beneficial to be prepared beforehand with a list of past and current health diagnoses as well as a complete list of medications, either prescribed or over-the-counter and supplements.

The physical examination is much like the one when first meeting a new doctor, with emphasis placed on measuring vital signs such as heart rate, blood pressure, listening to the heart and major blood vessels such as the carotid arteries in the neck. The neurological examination is built into the physical head-to-toe examination, such as evaluating eye movement speed or the ability to walk steadily with or without distractions to evaluate balance and gait.

Background for clinicians

History, history, history. This is still the number one step required in diagnosing dementia. If time is limited during the first visit, the assessment can be divided into sequential steps. A common problem healthcare professionals encounter is the unavailability or unreliability of the person's history, which requires a follow-up with a well-informed person who may not have been present at the first visit. For people living alone, a visit to their residence by a member of the healthcare team may be necessary. The history should describe the cognitive status, the onset and trajectory of the present cognitive symptoms, as well their impact on the person's autonomy and independence (Figure 1) (3).

In general, the physical examination in a new case of possible dementia should be comprehensive and in-person, looking for prevalent comorbid conditions such as cardiovascular diseases, carotid stenosis, organomegalies, hypothyroidism (perhaps evidenced by an enlarged thyroid gland), B12 or folate deficiency (possibly suggested by a red depapillated tongue). The neurological examination should look for any asymmetry in motor tone, strength, reflexes; this possibly due to a silent stroke. The reappearance of the involuntary unilateral grasp reflex may indicate a contralateral frontal, structural, vascular or tumoral lesion. Gait assessment is also vital for the diagnosis. One leg dragging may suggest stroke while short hesitant steps may be due to a parkinsonian syndrome.

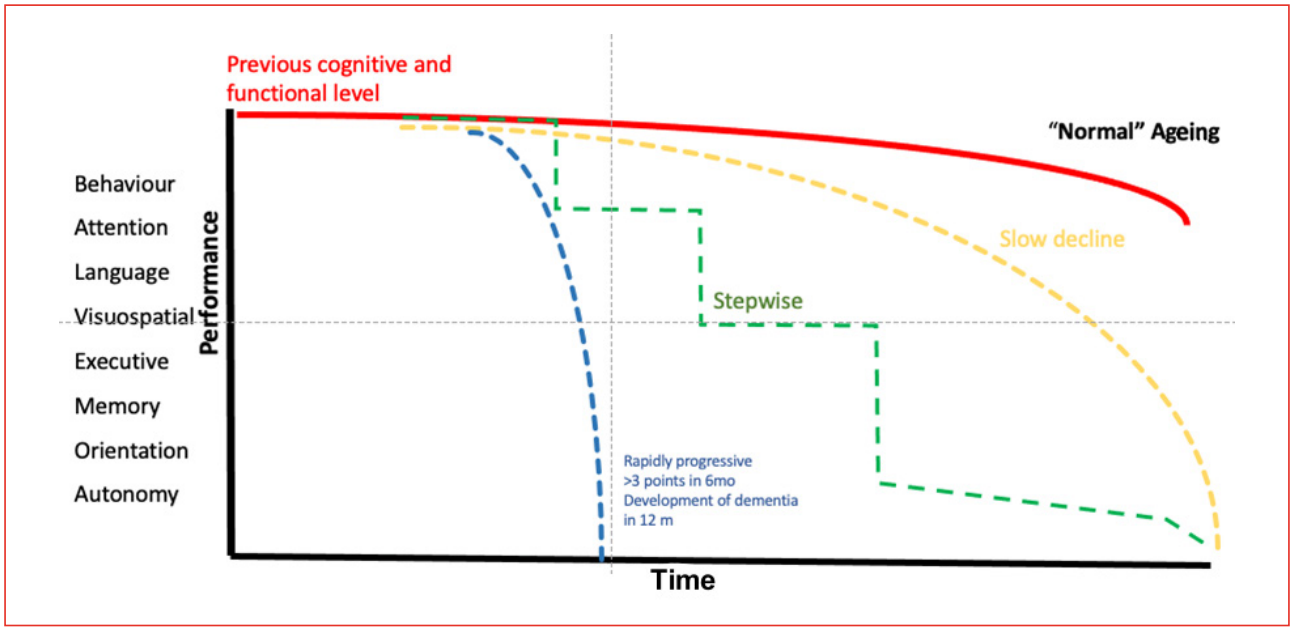


Figure 1. The clinical history should identity the cognitive domains affected and their trajectory since onset. The initial diagnosis will be derived from the analysis of this data.

Survey results

The survey participants unanimously indicated that clinical history, cognitive testing, and physical examination were part of the routine clinical examination.

The 1,111 multidisciplinary clinicians who responded to this survey indicated that 76% complete a basic medical history, physical examination and cognitive screening while 63% complete a full consultation. Only 16% refer the individual to a colleague after the basic assessment or immediately after discovering that there is a cognitive, functional, or behavioural issue suggestive of dementia.

Assessment goals

1. Identify cognition deficits involving more than one cognitive domain (learning and memory, language, executive function, complex attention, perceptual-motor, social cognition) or behaviour. If necessary, plan a visit with a neuropsychologist or with a psychiatrist.
2. Ascertain that the cognitive deficits represent a decline from the previous level of function.
3. Document the impact of the cognitive deficits in the person's autonomy and independence.
4. Identify neurological signs associate with disease.
5. Ascertain the absence non-degenerative causes of cognitive decline.
6. Whenever possible, identify the presence of disease pathophysiology with biomarkers.

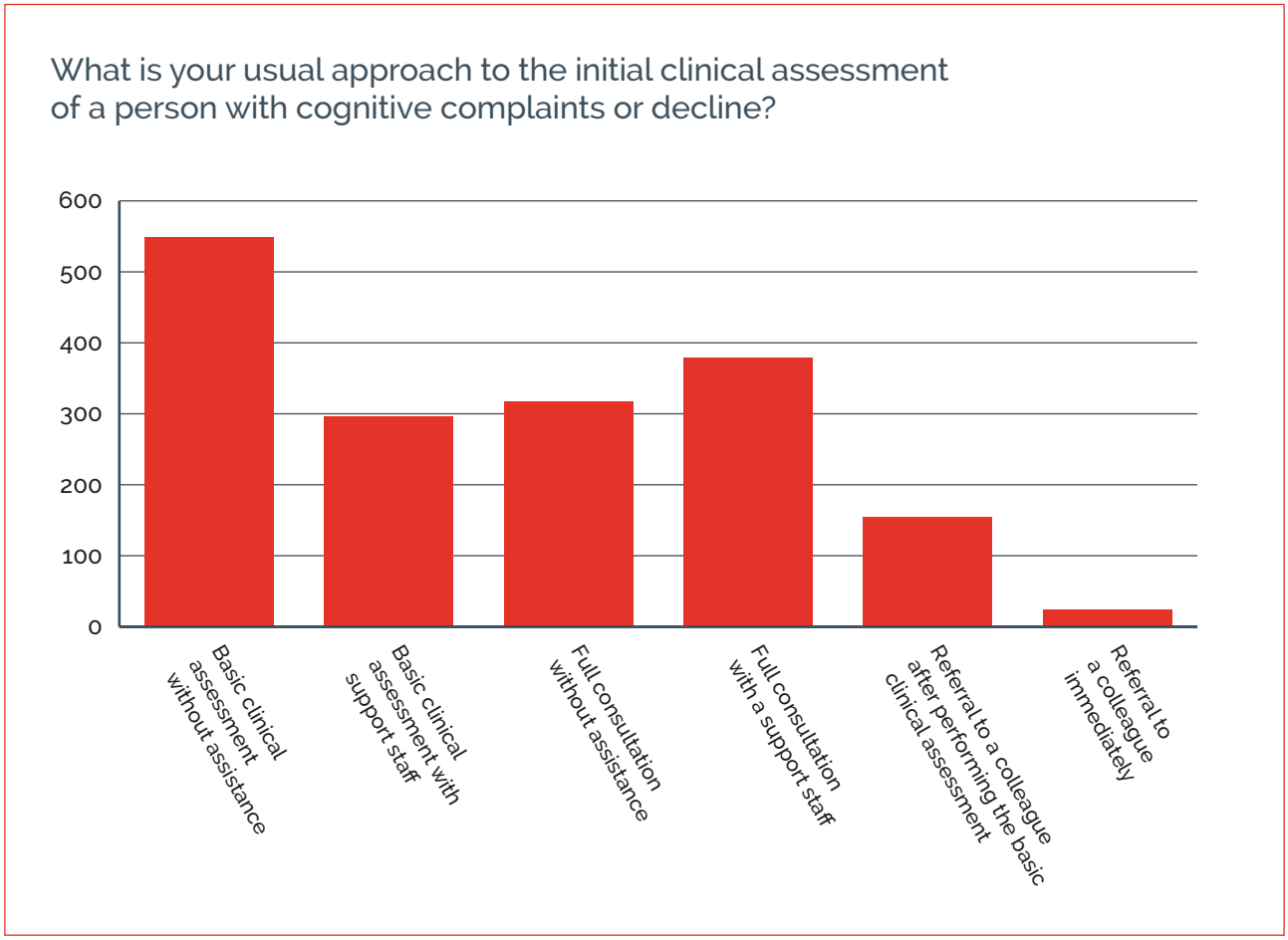


Chart 1. Clinician responses (multiple answers selected).

Conclusions

Cognitive decline has the potential to greatly impact a person's activities of daily living. That is why gathering as much information as possible is crucial to the diagnostic process. The healthcare professional may use a two-pronged approach combining interviews and task checklists to obtain a complete medical history, along with a comprehensive physical examination to assess which major neurocognitive domains are affected.

A complete diagnostic picture also includes details about when symptoms began or became noticeable, their frequency and duration. This may be provided by the person concerned or a partner, friend of family member who has witnessed the behaviour. All these are key elements to the diagnosis of dementia and its underlying causes.

Upcoming chapters will delve further into assessments of cognition, neuropsychiatric symptoms, and functional assessments (4).

Additional references

1. Galasko D. The diagnostic evaluation of a patient with dementia. Contin Lifelong Learn Neurol [Internet]. 2013 Apr [cited 2021 Jul 19];19(2):397–410. https://pubmed.ncbi.nlm.nih.gov/23558485/.
2. Apostolova LG. Alzheimer disease. Contin Lifelong Learn Neurol [Internet]. 2016 Apr 1 [cited 2021 Jul 19];22(2, Dementia):419–34. https://journals.lww.com/continuum/Fulltext/2016/04000/Alzheimer_Disease.8.aspx.
3. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. JAMA – J Am Med Assoc [Internet]. 2019 Oct 22 [cited 2021 Jul 9];322(16):1589–99. https://pubmed.ncbi.nlm.nih.gov/31638686/.
4. Sorbi S, Hort J, Erkinjuntti T, Fladby T, Gainotti G, Gurvit H, et al. EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia. Eur J Neurol [Internet]. 2012 Sep 1 [cited 2021 Jul 19];19(9):1159–79. https://onlinelibrary.wiley.com/doi/full/10.1111/j.1468-1331.2012.03784.x.

Chapter 4
Functional assessment

Serge Gauthier

Key points

- The functional assessment plays a key role in the diagnosis of dementia.
- Cognitive decline may have a direct impact on activities of daily living.
- Questions about changes in daily life are usually more reliably answered by a family member, close friend or co-worker.
- If information about daily activities is not available or cannot be reliably addressed, a visit to the person's home may be required.

General background

A thorough functional assessment plays an important role in the diagnosis of dementia as it not only determines a person's ability to manage their everyday needs but can also highlight whether there are concerns regarding their safety. Cognitive decline may have an impact on activities of daily living. This may range from leisure activities (playing card games), instrumental tasks (taking medication or paying bills on time) and basic activities (cooking, dressing, and grooming). People with cognitive complaints will be asked about changes in their daily life which may be directly related to the cognitive decline but can also be associated to other medical conditions altering muscle strength, vision, mobility, and more. Additional factors that may further complicate functional abilities are changes in behaviour, as well as the availability of adequate social and physical support in the person's environment, especially for individuals who live alone. Questions about changes in daily life are usually more reliably answered by a family member or a close friend, a neighbour and sometimes even by a work colleague. The assessment should be based be on activities or tasks that the person used to do well that may have recently changed or declined.

> **People experiencing cognitive decline tend to minimise their impairments.**

A decline in activities of daily living is a key component to the definition of dementia and requires clinical judgment to assess its significance; changes may be subtle and occur only in leisure activities. Some activities may have never been done before due to cultural or gender constraints, or there was no opportunity to perform them. One of the reasons family members or friends, referred to clinically as 'informants' when on a questionnaire, need to be asked about activities of daily living is that people experiencing cognitive decline tend to minimise their impairments. As some carers, particularly spouses, may also be in denial, it is recommended to seek as much input as possible from additional family members and/or friends, whenever possible.

Personal safety becomes of significant concern with an individual with cognitive decline due to their inability to perform certain tasks. Various rooms within the home, outdoor spaces or the workplace can increase the risk of falls and injuries. Kitchen appliances such as stoves, ovens, microwave ovens and toasters as well as barbeques have a high fire risk if used inappropriately. Bathrooms, bedrooms, and homes with many stairs can increase the risk of falls if anti-slip mats, handlebars, properly secured carpets and night lights are not installed. The inability to administer one's own medication, mistaking cleaning products for food or grooming supplies, as well as losing the ability to properly use utensils such as knives, scissors and razors can cause serious injury.

Another important concern regarding the impact of cognitive decline revolves around the complex topic of driving. Despite the person with dementia's capacity to recall their route, driving requires a tremendous number of quick reflexes and reactions and good peripheral vision, which decline as the condition progresses. Such things as differentiating the brake and gas pedals, recognising road signs, adhering to crossings, changing traffic colour lights, and the sudden appearance of cyclists and pedestrians require significant cognitive and visual awareness.

Financial vulnerability is another consequence of cognitive decline. A person may lose the ability to pay their bills on time, make random purchases, misuse credit and debit cards, as well as become victims of financial fraud via phone and email scams. Protecting the financial assets of a person with cognitive decline becomes of paramount importance that could involves multiple steps including obtaining a power of attorney or protection mandate.

Assessing a person's ability to drive and manage personal finances are two of the most delicate topics a healthcare professional will need to address as these are directly linked to maintaining an individual's independence. Any recommendation made that specifies that an individual can no longer perform one of these tasks needs to be delivered with compassion.

The functional assessment process involves completing a semi-structured questionnaire or a structured scale before or during the medical appointment. If information about initiation, planning and effective performance of daily activities is not available or cannot be reliably assessed, a visit to the person's home may be required by an occupational therapist, social worker or other qualified healthcare professional.

Examples of activities of daily living scales are listed in Table 1 below and some are critically reviewed in the expert essay by Dr. Isabelle Gélinas.

Table 1. Examples of activities of daily living scales

Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL)	Galasko D, Bennett D, Sano M, Ernesto C, Thomas R, Grundman M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord. 1997; 11 (Suppl 2): S33–9.
Amsterdam IADL Questionnaire	Sikkes SAM, de Lange-de Klerk E, Pijnenburg YAL, Gilissen F, Romkes R, Knol DL, Uitdehaag BMJ, Scheltens P: A new informant-based questionnaire for instrumental activities of daily living in dementia. Alzheimer's Dement 2012; 8: 536–543.
Bristol Activities of Daily Living Scale	Bucks, R. S., Ashworth, D. L., Wilcock, G. K., & Siegfried, K. (1996). Assessment of activities of daily living in dementia: Development of the Bristol Activities of Daily Living Scale. Age and Ageing, 25, 113–120.
Disability Assessment in Dementia (DAD)	Gelinas I, Gauthier L, McIntyre M, Gauthier S: Development of a functional measure for persons with Alzheimer's disease: the disability assessment for dementia. Am J Occup Ther 1999; 53:471–481.
Functional Activities Questionnaire (FAQ)	Pfeffer RI, Kurosaki TT, Harrah CH Jr, et al. Measurement of functional activities in older adults in the community. J Gerontol. 1982; 37:323–329.
Functional Assessment Staging (FAST)	Reisberg, B (1988) Functional assessment staging (FAST). Psychopharmacol Bull, 24, 653–659.
Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)	Jorm AF. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): Development and cross-validation. Psychol Med 1994; 24(1):145–153.
Interview for deterioration in Daily living activities in Dementia (IDDD)	Teunisse, S., Derix, M. M., & van Crevel, H. (1991). Assessing the severity of dementia. Patient and caregiver. Archives of Neurology, 48,274–277.
Nurses' Observational Scale for Geriatric Patients (NOSGER)	Spiegel R, Brunner C, Ermini-Fünfschilling D, Monsch A, Notter M, Puxty J, Tremmel L.J. (1991) A new behavioural assessment scale for geriatric out- and in-patients: the NOSGER (Nurses' Observation Scale for Geriatric Patients). Am Geriatr Soc. 39(4):339–47.
Progressive Deterioration Scale (PDS)	DeJong R, Osterlund OW, Roy GW. Measurement of quality-of-life changes in patients with Alzheimer's disease. Clin Ther. 1989; 11:545–54
Physical Self-Maintenance and Instrumental Activities of Daily Living (PSMS & IADL)	Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9(3 pt 1):179–186.

There is no perfect scale, but as previously indicated, having a structured approach based on clinical needs when asking about daily tasks is most beneficial. The short form (16 items) of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) may be particularly useful to clinicians as it compares a person's current cognitive and functional abilities and those abilities from ten years ago. It can also be completed prior to the medical assessment (1). The IQCODE short form appears below in Table 2. It is available online in its original version as well as in multiple languages.

Table 2. Informant questionnaire on cognitive decline in the elderly (iqcode) short form

Now we want you to remember what your friend or relative was like 10 years ago and to compare it with what he/she is like now. 10 years ago was in 20__. Below are situations where this person has to use his/her memory or intelligence and we want you to indicate whether this has improved, stayed the same or got worse in that situation over the past 10 years. Note the importance of comparing his/her present performance with 10 years ago. So if 10 years ago, this person always forgot where he/she had left things, and he/she still does, then this would be considered 'Hasn't changed much'. Please indicate the changes you have observed by circling the appropriate answer. Compared with 10 years ago, how is this person at: 1 2 3 4 5
1. *Remembering things about family and friends e.g. occupations, birthdays, addresses* Much improved – A bit improved – Not much change – A bit worse – Much worse
2. *Remembering things that have happened recently* Much improved – A bit improved – Not much change – A bit worse – Much worse
3. *Recalling conversations a few days later* Much improved – A bit improved – Not much change – A bit worse – Much worse
4. *Remembering his/her address and telephone number* Much improved – A bit improved – Not much change – A bit worse – Much worse
5. *Remembering what day and month it is* Much improved – A bit improved – Not much change – A bit worse – Much worse
6. *Remembering where things are usually kept* Much improved – A bit improved – Not much change – A bit worse – Much worse
7. *Remembering where to find things which have been put in a different place from usual* Much improved – A bit improved – Not much change – A bit worse – Much worse
8. *Knowing how to work familiar machines around the house* Much improved – A bit improved – Not much change – A bit worse – Much worse
9. *Learning to use a new gadget or machine around the house* Much improved – A bit improved – Not much change – A bit worse – Much worse
10. *Learning new things in general* Much improved – A bit improved – Not much change – A bit worse – Much worse
11. *Following a story in a book or on TV* Much improved – A bit improved – Not much change – A bit worse – Much worse
12. *Making decisions on everyday matters* Much improved – A bit improved – Not much change – A bit worse – Much worse
13. *Handling money for shopping* Much improved – A bit improved – Not much change – A bit worse – Much worse
14. *Handling financial matters e.g. the pension, dealing with the bank* Much improved – A bit improved – Not much change – A bit worse – Much worse
15. *Handling other everyday arithmetic problems e.g. knowing how much food to buy, knowing how long between visits from family or friends* Much improved – A bit improved – Not much change – A bit worse – Much worse
16. *Using his/her intelligence to understand what's going on and to reason things through* Much improved – A bit improved – Not much change – A bit worse – Much worse

Expert essay

Assessing functional performance in activities of daily living in individuals with Alzheimer's disease

Isabelle Gélinas

School of Physical & Occupational Therapy, McGill University, CANADA

Decline in the ability to perform daily activities is a predominant characteristic of Alzheimer's disease, which significantly impacts the quality of life of the affected individuals and their family members (1). It is a diagnostic criterion for Alzheimer's disease. The rate of decline in the performance of activities of daily living is also used to monitor disease progression and is a strong predictor of institutionalisation (2). Evidence suggests that decline in complex activities of daily living may be a predictor of conversion to dementia (3). The assessment of functional performance in activities of daily living is therefore a vital component of the diagnostic process as well as the care planning for individuals with Alzheimer's disease regarding decisions about intervention and the suitable level of care required. Functional measures of performance in daily activities usually include basic self-care or self-maintenance activities such as dressing, bathing and eating, and instrumental activities of daily living such as managing finances, cooking or household chores. These activities are key for determining a person's ability to live independently and to identify the level of assistance or care required. More advanced activities such as work and leisure are sometimes included.

As cognitive function deterioration appears to account for only some of the functional activity changes in Alzheimer's disease, clinicians should not solely rely on cognitive test results to predict functional performance. (4). Measures of functional ability in activities of daily living allow for the identification of tangible real-life difficulties experienced daily by people with Alzheimer's disease. These provide more meaningful answers for them and their family members. It is recommended to opt for functional measures that have been specifically developed or tested on people with Alzheimer's disease as they incorporate criteria that evaluates activities affected by the disease process and demonstrate progressive decline in functional performance if it occurs.

In a clinic setting, functional performance is evaluated using various methods, each drawing on different sources of information. These include self- or informant- reported measures as well as performance-based ones through direct observation. Each approach can offer valuable insight. This essay will focus on informant-based questionnaires which are quickly and easily administered, allow for the assessment of a wider range of activities and a comparison with previous levels of functioning. Self-reported measures can be more problematic to use as awareness of their own abilities may be impaired due to disease progression. Performance-based instruments, though they provide a more objective viewpoint of functional decline, are limited by the number of listed activities frequently engaged in and are more time-consuming to implement. A selection of informant-based questionnaires are currently available for use, and none have been singled out as the best option from the reviews that have been conducted to date (5–7). Choosing a measure that is suitable for clinical practice becomes complex. Several criteria should be considered when deciding on an applicable activities of daily living assessment for use.

An important criterion to consider is the population for whom the measure is intended, accounting for the severity of the disease (mild, moderate or severe) and the living environment (community or institution). We know there is a continuum of functional decline over the course of the disease. Decline occurred earlier in the more complex instrumental activities of daily living as they require greater cognitive organisation, while progressive changes in the more overlearned basic self-care activities were observed in later stages. Therefore, for the assessment of individuals with mild Alzheimer's disease, functional measures should include more complex parameters of instrumental activities of daily living. Notably, research findings support the inclusion of topics on financial management, telephone use, medication intake, transportation usage and consumption of everyday technology in the evaluation of individuals in the early stages of the disease (6). The Amsterdam IADL Questionnaire© (8) is an example of a measure which incorporates these types of activities. On the other hand, for residents of long-term care facilities, instruments including basic activities for daily living would be more appropriate, such as the Bristol Activities of Daily Living Scale, which has been used with nursing home residents with advanced dementia (9). However, to follow individuals with Alzheimer's disease and track changes over time, an instrument that includes a range of activities from complex to more basic would be preferable.

The proposed use and the quality of the instrument in terms of psychometric properties should also be considered. An important property to consider is the questionnaire's validity. Does it truly measure the functional status of activities of daily living? Are the important dimensions or components needed to identify problematic activities of daily living abilities in Alzheimer's disease included? For instance, if the questionnaire is to be used as a diagnostic tool, it will need to include activities that can also identify functional limitations in individuals affected by the disease. Again, instruments should include complex to basic activities affected by the disease over time. If the intent is also to determine a level of care or to guide intervention, it may be useful to select a questionnaire that provides parameters for the type of assistance, a description of how the activities are performed or areas of deficits which may impair functional performance. For example, the Disability Assessment for Dementia (DAD) (10) includes a range of basic and instrumental activities of daily living that are known to progressively decline over the course of the disease. These are examined in relation to executive functions, which are found to be a strong predictor of independent functioning in Alzheimer's disease (11). The reliability of the measure or the extent to which it is exempted from measurement error should also be considered. Should the questionnaire be administered by more than one person, steps must be taken to ensure that the results would be the same and not be influenced by the rater (inter-rater reliable). Measure reliability is also essential when used to monitor progress over time and is administered on more than one occasion (test-retest reliability). Sensitivity to meaningful or clinically important change (responsiveness) is another important property if the questionnaire is used to measure the impact of an intervention over time.

Other factors to consider when using a functional questionnaire include practicality and cultural relevance. Practicality entails the time required to administer the questionnaire and the related burden on both the clinician and informant when it consists of many questions that are complex to score. Costs and the need for intensive training may also influence the choice of questionnaire. Cultural relevance is particularly significant when an instrument was developed in another country and was subsequently translated. Information on how the instrument was adapted to account for culture-specific topics is needed, as well as assurances that the translated version underwent a cross-cultural validation. For example, in the Disability Assessment for Dementia (10), which was translated in more

than 55 languages, certain items such as choosing appropriate utensils for feeding needed to be adapted for countries where eating is performed without the use of cutlery.

Assessments of functional performance in activities of daily living provide important information to determine a person's ability to live independently in the community.

Several questionnaires are available for people living with Alzheimer's disease. To select the best measure to use in their practice, clinicians should consider the instrument's intended purpose, psychometric properties, practicality and cultural validity.

References

1. Andersen CK, Wittrup-Jensen KU, Lolk A, Andersen K, Kragh-Sørensen P. Ability to perform activities of daily living is the main factor affecting quality of life in patients with dementia. Health Qual Life Outcomes [Internet]. 2004 Sep 21 [cited 2021 Jul 8];2. https://pubmed.ncbi.nlm.nih.gov/15383148/
2. Gaugler JE, Duval S, Anderson KA, Kane RL. Predicting nursing home admission in the U.S: A meta-analysis. BMC Geriatr [Internet]. 2007 [cited 2021 Jul 8];7. https://pubmed.ncbi.nlm.nih.gov/17578574/
3. Luck T, Riedel-Heller SG, Luppa M, Wiese B, Bachmann C, Jessen F, et al. A hierarchy of predictors for dementia-free survival in old-age: Results of the AgeCoDe study. Acta Psychiatr Scand [Internet]. 2014 Jan [cited 2021 Jul 8];129(1):63–72. https://pubmed.ncbi.nlm.nih.gov/23521526/
4. Mlinac ME, Feng MC. Assessment of Activities of Daily Living, Self-Care, and Independence. Arch Clin Neuropsychol. 2016 Sep 1;31(6):506–16.
5. Kaur N, Belchior P, Gelinas I, Bier N. Critical appraisal of questionnaires to assess functional impairment in individuals with mild cognitive impairment. Int Psychogeriatrics [Internet]. 2016 Sep 1 [cited 2021 Jul 8];28(9):1425–39. https://pubmed.ncbi.nlm.nih.gov/27072886/
6. Jekel K, Damian M, Wattmo C, Hausner L, Bullock R, Connelly PJ, et al. Mild cognitive impairment and deficits in instrumental activities of daily living: A systematic review. Alzheimer's Res Ther. 2015;7(1).
7. Sikkes SAM, De Lange-De Klerk ESM, Pijnenburg YAL, Scheltens P, Uitdehaag BMJ. A systematic review of Instrumental Activities of Daily Living scales in dementia: Room for improvement. J Neurol Neurosurg Psychiatry [Internet]. 2009 Jan [cited 2021 Jul 8];80(1):7–12. https://pubmed.ncbi.nlm.nih.gov/19091706/
8. Sikkes SAM, De Lange-De Klerk ESM, Pijnenburg YAL, Gillissen F, Romkes R, Knol DL, et al. A new informant-based questionnaire for instrumental activities of daily living in dementia. Alzheimer's Dement [Internet]. 2012 Nov [cited 2021 Jul 8];8(6):536–43. https://pubmed.ncbi.nlm.nih.gov/23102123/
9. Boyd PA, Wilks SE, Geiger JR. Activities of Daily Living Assessment among Nursing Home Residents with Advanced Dementia: Psychometric Reevaluation of the Bristol Activities of Daily Living Scale. Heal Soc Work [Internet]. 2018 May 1 [cited 2021 Jul 8];43(2):101–8. https://pubmed.ncbi.nlm.nih.gov/29554326/
10. Gélinas I, Gauthier L, McIntyre M, Gauthier S. Development of a functional measure for persons with Alzheimer's disease: The disability assessment for dementia. Am J Occup Ther [Internet]. 1999 [cited 2021 Jul 8];53(5):471–81. https://pubmed.ncbi.nlm.nih.gov/10500855/
11. Marshall GA, Rentz DM, Frey MT, Locascio JJ, Johnson KA, Sperling RA. Executive function and instrumental activities of daily living in mild cognitive impairment and Alzheimer's disease. Alzheimer's Dement. 2011 May 1;7(3):300–8.
12. Jorm AF. A Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (Iqcode): Development and Cross-Validation. Psychol Med [Internet]. 1994 [cited 2021 Jul 8];24(1):145–53. https://pubmed.ncbi.nlm.nih.gov/8208879/

Conclusions

A comprehensive functional assessment has a dual purpose: to determine a person's ability to manage their everyday needs and validate concerns about their safety and independence. Major areas of concern are the risks associated with falls or injuries, driving and financial vulnerability.

Cognitive decline can certainly impact a person's activities of daily living and people with these complaints will be asked about the symptoms they are experiencing. However, clinicians are also encouraged to use a semi-structured questionnaire as a diagnostic tool to discuss with a person's partner, family member or friend. In this way, clinicians will gain reliable insight into the changes observed over time and compare previous and current abilities. These daily living activities can range from basic, leisure or instrumental tasks. Should another person be unavailable, a visit to the person's home may be warranted to obtain additional information. An important motivating factor is to assess whether a person can safely continue to live independently at home.

There are several informant-based questionnaires available and criteria for use should include the population being measured, the severity of the disease and the living environment. As well, one must consider which daily activity topics from basic to complex are included, psychometric properties of validity and reliability of the measurement tool, areas of deficit that may impair functional performance, practicality and cultural relevance.

Choosing to use a semi-structured cognitive assessment tool to evaluate a person's activities of daily living and demonstrate progressive decline provides meaningful and necessary information to a person living with dementia and their family members.

Chapter 5
Mood and behavioural assessment

Serge Gauthier

Key points

- Psychological symptoms associated with cognitive decline can be part of the disease process but may be reactions to what is happening.
- Depression is a common symptom in early dementia.
- Behaviours such as agitation, paranoia, aggressivity, sleep disturbances usually occur well after the diagnosis of dementia is made but can be present in earlier stages.
- The term anosognosia refers to limited awareness of cognitive and functional deficits, but also to impaired awareness of emotional changes.

General background

Given the ongoing and prospective adjustments that cognitive decline may have on a person's day-to-day life, it is hardly surprising that an increase in psychological symptoms may also be witnessed. These may consist of depressive feelings, paranoia, anxiety, apathy and irritability. Whether it be characteristic of the condition's progression or a reversible reaction to the changes taking place, the person seeking a diagnostic assessment should anticipate questions about their psychological state during the history taking. As this is meant to gain a better understanding, provide an accurate diagnosis and orient treatment, one should not be upset or surprised if the family member or friend accompanying them is also asked to provide their observations about such symptoms. Both of you may want to express your opinions in private to allow for open and direct communication.

Background for clinicians

Non-specific mood and behavioural changes may precede dementia or even overt cognitive decline; this is the theory behind the new diagnostic criterion of Mild Behavioural Impairment (MBI), measured by the MBI-Checklist (Table 1). Depression is the most common first symptom encountered in early dementia. However, it is necessary to be able to differentiate apathy due to dementia, often presented as a disinterest in the activities of daily living, versus the symptoms of depression. Global informant-rated scales such as the NPI-Q (2) or MBI-C (3) can identify such symptoms.

> **The person seeking a diagnostic assessment should anticipate questions about their psychological state.**

Table 1. Mild Behavioural Impairment Checklist as an example of a structured questionnaire about mood and behavioural changes in early dementia

Mild Behavioural Impairment Checklist (MBI-C)

Date:

Rated by: ☐ Clinician ☐ Informant ☐ Subject

Location: ☐ Clinic ☐ Research

Circle 'Yes' **only** if the behaviour has been present for at least **6 months** (continuously, or on and off) and is a **change** from her/his longstanding pattern of behaviour. Otherwise, circle 'No'.

Please rate severity: **1** = **Mild** (noticeable, but not a significant change); **2** = **Moderate** (significant, but not a dramatic change); **3** = **Severe** (very marked or prominent, a dramatic change). If more than 1 item in a question, rate the most severe.

	YES	NO	SEVERITY
This domain describes interest, motivation, and drive			
Has the person lost interest in friends, family, or home activities?	Yes	No	1 2 3
Does the person lack curiosity in topics that would usually have attracted her/his interest?	Yes	No	1 2 3
Has the person become less spontaneous and active – for example, is she/he less likely to initiate or maintain conversation?	Yes	No	1 2 3
Has the person lost motivation to act on her/his obligations or interests?	Yes	No	1 2 3
Is the person less affectionate and/or lacking in emotions when compared to her/his usual self?	Yes	No	1 2 3
Does she/he no longer care about anything?	Yes	No	1 2 3
This domain describes mood or anxiety symptoms			
Has the person developed sadness or appear to be in low spirits? Does she/he have episodes of tearfulness?	Yes	No	1 2 3
Has the person become less able to experience pleasure?	Yes	No	1 2 3
Has the person become discouraged about their future or feel that she/he is a failure?	Yes	No	1 2 3
Does the person view herself/himself as a burden to family?	Yes	No	1 2 3
Has the person become more anxious or worried about things that are routine (e.g., events, visits, etc.)?	Yes	No	1 2 3
Does the person feel very tense, having developed an inability to relax, or shakiness, or symptoms of panic?	Yes	No	1 2 3
This domain describes the ability to delay gratification and control behaviour, impulses, oral intake and/or changes in reward			
Has the person become agitated, aggressive, irritable, or temperamental?	Yes	No	1 2 3
Has she/he become unreasonably or uncharacteristically argumentative?	Yes	No	1 2 3
Has the person become more impulsive, seeming to act without considering things?	Yes	No	1 2 3

Does the person display sexually disinhibited or intrusive behaviour, such as touching (themselves/others), hugging, groping, etc., in a manner that is out of character or may cause offence?	Yes	No	1 2 3
Has the person become more easily frustrated or impatient? Does she/he have troubles coping with delays, or waiting for events or for their turn?	Yes	No	1 2 3
Does the person display a new recklessness or lack of judgement when driving (e.g. speeding, erratic swerving, abrupt lane changes, etc.)?	Yes	No	1 2 3
Has the person become more stubborn or rigid, i.e., uncharacteristically insistent on having their way, or unwilling/unable to see/hear other views?	Yes	No	1 2 3
Is there a change in eating behaviours (e.g., overeating, cramming the mouth, insistent on eating only specific foods, or eating the food in exactly the same order)?	Yes	No	1 2 3
Does the person no longer find food tasteful or enjoyable? Are they eating less?	Yes	No	1 2 3
Does the person hoard objects when she/he did not do so before?	Yes	No	1 2 3
Has the person developed simple repetitive behaviours or compulsions?	Yes	No	1 2 3
Has the person recently developed trouble regulating smoking, alcohol, drug intake or gambling, or started shoplifting?	Yes	No	1 2 3
This domain describes following societal norms and having social graces, tact, and empathy			
Has the person become less concerned about how her/his words or actions affect others? Has she/he become insensitive to others' feelings?	Yes	No	1 2 3
Has the person started talking openly about very personal or private matters not usually discussed in public?	Yes	No	1 2 3
Does the person say rude or crude things or make lewd sexual remarks that she/he would not have said before?	Yes	No	1 2 3
Does the person seem to lack the social judgement she/he previously had about what to say or how to behave in public or private?	Yes	No	1 2 3
Does the person now talk to strangers as if familiar, or intrude on their activities?	Yes	No	1 2 3
This domain describes strongly held beliefs and sensory experiences			
Has the person developed beliefs that they are in danger, or that others are planning to harm them or steal their belongings?	Yes	No	1 2 3
Has the person developed suspiciousness about the intentions or motives of other people?	Yes	No	1 2 3
Does she/he have unrealistic beliefs about her/his power, wealth or skills?	Yes	No	1 2 3
Does the person describe hearing voices, or does she/he talk to imaginary people or 'spirits'?	Yes	No	1 2 3
Does the person report or complain about, or act as if seeing things (e.g. people, animals or insects) that are not there, i.e., that are imaginary to others?	Yes	No	1 2 3

Based on the ISTAART-AA Research Diagnostic Criteria for MBI ©2016 (3) as a precursor to cognitive decline and dementia. Mild Behavioural Impairment (MBI) describes neuropsychiatric symptoms (NPS) of any severity, which are not captured by traditional psychiatric nosology, persist for at least 6 months, and occur in advance of or in concert with mild cognitive impairment. The detection and description of MBI has been operationalised in the International Society to Advance Alzheimer's Research and Treatment – Alzheimer's Association (ISTAART-AA).

For more information contact Zahinoor Ismail MD email: MBIchecklist@gmail.com or visit www.MBItest.org.

The most troublesome behaviours such as agitation, paranoia, aggressivity and sleep disturbances usually arise well after the dementia diagnosis is confirmed. However, visual hallucinations early on may suggest dementia with Lewy bodies while the loss of social inhibition is indicative of a frontotemporal dementia. As dementia progresses into the moderate stage, other structured questionnaires such as the Neuropsychiatric Inventory are useful.

Behavioural symptoms associated with dementia have a significant healthcare impact on carer fatigue, depression and possible burnout. These factors accelerate the need for additional at-home resources. Early symptom occurrence is a predictor that advanced transfer and admission to long-term care facilities may be needed.

> Behavioural symptoms associated with dementia have a significant healthcare impact on carer fatigue, depression and possible burnout.

Survey results

1,111 multidisciplinary clinicians indicated their preference when asking about mood and behavioural changes. Most disclosed that they use a semi-structured approach to question the person with dementia complaints as well as the individual accompanying them, while the remaining clinicians use a structured questionnaire completed before or during the consultation.

Expert essay

Measuring mood and behavioural changes as part of a complete dementia assessment

Zahinoor Ismail

Departments of Psychiatry, Clinical Neurosciences and Community Health Sciences, Cumming School of Medicine, University of Calgary, CANADA

Mood and behaviour changes in dementia are almost universal, occurring in up to 97% of people with dementia in the first five years after diagnosis (1). Termed neuropsychiatric symptoms, or behavioural and psychological symptoms of dementia, these changes include apathy, emotional dysregulation, agitation/impulse dyscontrol, disinhibited social behaviour, and psychotic symptoms. Neuropsychiatric symptoms are associated with greater functional impairment, accelerated cognitive decline, poorer quality of life, increased carer burden, higher rates of long-term care facility placement, greater mortality, and more neuropathological markers of dementia (2). Despite the clinical significance of behavioural changes, neuropsychiatric symptoms may be overlooked in a cognocentric dementia paradigm, where assessments focus on cognitive testing. However, awareness of non-cognitive markers of dementia is increasing (3), with inclusion of neuropsychiatric symptoms in this complementary symptom axis. Indeed, Canadian clinical guidelines emphasise the inclusion of neuropsychiatric symptoms for more thorough dementia assessments (4), as part of the cognition, behaviour, and function triad (5), all important factors to measure in clinical visits.

Other obstacles exist to fully assess the changes in mood and behaviour associated with dementia. These include clinician apprehension about causing distress, the perception that information may not be accurate, or an insufficient appreciation of the underlying neurobiology of neuropsychiatric symptoms – with an attendant belief that these changes are reasonable or simply attributable to cognitive impairment. Indeed, intervention, both pharmacological and non-pharmacological, is often required. The choice and implementation of treatments should be informed by appropriate and thorough assessments, grounded in the principles of measurement-based care.

Given the distress already associated with dementia, and/or a clinician's desire not to further upset the person during consultation, the path of least resistance may be to avoid inquiring about emotional or neuropsychiatric symptoms at all. On the face of it, this approach may appear kind and sensitive. However, failing to investigate these symptoms fundamental to their internal world, further diminishes the individual's personhood. Dementia can rob someone of their personhood by altering thoughts, feelings, and social behaviours. Understanding mood, behaviour, and emotion is essential to discerning the multifaceted aspects of dementia; neuropsychiatric symptoms are core dementia symptoms.

Notwithstanding the potential loss of decisional capacity as the condition runs its course, circumventing the assessment of neuropsychiatric symptoms can also diminish agency, namely the ability to influence their own personal circumstances. In fact, behavioural symptoms may very well be their attempt to communicate or exert agency (6). Assessing, exploring, and understanding these behaviours may contribute to better person-centred care. Conversely, if under-detected or untreated, neuropsychiatric symptoms can interfere with agency. Apathy, anxiety, poor frustration tolerance, impulsivity, suspiciousness or persecutory delusions can influence decision-making and an individual's ability to interact with the environment, possibly in contrast to long-standing habits. Assessing the neuropsychiatric symptoms can restore agency, allowing a person with dementia to influence their environment, more consistent with their pre-dementia selves.

Agency aside, the role of an informed carer, a family member, friend or formal carer (if in long-term care placement), is often overlooked when assessing neuropsychiatric symptoms. Indeed, who provides information is an important aspect of dementia care. Dementia is often associated with anosognosia, a lack of insight, which is linked with structural and functional changes in multiple brain regions, especially frontal and midline brain structures (7). Anosognosia can refer to limited awareness of cognitive and functional deficits, but also to impaired awareness of emotional changes, termed affective anosognosia (8). Research investigating report discrepancies between the person with dementia symptoms and the informant (respective carers or nurses) found that the person with dementia greatly underrated the severity of their depression symptoms (8). Thus, an approach that simply utilises a clinical interview, or that uses a measure that relies on personal endorsement

or self-reported symptoms may not accurately identify depressive symptoms, apathy, psychosis or behavioural disturbances associated with dementia. This insufficient appreciation of the extent or magnitude of neuropsychiatric symptoms can result in ongoing suffering or distress. If neuropsychiatric symptoms worsen and are only initially identified when exhibited in a crisis situation, a loss of autonomy, a change in living situation, or emergent pharmacotherapy may be required, none of which are optimal outcomes. Thus, early and ongoing assessment for neuropsychiatric symptoms is a component of good clinical care.

For some, a prevailing belief is that behavioural and psychological symptoms in dementia are 'noise', distracting from more concrete issues. However, an ever-increasing evidence base has elucidated the neurobiology of neuropsychiatric symptoms in dementia, with cortical and subcortical structures implicated, as well as traditional dementia markers of amyloid-β and tau (2). Indeed, the latest evidence suggests that dementia-related neuropsychiatric symptoms can emerge ahead of dementia, in prodromal or preclinical phases, associating with known dementia biomarkers (9). These findings again support the role of neuropsychiatric symptoms as core dementia features, necessitating assessment and monitoring, much the same way a clinician would assess and monitor cognition and function (2,5).

Clinically significant mood and behaviour changes in dementia require a cautious yet evidence-based treatment approach, grounded in measurement-based care. Scales for neuropsychiatric symptoms are recommended for routine screening, at the very least to identify a global neuropsychiatric burden (for example, the informant-rated Neuropsychiatric Interview Questionnaire), and to track these symptoms over time. Distress, safety issues, or impact on function point to neuropsychiatric symptoms that are clinically significant. First principles of behavioural changes in older adults apply, such that reversible causes first need to be ruled out, followed by non-pharmacological interventions, and then short-term pharmacological treatment if necessary (10). Frequent follow-up and measurement are required, balancing safety and efficacy, to optimise cognition, behaviour, function, and quality of life.

Therefore, while possibly uncomfortable or challenging, it is of utmost importance to regularly assess neuropsychiatric changes in a person with dementia. These mood and behavioural symptoms are a fundamental part of the dementia process, considered core criteria in dementia, associated with known dementia biomarkers, thus leading to poorer outcomes. Leveraging the knowledge and observations of an informed carer, as well as asking the person with dementia themselves about neuropsychiatric symptoms, is a person-centred approach to dementia, and should be routine practice.

References

1. Steinberg M, Shao H, Zandi P, Lyketsos CG, Welsh-Bohmer KA, Norton MC, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: The Cache county study. Int J Geriatr Psychiatry [Internet]. 2008 [cited 2021 Jul 8];23(2):170–7. https://pubmed.ncbi.nlm.nih.gov/17607801/.
2. Lanctôt KL, Amatniek J, Ancoli-Israel S, Arnold SE, Ballard C, Cohen-Mansfield J, et al. Neuropsychiatric signs and symptoms of Alzheimer's disease: New treatment paradigms [Internet]. Vol. 3, Alzheimer's and Dementia: Translational Research and Clinical Interventions. Alzheimers Dement (N Y); 2017 [cited 2021 Jul 8]. p. 440–9. https://pubmed.ncbi.nlm.nih.gov/29067350/.
3. Montero-Odasso M, Pieruccini-Faria F, Ismail Z, Li K, Lim A, Phillips N, et al. CCCDTD5 recommendations on early non cognitive markers of dementia: A Canadian consensus. Alzheimer's Dement Transl Res Clin Interv [Internet]. 2020 [cited 2021 Jul 8];6(1). https://pubmed.ncbi.nlm.nih.gov/33094146/.
4. Ismail Z, Black SE, Camicioli R, Chertkow H, Herrmann N, Laforce R, et al. Recommendations of the 5th Canadian Consensus Conference on the diagnosis and treatment of dementia. Alzheimer's Dement [Internet]. 2020 Aug 1 [cited 2021 Jul 8];16(8):1182–95. https://pubmed.ncbi.nlm.nih.gov/32725777/.
5. Tang-Wai DF, Smith EE, Bruneau MA, Burhan AM, Chatterjee A, Chertkow H, et al. CCCDTD5 recommendations on early and timely assessment of neurocognitive disorders using cognitive, behavioral, and functional scales. Alzheimer's Dement Transl Res Clin Interv [Internet]. 2020 [cited 2021 Jul 8];6(1). https://pubmed.ncbi.nlm.nih.gov/33209972/.
6. Boyle G. Recognising the agency of people with dementia. Disabil Soc. 2014;29(7):1130–44.
7. Wilson RS, Sytsma J, Barnes LL, Boyle PA. Anosognosia in Dementia [Internet]. Vol. 16, Current Neurology and Neuroscience Reports. Curr Neurol Neurosci Rep; 2016 [cited 2021 Jul 8]. https://pubmed.ncbi.nlm.nih.gov/27438597/.
8. Verhülsdonk S, Quack R, Höft B, Lange-Asschenfeldt C, Supprian T. Anosognosia and depression in patients with Alzheimer's dementia. Arch Gerontol Geriatr [Internet]. 2013 Nov [cited 2021 Jul 8];57(3):282–7. https://pubmed.ncbi.nlm.nih.gov/23597486/.
9. Ismail Z, McGirr A, Gill S, Hu S, Forkert ND, Smith EE. Mild Behavioral Impairment and Subjective Cognitive Decline Predict Cognitive and Functional Decline. J Alzheimers Dis [Internet]. 2021 [cited 2021 Jul 8];80(1):459–69. https://pubmed.ncbi.nlm.nih.gov/33554909/
10. Ismail Z, Goodarzi Z. Neuropsychiatric Aspects of Alzheimer's Disease Clinically significant neuropsychiatric symptoms need evidence-based treatment. Pract Neurol [Internet]. 2019 [cited 2021 Jul 8];(June):78–83. http://v2.practicalneurology.com/pdfs/PN0619_CF8_NPS&AD.pdf.

Conclusions

Given the significant impact of dementia on an individual's quality of life, an increase in mood and behavioural symptoms such as depressive feelings, paranoia, anxiety, apathy and irritability may become present. These neuropsychiatric symptoms, whether associated with changes to the brain or an emotional reaction to current circumstances, need to be assessed in a comprehensive manner. In fact, these symptoms may precede dementia but are often overlooked when the focus is on cognitive testing.

Also frequently overlooked is the role of an informed carer who is understandably well-placed to observe these symptoms. When anosognosia is factored in, the impaired awareness of cognitive and emotional changes, this makes a carer's feedback even more relevant. Thus, a combined approach of self-reporting and informant interview and/or questionnaire will yield a more complete picture. This may occur in a semi-structured interview setting and/or by using a structured tool such as the MBI-Checklist.

Additional references

1. Sheikh JI, Yesavage JA. 9/geriatric depression scale (Gds) recent evidence and development of a shorter version. Clin Gerontol [Internet]. 1986 Nov 18 [cited 2020 Oct 1];5(1–2):165–73. https://www.tandfonline.com/doi/abs/10.1300/J018v05n01_09.
2. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The neuropsychiatric inventory: Comprehensive assessment of psychopathology in dementia. Neurology [Internet]. 1994 [cited 2021 Jul 8];44(12):2308–14. https://pubmed.ncbi.nlm.nih.gov/7991117/.
3. Ismail Z, Agüera-Ortiz L, Brodaty H, Cieslak A, Cummings J, Fischer CE, et al. The Mild Behavioral Impairment Checklist (MBI-C): A Rating Scale for Neuropsychiatric Symptoms in Pre-Dementia Populations. J Alzheimer's Dis [Internet]. 2017 [cited 2021 Jul 8];56(3):929–38. https://pubmed.ncbi.nlm.nih.gov/28059789.

Chapter 6
Cognitive assessments

Serge Gauthier

Key points

- Cognitive assessments are required for the diagnosis of dementia and to track changes over time.
- The cognitive screening tests most used by clinicians are the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA).
- Complementary cognitive tests may be required based on symptoms.
- Tests that overcome the influence of language differences are needed, such as the Visual Cognitive Assessment Test (VCAT).
- As a result of the COVID-19 pandemic, many clinicians have incorporated telemedicine into their practice.
- As with in-person assessment, telemedicine encounters require the protection of patient privacy and confidentiality.
- The clinician must be aware of telemedicine limitations and decide whether an in-person encounter is necessary.
- For telemedicine assessments, carers are often required to facilitate the visit.

General background

Cognitive assessment is most often conducted with well-established tests in use for many years and familiar to clinicians. Noteworthy are the Mini Mental State Examination (MMSE) developed by Folstein et al. in 1975 (1), and the Montreal Cognitive Assessment (MoCA) developed by Nasreddine et al. in 2005 (2). Implementation of these screening tests was confirmed by the clinician survey appearing below. These tests were developed in Western populations with English as the primary language and a minimal grade 7 educational requirement, thus limiting their use in other world populations, as discussed by Ng et al. in their essay. Newly identified factors restricting use include copyright issues and the request for payment to either use the test or obtain training to administer it. Another key factor that was recently propelled to the forefront is the fact that these tests were developed for in-person testing. The COVID-19 pandemic impeded people living with dementia from visiting their healthcare professional. Fortunately, many clinicians adapted and incorporated remote telemedicine into their practice as described by Geddes et al. (3). Surveyed clinicians responded positively to the implementation of remote assessments.

Survey results

1,111 multidisciplinary clinicians responded to this survey and indicated that they routinely use the Mini Mental Sate Examination (81%), and the Montreal Cognitive Assessment (61%) with people concerned about their cognition. Many also use short screening tools such as the Five-word test (11%) and the Mini-Cog (11%). A significant number of additional cognitive tests are also used (31%). When special circumstances require it, such as a person with pre-existing intellectual disabilities that impede the use of standard cognitive tests, most clinicians will rely on functional decline and behavioural symptoms as indicators of dementia (54%) while many will use shorter versions of the MMSE or other commonly used cognitive tests (38%) and others switch to special scales for that individual (20%). In many instances, they refer to a neuropsychologist (38%) or a clinician with experience in such cases (21%). Based on the experienced gained from the COVID-19 pandemic, most clinicians responded favourably to using remote cognitive assessments in their practice for people previously diagnosed and in need of follow-up (52%) and for people living with dementia who could not attend an in-person consultation (63%). This may help to alleviate geographical healthcare inequalities and provide support for those living in rural communities in the future.

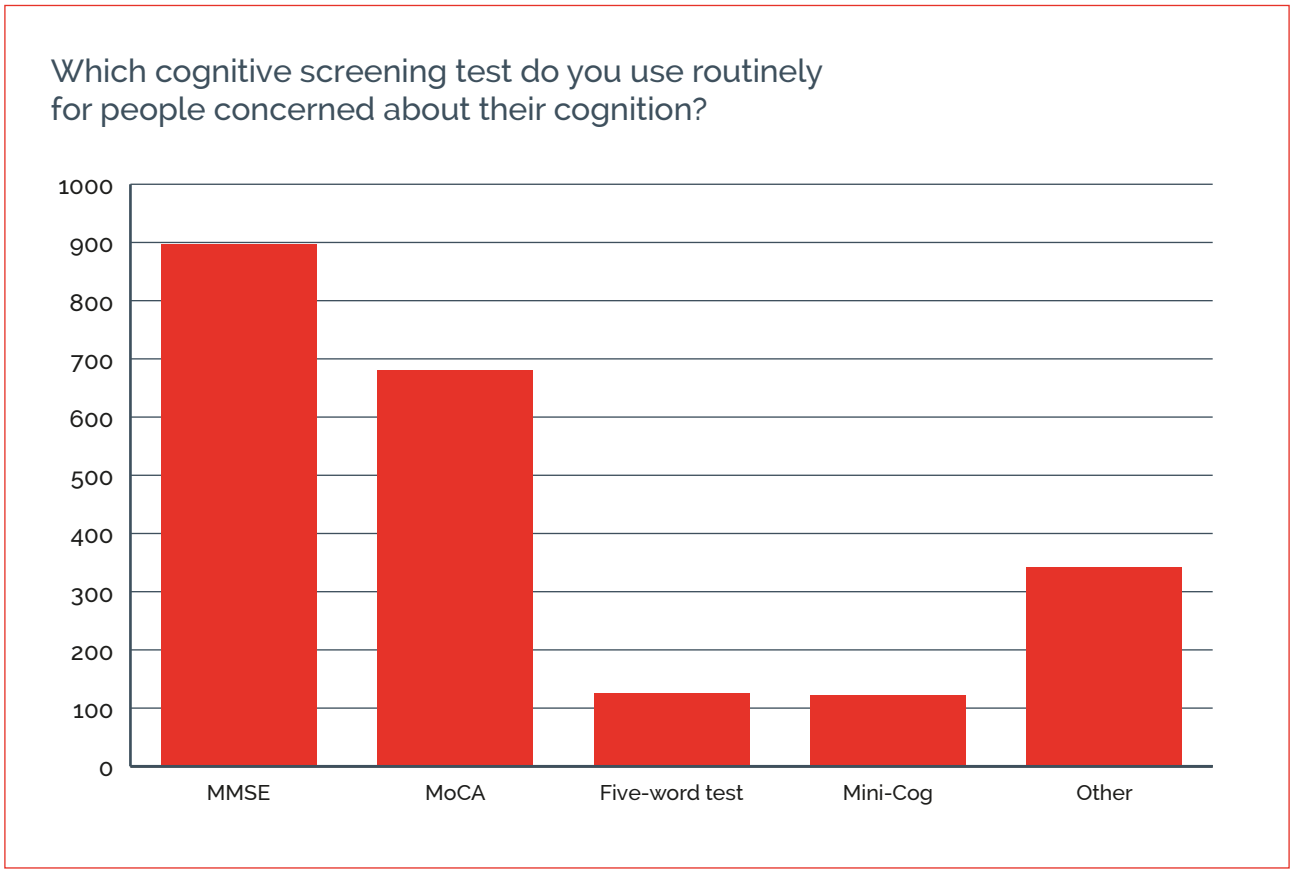


Chart 1. Clinician responses (multiple answers selected).

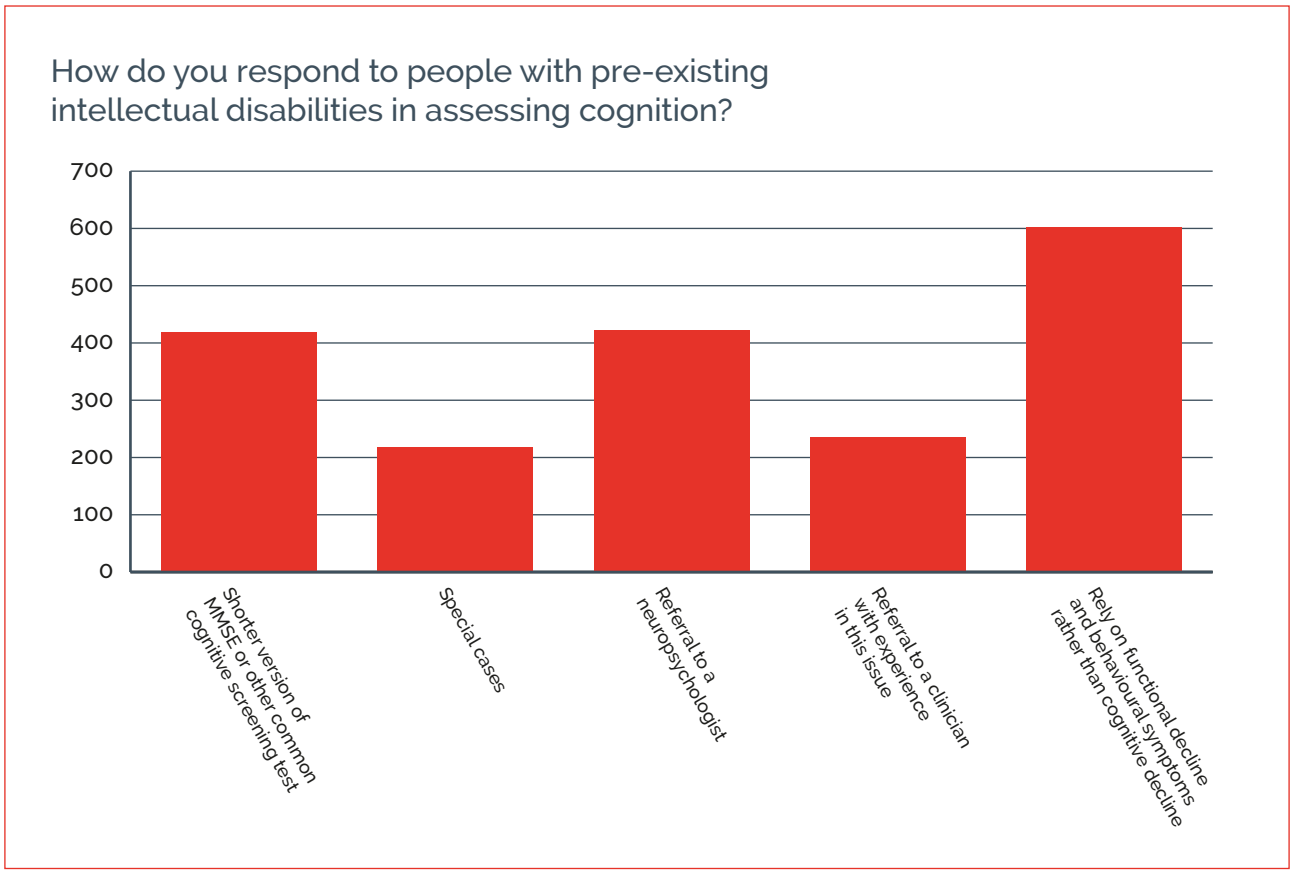


Chart 2. Clinician responses (multiple answers selected).

Expert essay

Remote cognitive assessment: guiding principles and future directions

Maiya R. Geddes,[1] John D. Fisk,[2] Richard Camicioli,[3] Zahinoor Ismail,[4] Megan E. O'Connell,[5] C. Munro Cullum[6]

1 Department of Neurology and Neurosurgery, McGill University, CANADA
2 Department of Psychology and Neuroscience, Dalhousie University, CANADA
3 Neuroscience and Mental Health Institute and Department of Medicine, Division of Neurology, University of Alberta, CANADA
4 Departments of Psychiatry, Clinical Neurosciences, and Community Health Sciences, Cumming School of Medicine, University of Calgary, CANADA
5 Department of Psychology, University of Saskatchewan, CANADA
6 Division of Psychology, Department of Psychiatry, O'Donnell Brain Institute, University of Texas Southwestern Medical Center, UNITED STATES

Systematic assessment of cognition represents a vital component of the evaluation of known or suspected cognitive decline associated with neurodegenerative conditions. These assessments range from brief cognitive screening tasks to comprehensive neuropsychological evaluations characterising a variety of cognitive domains. Assessment is required to establish, confirm, or rule out diagnoses, distinguish amongst disorders, and track cognitive changes over time and with treatment. The COVID-19 pandemic catalysed a rapid embrace of telemedicine that has been particularly important for vulnerable older adults. Despite challenges, current literature and practice support implementation of remote cognitive evaluation. Here, we provide guiding principles on remote assessment of cognition.

Current practice

It is critical to adopt strategies that minimise the burden of people with dementia and their carers while maximising safety and the value of collected information.

The same clinical and ethical standards apply to both in-person and telemedicine encounters. The interests and welfare of the person with dementia are of primary concern and clinicians must be transparent in disclosing the rationale for and limitations of remote care, including issues related to confidentiality and data acquisition/interpretation. As guidelines for implied consent in telemedicine are not yet defined, it is critical to obtain informed verbal consent and verification of the person's identity. Protection of personal privacy and confidentiality requires encrypted, password-protected videoconferencing software that is user-friendly and compatible across devices. A telephone number, as a back-up method of communication, should be obtained prior to the telemedicine encounter in the case of technical failures. Clinician empathy is critically associated with health outcomes and can be communicated with verbal and non-verbal techniques during the telemedicine encounter and further improved with clinician training. Disclosure of a diagnosis using telemedicine can be especially challenging and requires planning in advance to ensure this process supports people with dementia and their carers. Written summaries that include a management plan, educational materials and information about community resources enhance the continuity of care.

Strategies to improve the validity of remote assessment should be considered before, during and after the remote cognitive assessment

Independent historical corroboration with a collateral informant is an important component of cognitive assessment for people with known or suspected neurodegenerative conditions. For telemedicine assessments, carers may also be required to facilitate the visit. People with dementia and carers should be provided educational and technical resources beforehand to support the telemedicine encounter. To optimise the validity of the examination, clinician and home environments should be quiet, private, and free from distracting or orienting cues.

To fulfil competency of care in telemedicine, the clinician and person at home must be comfortable with technology. The clinician must take into account the limitations inherent to telemedicine and decide whether an in-person consultation is necessary. Clinicians should consider perceptual, language, educational, cultural, sociodemographic

and cognitive barriers to data collection and its fidelity and interpretability. This information should be considered in advance to determine whether there is an appropriate indication for a remote assessment. Validity of remote measurement requires adequate audio-visual quality, Internet connectivity speed and access to necessary visual and hearing aids for the person with dementia. Alternative modalities (for example, the telephone) should be offered to minimise obtrusiveness, if appropriate.

While cognitive screening can be completed by telephone, videoconferencing provides a more personal connection and allows for a neurobehavioural status examination and behavioural observations that cannot be made over the telephone. Videoconferencing also expands the repertoire of available tests and allows for the presentation of visual stimuli (for example, via screen sharing). Specialised brief screening tools designed for telephone administration have been developed and validated, while other widely-used cognitive screening tools have been adapted for telephone administration (1,2). However, we recommend the triangulation of data from the clinical interview, validated by brief remote testing (for example, cognitive screening, cognitive domain-specific tests, neuropsychiatric symptom, behavioural and function questionnaires) and videoconferenced neurobehavioural status examination when possible. Confidence in the clinical interpretation of cognitive assessment and diagnosis is increased when there is convergence across different sources of information.

Remote cognitive assessment is largely feasible and acceptable

Remote neuropsychological testing has been found to be feasible and acceptable when used for dementia diagnostic evaluations (3). Individual satisfaction with telemedicine assessment is high, including in those with cognitive impairment (4). Comparisons of remotely delivered versus in-person neuropsychological test administration in older persons with and without cognitive impairment have reported similar and highly correlated scores on a variety of standard tests (5–7). Thus, there is a growing evidence base for teleneuropsychology that supports the feasibility, validity, reliability, and acceptability of remote cognitive assessment. This should be integrated with the understanding that non-standardised test administration and the unknown impact of applying normative comparison standards gathered from in-person assessment may affect the interpretation of findings from remote cognitive assessments (8).

Future directions

Further work is needed to determine the validity, barriers and outcomes of remote cognitive assessment.

As with in-person assessment, it is critical that approaches to remote cognitive assessments are unbiased across race, ethnicity, educational attainment, language and sensorimotor abilities. Opportunities and future directions include validation of additional instruments in diverse cultural and linguistic populations, examination of in-home assessment effects, and development of new tools that capitalise on the virtual environment. The latter include response recording and scoring, computer-administered tests, and the use of mobile devices. Data gathered from wearable devices or remote sensor data may provide methods to monitor multiple aspects of physical and behavioural functioning, including sleep, movement and vital signs. Ultimately, these metrics may lead to the discovery of digital biomarkers earlier in the course of illness (9). Further development of open-source technological tools that assess visual fields, eye movements, hearing and subtle behavioural features such as task engagement, attention, and body language may enhance the remote neurobehavioural status examination. Harmonisation of metrics across platforms and best practice protocols will be required for appropriate use of these technologies.

Future work is required to maximise the safety of the person with dementia and the value of information gathered. Development of intuitive user interfaces will help to minimise the burden of remote cognitive assessment on them and their carers. Virtual design solutions will help to expand the repertoire of telemedicine-enabled cognitive assessments. The pandemic has highlighted the digital divide across demographic and socioeconomic groups which impacts the accessibility of telemedicine and places the burden of access on people with dementia and their families. Equitable access to remote cognitive assessment irrespective of disease stage and level of carer support is critical. Building health system infrastructures that support delivery of cognitive telemedicine at local community health service centres could improve access for those with limited social or technological resources.

The COVID-19 pandemic created challenges that catalysed a rapid adoption of telemedicine. Despite its inherent limitations, this expansion of telemedicine may improve access to diagnostic and supportive care of older patients with known or suspected neurodegenerative disorders and cognitive impairment, if applied judiciously. Telemedicine should not seek to replace or undermine the power and art of the in-person diagnostic evaluation. Rather, telemedicine is a tool that offers the potential to enhance neurobehavioural diagnostic capabilities and access to subspecialty care to better serve people with and their families. In addition to supporting cognitive assessment and clinical diagnosis, telemedicine may facilitate improved care through counselling, behaviour management, and rehabilitation. This presents an opportunity to innovate clinical practice beyond the current pandemic.

References

1. Geddes MR, O'Connell ME, Fisk JD, Gauthier S, Camicioli R, Ismail Z. Remote cognitive and behavioral assessment: Report of the Alzheimer Society of Canada Task Force on dementia care best practices for COVID-19 [Internet]. Vol. 12, Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring. Alzheimers Dement (Amst); 2020 [cited 2021 Jul 8]. https://pubmed.ncbi.nlm.nih.gov/32999916/.
2. Carlew AR, Fatima H, Livingstone JR, Reese C, Lacritz L, Pendergrass C, et al. Cognitive Assessment via Telephone: A Scoping Review of Instruments [Internet]. Vol. 35, Archives of Clinical Neuropsychology. Arch Clin Neuropsychol; 2020 [cited 2021 Jul 8]. p. 1215–33. https://pubmed.ncbi.nlm.nih.gov/33106856/.
3. Loh PK, Donaldson M, Flicker L, Maher S, Goldswain P. Development of a telemedicine protocol for the diagnosis of Alzheimer's disease. J Telemed Telecare [Internet]. 2007 Jun 24 [cited 2021 Jul 8];13(2):90–4. https://journals.sagepub.com/doi/abs/10.1258/135763307780096159.
4. Parikh M, Grosch MC, Graham LL, Hynan LS, Weiner M, Shore JH, et al. Consumer acceptability of brief videoconference-based neuropsychological assessment in older individuals with and without cognitive impairment. Clin Neuropsychol [Internet]. 2013 Jul 1 [cited 2021 Jul 8];27(5):808–17. https://www.tandfonline.com/doi/abs/10.1080/13854046.2013.791723.
5. Munro Cullum C, Hynan LS, Grosch M, Parikh M, Weiner MF. Teleneuropsychology: Evidence for video teleconference-based neuropsychological assessment. J Int Neuropsychol Soc. 2014 Nov 10;20(10):1028–33.
6. Brearly TW, Shura RD, Martindale SL, Lazowski RA, Luxton DD, Shenal B V., et al. Neuropsychological Test Administration by Videoconference: A Systematic Review and Meta-Analysis [Internet]. Vol. 27, Neuropsychology Review. 2017 [cited 2021 Jul 8]. p. 174–86. http://link.springer.com/10.1007/s11065-017-9349-1.
7. Marra DE, Hamlet KM, Bauer RM, Bowers D. Validity of teleneuropsychology for older adults in response to COVID-19: A systematic and critical review [Internet]. Vol. 34, Clinical Neuropsychologist. Clin Neuropsychol; 2020 [cited 2021 Jul 8]. p. 1411–52. https://pubmed.ncbi.nlm.nih.gov/32519594/.
8. Bilder RM, Postal KS, Barisa M, Aase DM, Cullum CM, Gillaspy SR, et al. InterOrganizational practice committee recommendations/guidance for teleneuropsychology (TeleNP) in response to the COVID-19 pandemic. Clin Neuropsychol [Internet]. 2020 [cited 2021 Jul 8];34(7–8):1314–34. https://pubmed.ncbi.nlm.nih.gov/32673163/.
9. Au R, Ritchie M, Hardy S, Fang T, Ang A, Lin H. Aging Well: Using Precision to Drive Down Costs and Increase Health Quality. Adv Geriatr Med Res. 2019.

Expert essay

Cognitive assessment for multilingual societies in Asia and globally

Kok Pin Ng, Wilbur Koh, Nagaendran Kandiah

Department of Neurology, National Neuroscience Institute, Singapore, SINGAPORE

Cognitive tests that measure both global and domain specific cognitive abilities such as memory, attention, visuospatial, language, and executive function play an important role in complementing the clinical history of individuals who present with cognitive symptoms to allow a timely and accurate diagnosis of mild cognitive impairment or dementia to be made. The Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) are examples of cognitive tests that are commonly used worldwide. However, many of these cognitive tests were established for monolingual Western populations (usually English) where they were first developed. Therefore, the diversity of languages and cultures worldwide poses a significant barrier in using them in their original language and form (1). This is especially relevant in regions of the world where the populations are often multilingual with numerous native dialects such as Asia. While there has been progress in the Indigenous development of original tests that are specific to regional Asian contexts over the past decades, more work has been dedicated to the translation and adaptation of existing tests (2,3), many of which are used in Asia for comparability and generalisability to existing research literature.

Translating existing cognitive tests to the multilingual Asian context has the advantage of being familiar and accessible as well as less time-consuming than developing new, original tests. Importantly, this enables the comparison of scores obtained from a common test between international and inter-cultural cohorts, although such comparisons may not allow for insights into culturally-specific differences. The substantial work done in translating and validating the Montreal Cognitive Assessment (4) test across many world centres and the efforts by the 10/66 Dementia Research Group (5) are examples that make well-established tests available in numerous languages, and therefore accessible and usable worldwide. On the other hand, there are several confounders when translating cognitive tests. Firstly, some languages/dialects do not have a well-defined or well-known writing system (for example, Hokkien; a dialect of Mandarin) and thus cannot be easily translated into a written format. Secondly, the process of translating cognitive tests introduces measurement error due to linguistic differences (such as differential item functioning) (6) and replacement of items that cannot be translated. Thirdly, cross-linguistic artefacts in translation and variation in administration or scoring procedures may cause method bias (7). Consequently, scores of translated and original versions of cognitive tests may not be comparable when executed in different linguistic groups of the same population and in multinational studies. Presently, there are only a few cognitive tests that have been developed and validated in Asia and a dearth of published validation studies in many Asian nations and languages (3). Therefore, a concerted effort to develop tools that overcome the influence of language differences by mitigating the need for translation is greatly warranted.

One such effort is the development of visual-based cognitive tests that are designed to overcome language barriers. For instance, the Cross-Cultural Dementia Screening (CCD) test was developed to overcome linguistic and cultural differences in the cognitive assessment of elderly immigrant populations in Europe (8). The CCD is a digital test that uses pictures of familiar, everyday objects to assess episodic memory, mental speed, and executive function. Psychometrically, it is found to outperform the MMSE in discriminating between normal controls from people with dementia. Method bias resulting from administrative or scoring variations is also reduced given that the test is administered by a computer. However, this test is only available in six languages (namely, Dutch, Turkish, Moroccan-Arabic, Tarifit, Sranantongo, and Sarnámi-Hindustani), none of which are commonly used in Asia. Similarly, while other visual-based tests have been developed by Western cohorts such as the Picture-Based Memory Impairment Screen for dementia and the Phototest, they are not widely used in Asia (3). Recognising this gap, the Visual Cognitive Assessment Test (VCAT) which uses pictures of familiar objects and scenes to assess episodic memory, visuospatial, executive function, language, and attention has recently been developed in Asia (9). The VCAT is demonstrated to be a reliable and effective screening for mild cognitive impairment and dementia and the construct validity and efficacy of the VCAT in comparison to the MMSE and MoCA have been previously reported, with the VCAT performing comparably to the MoCA and better than the MMSE in detecting cognitive impairment (10). A shortened version of the VCAT (the VCAT-S) has also been

developed and found to be comparable to the original test (11). More importantly, the VCAT can be administered in multilingual populations and has been validated in a multi-site study across centres in Southeast Asian (Singapore, Malaysia, Indonesia, and the Philippines(12)). Given this, the VCAT shows promise as a potential cross-linguistic tool and efforts to validate it in centres outside Asia, including Brazil, India, South Korea and Canada are underway. While the above efforts aim to address the issues linked to test translation in multilingual societies, it is important to note that other factors such as education, literacy rates, social-economic status, cultural norms and nation development/industrialisation will need to be accounted for as these play a significant role in influencing cognitive performance (13,14).

Future directions

There needs to be international efforts to form large multi-centre cohorts by pooling cognitive and biomarker data from institutions across the world to study the pathophysiology of neurocognitive diseases. Furthermore, clinical trials are increasingly globalised with the inclusion of international sites. Therefore, it is imperative to have a valid and reliable cognitive test with minimal influence from language differences that is comparable across multinational and multilingual populations. The recently developed visual-based language-neutral tools have shown promise in detecting cognitive impairment. However, further validation studies are needed before these tools can be applied internationally. In addition, there is a growing trend in adopting digital technology to conduct cognitive assessment in place of the traditional paper and pencil method, given the potential benefits of enhancing the efficiency of cognitive evaluations such as automatic scoring to reduce scoring errors (15). Digital technology enables the test to be performed remotely, which is especially important in the current COVID-19 pandemic given the limitation of in-person evaluations in a clinic setting. For visual-based tests, digital technology may eliminate administration/scoring bias by standardising the administration of the test in multiple languages. However, these benefits will need to be weighed against the challenges and potential pitfalls of digitalisation as elaborated in a recent review (15). With ageing of populations worldwide, digital-based, language-neutral cognitive evaluations will allow for harmonised clinical evaluations and meaningful international collaborations.

References

1. Ng KP, Chiew HJ, Lim L, Rosa-Neto P, Kandiah N, Gauthier S. The influence of language and culture on cognitive assessment tools in the diagnosis of early cognitive impairment and dementia. Vol. 18, Expert Review of Neurotherapeutics. 2018. p. 859–69.
2. Ponsford J. International growth of neuropsychology. Neuropsychology. 2017;31(8):921–33.
3. Rosli R, Tan MP, Gray WK, Subramanian P, Chin AV. Cognitive assessment tools in Asia: A systematic review. Vol. 28, International Psychogeriatrics. 2016. p. 189–210.
4. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc [Internet]. 2005 [cited 2021 Jul 8];53(4):695–9. https://pubmed.ncbi.nlm.nih.gov/15817019
5. Prince MJ. The 10/66 dementia research group – 10 years on. Indian J Psychiatry [Internet]. 2009;51 Suppl 1:S8–15. http://www.ncbi.nlm.nih.gov/pubmed/21416024%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3038536
6. Ramirez M, Teresi JA, Holmes D, Gurland B, Lantigua R. Differential item functioning (DIF) and the Mini-Mental State Examination (MMSE): Overview, sample, and issues of translation. Vol. 44, Medical Care. 2006.
7. He J, van de Vijver F. Bias and Equivalence in Cross-Cultural Research. Online Readings Psychol Cult. 2012;2(2):1–19.
8. Goudsmit M, Uysal-Bozkir Ö, Parlevliet JL, van Campen JPCM, de Rooij SE, Schmand B. The Cross-Cultural Dementia Screening (CCD): A new neuropsychological screening instrument for dementia in elderly immigrants. J Clin Exp Neuropsychol. 2017;39(2):163–72.
9. Kandiah N, Zhang A, Bautista DC, Silva E, Ting SKS, Ng A, et al. Early detection of dementia in multilingual populations: Visual cognitive assessment test (VCAT). J Neurol Neurosurg Psychiatry. 2016;87(2):156–60.
10. Low A, Lim L, Lim L, Wong B, Silva E, Ng KP, et al. Construct validity of the Visual Cognitive Assessment Test (VCAT) – A cross-cultural language-neutral cognitive screening tool. Int Psychogeriatrics. 2020;32(1):141–9.
11. Koh W, Lim L, Low A, Wong B, Lim L, Silva E, et al. Development and validation of a brief visual based cognitive screening tool for dementia: The Visual Cognitive Assessment Test short-form (VCAT-S). Vol. 91, Journal of Neurology, Neurosurgery and Psychiatry. 2020. p. 1122–3.
12. Lim L, Ng TP, Ong AP, Tan MP, Cenina AR, Gao Q, et al. A novel language-neutral Visual Cognitive Assessment Test (VCAT): Validation in four Southeast Asian countries. Alzheimer's Res Ther. 2018;10(1).
13. Manly JJ. Critical issues in cultural neuropsychology: Profit from diversity. Vol. 18, Neuropsychology Review. 2008. p. 179–83.
14. Franzen S, Van Den Berg E, Goudsmit M, Jurgens CK, Van De Wiel L, Kalkisim Y, et al. A Systematic Review of Neuropsychological Tests for the Assessment of Dementia in Non-Western, Low-Educated or Illiterate Populations. Vol. 26, Journal of the International Neuropsychological Society. 2020. p. 331–51.
15. Staffaroni Adam M., Tsoy Elena, Taylor Jack, Boxer Adam L., Possin Katherine L. Digital Cognitive Assessments for Dementia. Pract Neurol. 2020;NOVEMBER/D:24–45.

Visual Cognitive Assessment Test (VCAT)

Memory (part 1) — **Total Score**

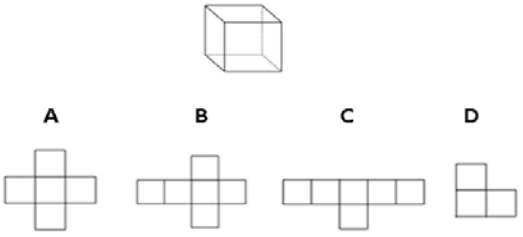
Scenario
Please look at the picture and (a) name the location and (b) name the items that you can see.
(Refer to picture page)

Dog	Coconut Tree	Kite	Crab	Lady	Bone

No marks

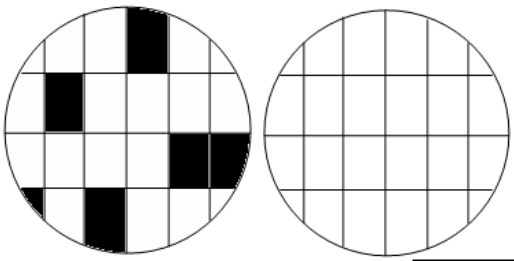
Visuospatial

(a) Cube
Which of the following option (A, B, C or D) when folded up will result in the figure below? Please circle one option.



/ 1

(b) Grid
Please copy the figure from on the left to the empty one on the right as fast as you can.



/ 2*

***Refer to scoring table**

___ / 3

Memory (part 2)

(a) Scenario
3 objects below were **NOT** present in the picture earlier. Please circle these three items.

1 point for EACH correct answer

/ 3

(b) Shapes
Please look at the shapes and try to remember as many elements as you can. You will be asked about this later.
(Refer to picture page)

No marks

Language

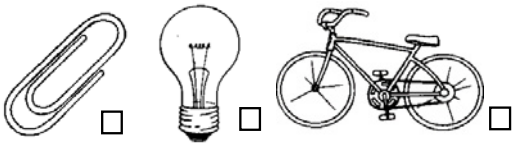
(a) Fluency
Please name as many vegetables as you can in 1 minute.

Total:

/ 2*

(b) Naming
Please name the items below.

1 point for EACH correct answer



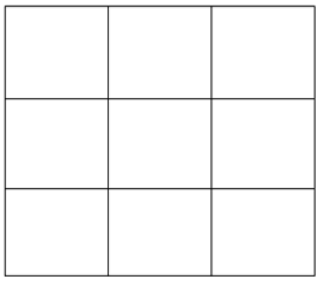
__ / 3

***Refer to scoring table**

___ / 5

Memory (part 3)

(a) Shapes
You were showed you some shapes earlier. Please try to recall and fill in the boxes below with the shapes you saw.



__ / 2*

***Refer to scoring table**

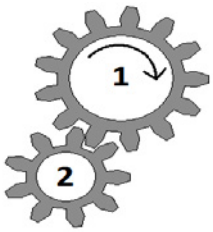
(b) Objects
Please name the objects. Repeat all of them twice and remember these FOUR objects. You will be asked about them later.
(Refer to picture page)

No marks

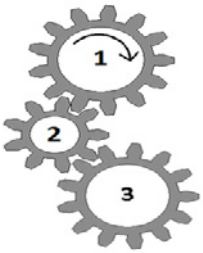
Executive Function

(a) Gears

(a) If Gear 1 is turning in the indicated direction, please draw the arrow in which will Gear **2** turn?



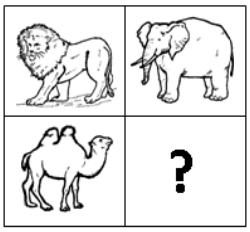
b) If Gear 1 turns in the indicated direction, in which direction will Gear **3** turn?

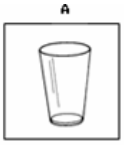


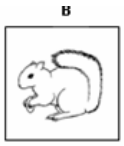
/ 3*

(b) Category

Which of the following options (A, B or C) is the best option to place inside the empty box? Please circle your option.





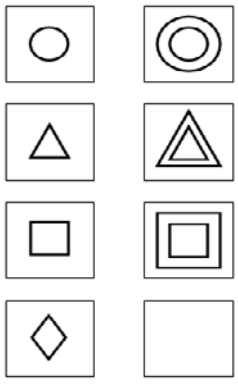


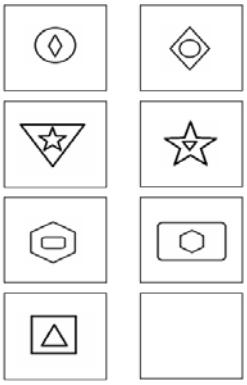
__ / 1

(c) Patterns

Take a look at the patterns below and fill in the empty boxes with the correct patterns.

1 point for EACH correct answer





__ / 2

___ /6

Memory (4)

Objects

You were showed four objects earlier. Can you recall what the four objects are?

	1	2	3	4	Score
Uncued (2 points)					
Cued (1 point)					

/ 8

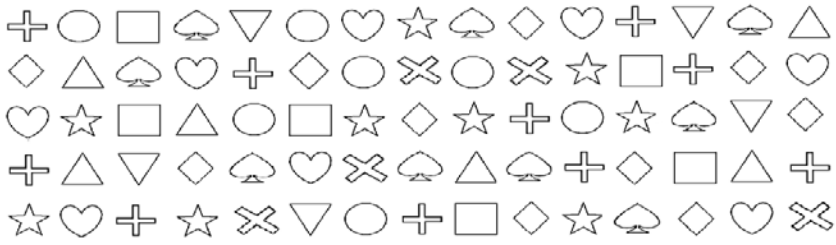
Total Memory (2)+(3)+(4)

___ / 13

Working memory/ Attention

Shape cancellation

Cancel the following shapes:  and  . You have 1 minute.



__ / 3*

*Refer to scoring table

___ / 3

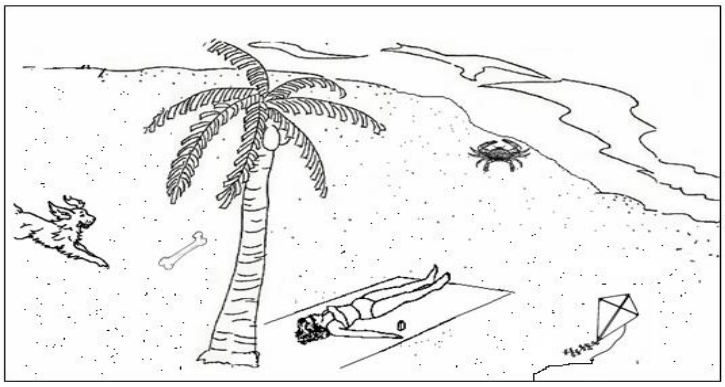
TOTAL SCORE:

*Refer to scoring table

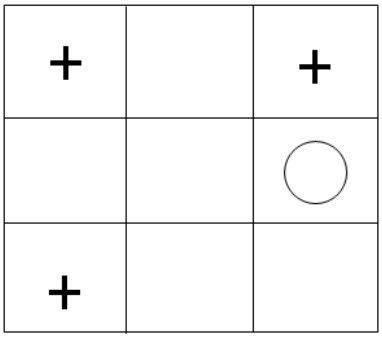
Visual Cognitive Assessment Test (VCAT)

Picture Page

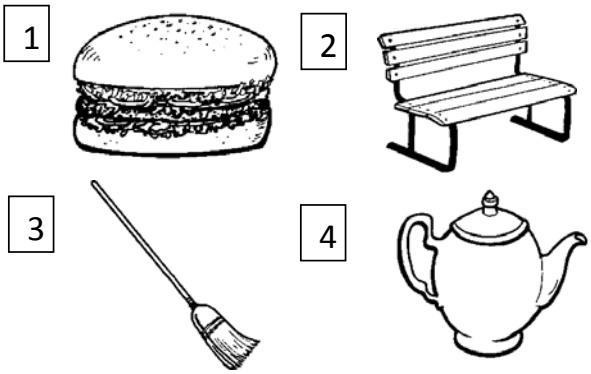
Memory: Scenario



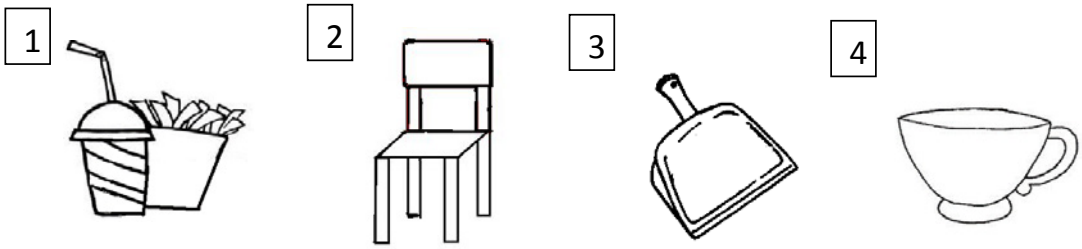
Memory: Shapes



Memory: Objects



Memory: Objects (Cues)



Scoring Table

Visuospatial: *Grid* In 30s, 0 – 3 correct boxes = 0 point 4 – 5 correct boxes = 1 point 6 (All) correct boxes = 2 points	*Memory: Shapes* 0 – 1 shape and position correct = 0 point 2 – 3 shape and position correct = 1 point 4 (All) shape and position correct = 2 points
	Executive function: Gears Both gears wrong = 0 point Either 1 of the gears correct = 1 point 2 gears correct = 3 points
Language: Fluency 8 – 10 vegetables = 1 point 11 or more vegetables = 2 points	*Attention/ Working Memory* 3 or more errors = 0 point 2 errors = 1 point 0 -1 error = 3 points

Expert essay

Language in normal ageing and dementia

Paolo Vitali

McGill University Research Centre for Studies in Aging, CANADA

Older adults may consult their primary healthcare professional with atypical or unexpected cognitive symptoms. If not adequately acknowledged, there is a risk these will not be addressed in a timely manner. For example, acquired language deficits (aphasia) are frequently underestimated by the general practitioner who is typically more concerned by the individual's memory issues. However, word-finding concerns are among the most frequent complaints in the normal ageing population (1). While occasional verbal difficulties are common occurrences in the healthy ageing process and usually characterise as a benign phenomenon, progressive deficits in motor speech, language production and comprehension with a significant functional impact may represent symptomatic manifestations of specific neurodegenerative processes. In general, healthy ageing is associated with the preservation or even the expansion of vocabulary skills, even if lexical retrieval tends to be slower. Sentences are usually shorter and less grammatically complex. Oral production is characterised by frequent hesitations and fillers. There is an increased use of indefinite words, and the tip-of-the-tongue phenomenon is pervasive (2–3). In addition, other age-related confounding factors such as hearing and vision difficulties, medications, and multifactorial articulation inaccuracy could negatively affect verbal communication. Nevertheless, a significant halted, circumlocutory, not informative speech, with many pauses as well as sound and word transformations (paraphasias), is definitively abnormal, and deserves further investigation. In addition, while struggling to name a famous actor is generally not worrisome, forgetting the names of family members or common objects is very unusual. Moreover, progressive recurrent difficulties in following conversations, especially in the context of multiple speakers, or understanding a televised newscast could represent a verbal comprehension impairment.

Obviously, investigating how these aphasic symptoms began is essential to determine their underlying aetiology, (causes or origins), to correctly orientate clinical management. A sudden onset in a previously asymptomatic person is likely the manifestation of an acute cerebrovascular accident (stroke); a subacute progressive process could be due to a space-occupying brain lesion (tumours or abscesses), while more chronic, slowly progressive difficulties are generally related to neurodegenerative conditions (dementia).

It is worth noting that there is growing clinical evidence that specific language difficulties may be one of the most sensitive cognitive biomarkers of conversion in individuals with mild cognitive impairment (4) (namely semantic fluency and naming impairments) to Alzheimer's disease and in normal controls (5). Furthermore, besides Alzheimer's disease, language deficits are present in multiple dementia syndromes where word-finding impairment and some semantic decline are especially evident, but also in dementia with Lewy bodies, vascular dementia (lexical retrieval deficit), and corticobasal disease (motor speech impairment). Similarly, language disorders are the core clinical feature of primary progressive aphasias, a heterogeneous group of neurodegenerative diseases that affect an individual's ability to effectively communicate. In essence, this is a rare nervous system syndrome with symptoms manifesting distinctive language impairments in a gradually and progressively manner (6).

Generally, three major primary progressive aphasia variants are described in the literature, each one with a specific dysfunctional language profile (7).

Nonfluent-agrammatic variant (nfv-PPA): Characterised by a person's struggle to pronounce and get words out correctly, this apraxia of speech chiefly presents with sound distortions, slowed articulation or changes in prosody for articulatory complex words and/or agrammatism where telegraphic speech may be used with preserved word meaning.

Semantic variant (sv-PPA): Characterised by a pervasive decline in understanding the meaning of words, concepts and as well as naming familiar people, places or objects, this severe anomia presents with semantic paraphasias and preservation of motor speech and sentence repetition.

Logopenic variant (lvPPA): Characterised by an individual's increased difficulty in finding the words they want to use, this variant presents with hesitant verbal production, phonological paraphasias, and deficits in long sentence repetition due to phonological working memory difficulties. Word meaning and semantics are preserved.

It is imperative to accurately determine the abnormal language profile in a PPA individual as the three PPA variants represent different neurodegenerative diseases with distinct

neuropathological findings. nfvPPA is principally a tauopathy, sv-PPA is associated with TDP-43 type C pathology, and lv-PPA with Alzheimer's disease neuropathological changes (8). Implications for genetics analysis, disease progression, language and pharmacological therapies, access to clinical trials, are unique for the three variants.

It is thus crucial for primary healthcare providers to be sensitive to language concerns from individuals and their families and to be able to differentiate between normal age-related and pathological changes in verbal skills. Some simple tasks can be useful in identifying language deficits in symptomatic people: picture naming, word and sentence repetition, regular and irregular word spelling, verbal fluency, motor speech, and single word comprehension (semantics). In Canada, a quick screening tool that could be used during routine clinic visits to accurately assess language disorders in neurodegenerative diseases has recently been developed (9). Norms for the Detection Test for Language Impairments in Adults and the Aged (DTLA) were obtained from a sample of 545 healthy, community-dwelling, French-speaking adults from four French-speaking countries (Belgium, Canada (Quebec), France, and Switzerland). The translation and validation of the test in English and in other languages are currently ongoing.

The use of DTLA or other screening tools in a clinic setting has the potential to positively impact the early diagnosis of neurodegenerative disease in individuals, more particularly, those whose language is affected early on. Ultimately, the guiding principle here is to be able to fast-track both medical attention as well as access to services tailored to their individual circumstances.

Indeed, though there is currently no definitive cure for neurodegenerative aphasic syndromes, bear in mind that current multiple non-pharmacological approaches could dramatically improve an aphasic individual's quality of life, including, but not limited to, the adoption of alternative, non-verbal communication strategies, meditation for stress and anxiety reduction, participation in support groups and regular physical activity.

References

1. Martins IP, Mares I, Stilwell PA. How subjective are subjective language complaints. Eur J Neurol. 2012;19(5):666–71.
2. Glisky E. Changes in Cognitive Function in Human Aging. In: Riddle DR. Brain Aging: Models, Methods, and Mechanisms. Boca Raton, FL: CRC Press/Taylor & Francis; 2007. p. 3–20.
3. Craik FIM, Bialystok E. Cognition through the lifespan: Mechanisms of change. Mem Attention, Aging Sel Work Fergus I M Craik. 2016;10(3):158–73.
4. Jokel R, Seixas Lima B, Fernandez A, Murphy KJ. Language in Amnestic Mild Cognitive Impairment and Dementia of Alzheimer's Type: Quantitatively or Qualitatively Different? Dement Geriatr Cogn Dis Extra. 2019;9(1):136–51.
5. Eyigoz E, Mathur S, Santamaria M, Cecchi G, Naylor M. Linguistic markers predict onset of Alzheimer's disease. EClinicalMedicine. 2020;28.
6. Mesulam M. Slowly progressive aphasia without generalized dementia. Ann Neurol. 1982;11:592.
7. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology [Internet]. 2011;76(11):1006–14. https://dx.doi.org/10.1212/wnl.0b013e31821103e6
8. MacKenzie IRA, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, et al. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: An update. Acta Neuropathol. 2010;119(1):1–4.
9. Macoir J, Fossard M, Lefebvre L, Monetta L, Renard A, Tran TM, et al. Detection Test for Language Impairments in Adults and the Aged – A New Screening Test for Language Impairment Associated with Neurodegenerative Diseases: Validation and Normative Data. Am J Alzheimers Dis Other Demen. 2017;32(7):382–92.

Conclusions

Cognitive assessment has long relied on the enduring tests that most clinicians are accustomed to using as measurement tools. These include the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). However, in this changing world, one that is experiencing both a growth in the ageing population and the wrath of a global pandemic, clinicians have had to adapt to these circumstances.

These well-established tests were developed in Western countries and employ in-person assessment with English as the primary language. These parameters limit their use in other countries as well as hinder vulnerable older adults living with dementia from visiting their healthcare professional because of imposed pandemic restrictions. Hence, the rapid introduction of telemedicine to remotely administer these assessments, an alternative that most clinicians favour.

While telemedicine has facilitated the implementation of remote cognitive evaluation, there exist certain constraints such as ensuring the collected information is based on informed verbal consent, safe digital environments, and respects the individual's confidentiality. Other barriers such as educational, cultural, sociodemographic considerations should factor into the decision to administer a test remotely.

While videoconferencing does allow for the presentation of visual stimuli or behavioural observations, unlike a consultation over the telephone, it is critical that any remote approach be unbiased across race, ethnicity, educational attainment, language and sensorimotor abilities. Equitable access to remote cognitive assessment irrespective of disease stage and level of carer support is critical. Therefore, there is a concerted effort underway to overcome language and cultural barriers with the development of new tests such as the Cross-Cultural Dementia Screening (CCD) test and the Visual Cognitive Assessment Test (VCAT). This brings to the forefront the idea that an international effort to form large multi-centre cohorts by pooling cognitive and biomarker data from institutions across the world to study the pathophysiology of neurocognitive diseases is needed.

Additional references

1. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res [Internet]. 1975 [cited 2021 Jul 8];12(3):189–98. https://pubmed.ncbi.nlm.nih.gov/1202204/
2. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc [Internet]. 2005 [cited 2021 Jul 8];53(4):695–9. https://pubmed.ncbi.nlm.nih.gov/15817019/
3. Geddes MR, O'Connell ME, Fisk JD, Gauthier S, Camicioli R, Ismail Z. Remote cognitive and behavioral assessment: Report of the Alzheimer Society of Canada Task Force on dementia care best practices for COVID-19 [Internet]. Vol. 12, Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring. Alzheimers Dement (Amst); 2020 [cited 2021 Jul 8]. https://pubmed.ncbi.nlm.nih.gov/32999916/

Chapter 7
Preliminary diagnosis of cognitive decline

Serge Gauthier

Key points

- The clinical diagnosis of dementia is usually determined in the primary healthcare setting.
- An investigation is subsequently conducted to determine the cause of dementia.
- At the primary level, treatable causes of cognitive decline should be identified.
- Specialised assessment and advanced biomarker studies should be conducted in individuals with atypical, early-onset and rapidly progressive dementias.

General background

The diagnostic process is a journey, and it starts at the first medical appointment where the primary goal is to summarise the progression of the person's memory and thinking problems, from the beginning to present-day. This consists of having the individual experiencing forgetfulness and a knowledgeable informant (carer, family member or friend) relate their experiences and observations about changes in memory, thinking, and personality over the past few years. Through careful questioning, the consultation aims to identify what cognitive or behavioural problems the individual has undergone, when these changes were initially perceived and how they have declined since that time. The healthcare professional will then assess memory, thinking and mood using standardised questionnaires as well as conduct a physical examination. Supplementary questions are meant to ascertain any limitations their cognitive problems have imposed on their activities of daily living. This information will help to determine whether the person has dementia as well as orient and design an investigation plan to determine its cause. When necessary, the healthcare professional will request blood tests and a brain scan to exclude other treatable causes of cognitive decline. There are several scenarios to consider once the clinical assessments and laboratory tests are completed and reviewed. From a practical perspective, distinguishing between a typical case of a person with dementia from those who may benefit from additional assessment tests available in specialised centres is imperative.

Survey results

The 1,111 multidisciplinary clinicians who participated in the survey unanimously indicated that clinical history, cognitive testing, and a physical examination were all valued components of a routine clinical assessment to determine dementia. Despite 12% of diagnoses occurring in a single visit, given the multiple facets involved in the diagnostic process, most agreed that it takes more than one visit to diagnose dementia.

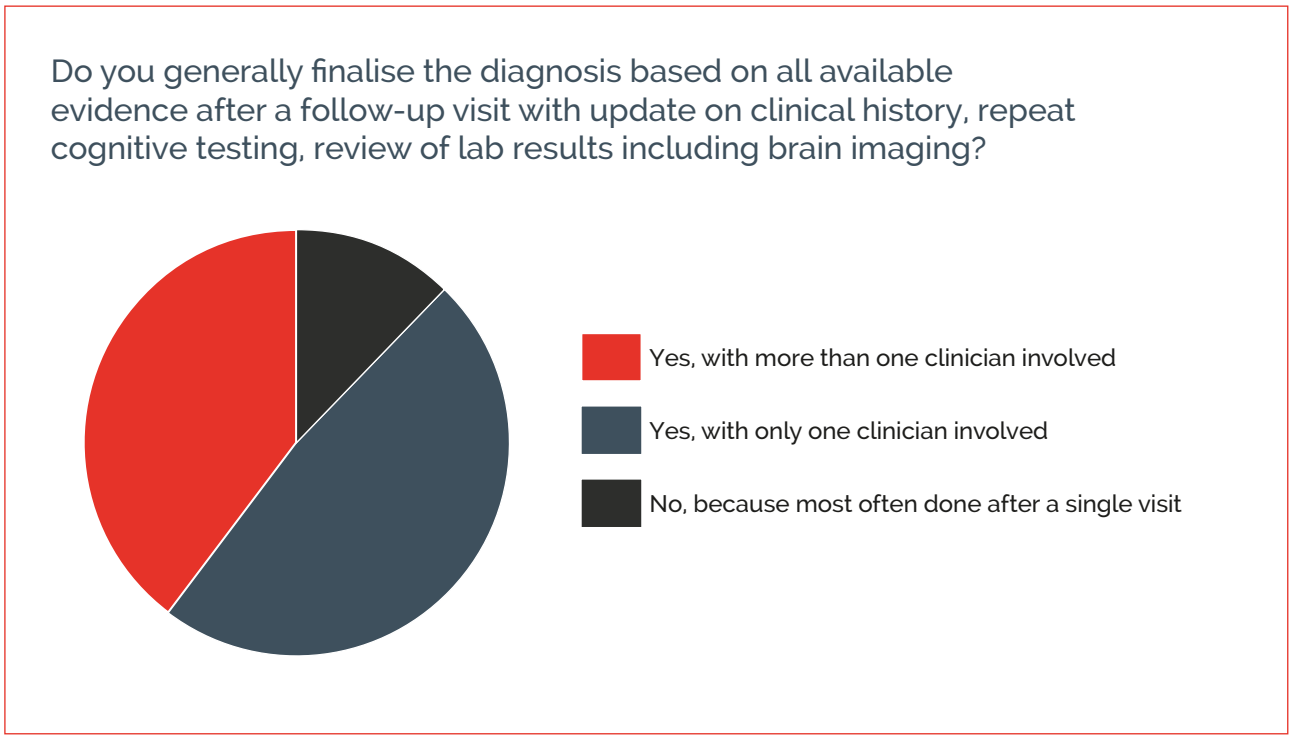


Chart 1. Clinician responses.

Medical history and clinical examination

As life expectancy around the world continues to rise, it is critical that clinicians become comfortable with the process of diagnosis, counselling, community and specialist referral, as well as pharmacological and non-pharmacological treatment options. Indeed, early diagnosis may allow for the identification of reversible causes, improved symptom management, and planning for the future. Cognitive decline may be part of normal ageing. Several genetic, socio-economic, cultural, and environmental factors contribute to a faster rate of age-related cognitive decline in healthy individuals. However, abnormal cognitive decline suggests the presence of a brain disease.

When a person presents with amnestic complaints, those characterised by an impairment to learn or recall new information, clinicians must consider differential diagnoses, among them dementia, delirium, depression, or psychosis. Comprehensive evaluations in specialised centres provide additional insight and corroborating evidence of a health concern or preliminary diagnosis. That is why people with atypical, young-onset and rapidly progressive symptoms benefit from these ancillary assessments. These centres have the expertise to guide the subsequent steps of the diagnostic journey in complex cases (1,2).

Past medical history should include learning disabilities, psychiatric disorders, alcohol or recreational drug abuse and risk factors of cerebrovascular disease. In addition to the routine review of systems, one should methodically investigate sleep abnormalities (hallucinations, sleep apnoea, somniloquy, patterns of movements or agitation), and endocrine. A complete drug history may reveal undesired interactions. Any family history of psychiatric and neurodegenerative conditions should also be systematically recorded. Finally, the clinical examination should include precise cardiovascular and neurological assessments.

Following a routine assessment (refer to Chapters 3–6), a preliminary diagnosis of an individual with cognitive complaints is based on the convergence of the information acquired. This inclusive and multidimensional perspective includes the (1) medical history (2) cognitive screening, (3)

functional assessments, (4) neuropsychiatric assessments, as well as the (5) physical examination. Collectively, data provide the basis for classifying whether the cognitive complaints the individual described are clinically significant, associated with mood changes and/or interfere with their daily activities.

Based on the results of the cognitive screening, a person may be considered cognitively unimpaired or impaired. Assessment of daily living activities, or functional skills, provides evidence of decline from a previous level of independence and autonomy in tasks such as managing finances, driving, participation in social and family activities, as well as household tasks.

Individuals with progressive cognitive complaints without deficits are characterised as having subjective cognitive decline. Individuals receive the diagnosis of mild cognitive impairment when their cognitive screening is abnormal, but their daily living activities remain unaltered or only minimally altered (3,4). People receive a dementia diagnosis when the screening tests indicating more than one cognitive abnormality are accompanied by a loss of independence or autonomy. It is important to emphasise that the diagnosis of mild cognitive impairment or dementia assumes that no other acute systemic or psychiatric condition that can explain the person's cognitive or functional abnormalities (1).

The determination of a person's dominant cognitive deficit, their respective age at onset and the rate of progression all provide the foundation to determine whether they have a typical or atypical presentation of cognitive decline. Typical dementia is characterised by slow and progressive cognitive decline with forgetfulness and difficulties retaining new information being the prevailing symptoms. This necessarily imposes significant limitations on an individual and highlights the uncertainty surrounding their ability to maintain their autonomy. Typical dementia is usually managed at the primary care level, as nearly 80% of people are diagnosed with Alzheimer's disease.

Atypical dementia designates those individuals where clinical presentation is dominated by non-memory deficits affecting language, behaviour, executive function, complex attention, perceptual-motor and social cognition. Early-onset dementia specifies those whose symptoms start before 65 years of age. Rapidly progressive dementia designates people whose decline within the MMSE parameters exceeds 3 points in 6 months. As a larger number of disease processes can cause atypical, early-onset or rapid progressive dementias, an accurate diagnosis is imperative for guiding families regarding prognosis. In summary, people with atypical, early-onset and rapidly progressive dementias require advanced diagnostic tests in specialised centres.

At the end of the preliminary assessment, healthcare professionals should indicate whether the patient has a normal cognition, mild cognitive impairment, a typical or an atypical dementia. The possible outcomes of the preliminary assessments are summarised in Table 1.

Table 1. Preliminary diagnosis of decline

Preliminary diagnosis	History				Basic assessments			Specialised assessments
	Age at onset	Clinical course	Dominant symptom	Psychiatric symptoms	Cognitive screening	Functional assessments	Clinical examination	
SCD		slow	memory	one or mild	normal	normal	normal	not necessary
MCI	65 +	slow	memory	none or mild	abnormal	minimal impact	normal	not necessary
Typical presentation	65 +	slow	memory	none or mild	abnormal	loss of autonomy	normal	not necessary
Atypical presentation	< 65	fast or stepwise	language behaviour executive function, complex attention, perceptual-motor, social cognition	none or mild or severe	normal/ abnormal	loss of autonomy	normal/ abnormal	recommended

Subsequent laboratorial evaluations to be conducted at primary care level

At the primary care level, it is important to rule out treatable causes of cognitive decline. These causes may include stroke, chronic subdural haematoma; meningitis, encephalitis, abscess; medication side effects or toxicity; vitamin B12, thiamine, or niacin deficiency; metabolic disorders such as hypothyroidism, hepatic encephalopathy, hypercalcemia, hyper- and hypoglycaemia, hyper- and hyponatremia. syphilis, HIV, accidental exposure to toxic substances, substance abuse, delirium; primary psychiatric conditions; or brain tumours. The frequency of treatable cases of cognitive decline might change depending on cultural, social economic and geographical circumstances (5).

Laboratory testing

A universal list of laboratory tests that can exclude reversible causes of dementia remains a matter of debate given the absence of studies conducted on a global level. The economic and medical impact of these tests is discussed in Chapter 12. Apart from a complete blood count, screening for vitamin B12 deficiency and hypothyroidism, additional tests such as screening for neurosyphilis and HIV should be ordered depending on the clinical history and specific cultural socioeconomic and geographic circumstances (refer to Chapter 8). The same reasoning is applicable for electrolytes, liver, kidney function panels as well as screening for hyperlipemia and diabetes (Chapter 8).

Neuroimaging

Structural neuroimaging obtained with either head Computed Tomography (CT) or Magnetic Resonance Imaging scans identify focal brain atrophies, the hallmark of neurodegenerative conditions. There is a consensus regarding the importance of CT or MRI scans at the primary care level for assessing people with possible cerebrovascular disease or atypical, rapidly progressive or early-onset dementia cases. However, neuroimaging for typical dementia assessments is not universally supported given its high cost and limited availability in certain low- and middle-income countries (refer to Chapter 9).

Specialised neuropsychological and speech assessments

After ruling out the presence of other diseases that may exacerbate dementia symptoms, it is plausible to request specialised care for patients with the atypical (non-amnestic) presentation of dementia, given the complexities associated with the diagnosis and management of these cases. The same is applicable for young-onset and rapid progressive cases. Dementia specialised centres or memory clinics have the expertise to guide the subsequent steps of the diagnosis journey in complex cases.

Specialised neuropsychological and speech assessments

Formal neuropsychological assessment testing is recommended to further characterise cognitive deficits in memory, language, behaviour, executive function, complex attention, perceptual-motor or social cognition. A complete neuropsychological assessment quantifies deficits not fully revealed by the routine cognitive screening tests. Speech-language assessments are relevant for detailing language deficits and speech abnormalities in people with primary progressive aphasia (6–8).

Specialised genetic assessments

There are a few scenarios where genetic assessments are required to corroborate a dementia diagnosis. In fact, numerous instances of dementia diagnosis within a family frequently prompts a cognitively impaired or unimpaired individual to seek a medical consultation. An autosomal dominant familial gene pattern justifies a genetic assessment. Another common situation may be that clinicians are asked to provide guidance regarding results obtained from direct-to-consumer genetic testing (9).

Biomarkers

Biomarkers are biological measures that detect the presence of a disease process causing dementias (10). These special biomarker laboratory tests can be obtained using Positron Emission Tomography (PET scans; Chapter 10), Single-photon Emission tomography (SPECT, Chapter 13), analysis of the cerebrospinal fluid (Chapter 11) and more recently, blood tests (Chapter 13). Biomarkers indicate the degenerative process present in the brain of people with dementia. In some countries, dementia biomarker tests have been approved for clinical use under specific Appropriate Use Criteria (AUC). In general, these clinically approved tests can identify the presence of amyloid plaques, neurofibrillary tangles, or dementia-related brain injury.

Conclusions

The clinical diagnosis of dementia is reached at the primary healthcare setting. It starts with medical history, questioning the person with dementia about symptoms, and the person accompanying them to the appointment about observed cognitive changes and conducting a physical examination. From there, the assessment may include screening for cognitive deficits, psychiatric symptoms and a function-focused approach regarding the extent of the individual's abilities to perform activities of daily living. A primary care clinician may request blood screening and neuroimaging to rule out treatable causes of cognitive decline.

While the vast majority of individuals will remain, and receive treatment, in the primary care setting, those who present with atypical dementia symptoms, early-onset or rapidly progressive dementias benefit from additional assessments in specialised centres. At the end of the preliminary assessment, healthcare professionals should indicate whether the person has a normal cognition, mild cognitive impairment, a typical or an atypical dementia.

In the prospects for upcoming disease-modifying interventions for dementia, biomarkers may become an important tool for primary care. Biomarker testing including PET, SPECT and even blood tests are significant indicators of the degenerative process occurring in the brain and clinical use of these tests at the primary care level for dementia diagnosis are promising for forthcoming therapies.

Additional references

1. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement [Internet]. 2011 [cited 2021 Jul 8];7(3):263–9. https://pubmed.ncbi.nlm.nih.gov/21514250/
2. Nakamura A, Kaneko N, Villemagne VL, Kato T, Doecke J, Doré V, et al. High performance plasma amyloid-β biomarkers for Alzheimer's disease. Nature [Internet]. 2018;554(7691):249–54. https://doi.org/10.1038/nature25456
3. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement [Internet]. 2011 May 1 [cited 2021 Jul 19];7(3):270–9. https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1016/j.jalz.2011.03.008
4. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement [Internet]. 2011 May 1 [cited 2021 Jul 19];7(3):280–92. https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1016/j.jalz.2011.03.003
5. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. JAMA – J Am Med Assoc [Internet]. 2019 Oct 22 [cited 2021 Jul 9];322(16):1589–99. https://pubmed.ncbi.nlm.nih.gov/31638686
6. Botha H, Josephs KA. Primary progressive aphasias and apraxia of speech. Contin Lifelong Learn Neurol. 2019;25(1):101–27.
7. Krein L, Jeon YH, Amberber AM, Fethney J. The Assessment of Language and Communication in Dementia: A Synthesis of Evidence. Am J Geriatr Psychiatry [Internet]. 2019;27(4):363–77. https://dx.doi.org/10.1016/j.jagp.2018.11.009
8. Warren JD, Warrington EK. Chapter 14 Cognitive Neuropsychology of Dementia Syndromes. Vol. 30, Blue Books of Neurology. ; p. 329-80: Elsevier; 2007. 329–380 p.
9. Koriath CAM, Kenny J, Ryan NS, Rohrer JD, Schott JM, Houlden H, et al. Genetic testing in dementia – utility and clinical strategies. Nat Rev Neurol [Internet]. 2021;17(1):23–36. https://dx.doi.org/10.1038/s41582-020-00416-1
10. Hansson O. Biomarkers for neurodegenerative diseases [Internet]. Vol. 27, Nature Medicine. Nature Publishing Group; 2021 [cited 2021 Jul 12]. p. 954–63. https://www.nature.com/articles/s41591-021-01382-x.

Part II
Laboratory tests

Chapter 8
General laboratory tests

José A. Morais

Key points

- The performance of general blood tests is an important step in the diagnostic process to rule out causes of cognitive changes.
- The list of blood tests is comparable to an annual general assessment for health status in mid or late life.
- Specific tests may be added based on findings from the general physical examination.

General background

The selection of blood tests for the average person over the age of 65 with symptoms suggestive of dementia are predominantly based on that person's medical history and, to some degree, on the physical examination. For instance, nearly everyone gets a screening test for hypothyroidism using the Thyroid Stimulating Hormone test, but the finding of a goitre (enlarged thyroid gland on palpation of the neck) during the physical exam may require additional tests such as an ultrasound. Similarly, a murmur heard over the carotid artery usually leads to an ultrasound study.

In guidelines established since 1991, there is a minimal set of blood tests used by most clinicians around the world (Table 1). Over time, guidelines evolve as additional information emerges and the general health of populations evolve. At the time of writing, a major update is expected from a US consensus group led by Drs. Alireza Atri and Brad Dickerson.

> **“** There is a need to have an individual approach for each person, rather than having long lists of tests for everyone that add costs without adding clinically meaningful information.

Table 1. General laboratory tests recommended in published guidelines

	Ref 1 1991	Ref 2 1994	Ref 3 1994	Ref 4 1995	Ref 5 1996
CBC	XX	XX	XX	XX	XX
Sed rate				XX	
TSH	XX	XX	XX	XX	XX
T4			XX		XX
Electrolytes	XX	XX	XX	XX	XX
Calcium	XX	XX	XX	XX	XX
BUN		XX	XX	XX	XX
Creatinine		XX	XX	XX	XX
Glycemia	XX	XX	XX		XX
ALT			XX	XX	XX
B12	Added in 1999	XX	XX	XX	XX
Folate		XX			
Syphilis serology		XX	XX	XX	XX
HIV screen				XX	

Survey results

The 1,111 multidisciplinary clinicians who answered the survey were asked which blood tests they ordered most often in an individual's workup presenting with cognitive decline. In order of frequency, they were B12/folate (87%), TSH (87%), hemogram (77%), electrolytes including calcium (73%), BUN/creatinine (77%), liver enzymes ALT/AST (61%), HbA1C (54%), VDRL (43%) and homocysteine (20%), which can be used to rule out cognitive decline resulting from other causes.

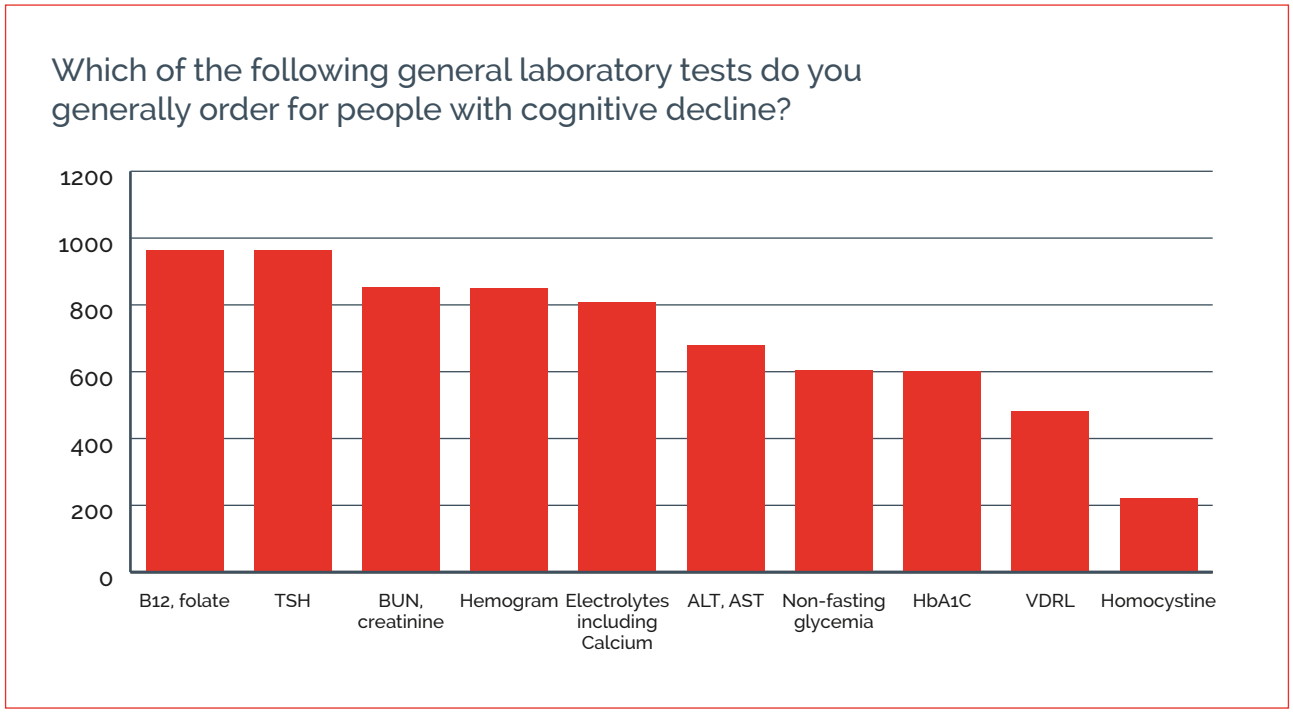


Chart 1. Clinician responses (multiple answers selected).

Expert essay

Routine laboratory tests in the diagnosis of dementia

Lucas Porcello Schilling

Brain Institute of Rio Grande do Sul (BraIns), Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, BRAZIL

As discussed in the first part of this World Alzheimer Report, the syndromic diagnosis of dementia is based on clinical criteria, requiring an impairment in at least two cognitive domains and impact on the individual's functionality. Different aetiologies can lead to a clinical picture of dementia, some of which, such as Alzheimer's disease, are related to degenerative processes of the central nervous system. However, there are several other clinical and sometimes potentially reversible causes of cognitive impairment which should be evaluated in an initial assessment for dementia.

Within this scenario, a detailed initial clinical evaluation is essential to attain an accurate clinical diagnosis. The initial assessment seeks also to identify the presence of comorbidities and other risk factors for the development and progression of dementia. There is no evidence-based data that justify carrying out specific routine blood tests; however, most expert opinion recommends a laboratory screening for secondary causes of cognitive decline (1,2).

The performance of blood tests is an important step in the evaluation process, and seeks to rule out clinical causes (metabolic, infectious, vitamin deficiencies and electrolytic abnormalities) that may be associated with an individual's clinical condition. This laboratory screening includes a haematological evaluation, kidney, liver and thyroid function, glucose, electrolyte evaluation, vitamin levels and inflammatory and infectious blood markers (3,4).

The list of specific screening tests includes complete blood count with platelet count, serum creatinine and urea concentration, glucose, glycated haemoglobin, lipid profile, albumin, liver assessment with transaminases and prothrombin time, electrolyte measurement (sodium, potassium and calcium), thyroid hormones, vitamin B12 and folic acid measurement (in countries without folate flour fortification), erythrocyte sedimentation rate and C-reactive protein. It is also suggested to carry out screening tests for the main infections, especially in people under the age of 60, such as syphilis, HIV and hepatitis B and C (5,6).

The performance of some of those routine blood tests helps to rule out prevalent conditions, such as diabetes mellitus and dyslipidaemia, which can lead to vascular cognitive impairment and worsen neuropathological conditions as Alzheimer's disease. These laboratory tests also allow the identification of important clinical issues that can lead to cognitive decline, such as hepatic and kidney failure. Some others dementia aetiologies are not as prevalent, however, since they can have specific and possibly curative treatment – as neurosyphilis – its inclusion into this initial routine laboratory assessment is justified.

It is very important to emphasise that an individual's clinical history is the key to defining which exams and investigation should be performed. In cases considered atypical or early-onset, further tests may be necessary. If a person has a previous history of any pathology or any symptoms suggestive of other diseases, such as weight loss or characteristics of inflammatory diseases, further investigation with more specific tests would be recommended (7–9).

References

1. Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, Relkin N, et al. Practice parameter: Diagnosis of dementia (an evidence-based review): Report of the quality standards subcommittee of the american academy of neurology. Neurology [Internet]. 2001 May 8 [cited 2021 Jul 8];56(9):1143–53. https://pubmed.ncbi.nlm.nih.gov/11342678
2. Nitrini R, Caramelli P, De Campos Bottino CM, Pereira Damascene B, Dozzi Brucki SM, Anghinah R. Diagnosis of Alzheimer's disease in Brazil: Diagnostic criteria and auxiliary tests. Recommendations of the Scientific Department of Cognitive Neurology and Aging of the Brazilian Academy of Neurology [Internet]. Vol. 63, Arquivos de Neuro-Psiquiatria. Academia Brasileira de Neurologia – ABNEURO; 2005 [cited 2021 Jul 8]. p. 713–9. http://www.scielo.br/j/anp/a/zJ8nq5mDBV8V4hfrqDMVzbx/?lang=pt
3. Van Der Flier WM, Scheltens P. Epidemiology and risk factors of dementia [Internet]. Vol. 76, Neurology in Practice. BMJ Publishing Group Ltd; 2005 [cited 2021 Jul 8]. p. v2–7. https://jnnp.bmj.com/content/76/suppl_5/v2
4. Hort J, O'Brien JT, Gainotti G, Pirttila T, Popescu BO, Rektorova I, et al. EFNS guidelines for the diagnosis and management of Alzheimer's disease [Internet]. Vol. 17, European Journal of Neurology. Eur J Neurol; 2010 [cited 2021 Jul 8]. p. 1236–48. https://pubmed.ncbi.nlm.nih.gov/20831773
5. Clarfield AM, Bass MJ, Cohen C, Feightner JW, Gauthier S, Patterson C, et al. Assessing dementia: The Canadian consensus [Internet]. Vol. 144, CMAJ. Canadian Medical Association; 1991 [cited 2021 Jul 8]. p. 851–3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1335280
6. Rossor MN. Management of neurological disorders: dementia. J Neurol Neurosurg Psychiatry [Internet]. 1994 [cited 2021 Jul 8];57(12):1451. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1073222
7. Practice parameter for diagnosis and evaluation of dementia. (summary statement) Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology [Internet]. 1994 [cited 2021 Jul 8];44(11):2203–6. https://pubmed.ncbi.nlm.nih.gov/7969988
8. Corey-Bloom J, Thai LJ, Galasko D, Folstein M, Drachman D, Raskind M, et al. Diagnosis and evaluation of dementia [Internet]. Vol. 45, Neurology. Neurology; 1995 [cited 2021 Jul 8]. p. 211–8. https://pubmed.ncbi.nlm.nih.gov/7854514
9. Geldmacher DS, Whitehouse PJ. Evaluation of Dementia. N Engl J Med [Internet]. 1996 Aug [cited 2021 Jul 8];335(5):330–6. https://pubmed.ncbi.nlm.nih.gov/8663868

Conclusions

There is a consensus that using laboratory tests as complementary tools to a standard cognitive evaluation is necessary to determine whether there are any treatable medical conditions that may affect cognition.

Basic laboratory tests are most often performed immediately after the initial clinical assessment, and clinically significant findings such as low B12 bring about replacement therapy that may help one component of the dementia pathophysiology.

Chapter 9
Brain imaging using CT and MRI

Pedro Rosa-Neto

Key points

- Head magnetic resonance imaging (MRI) or computed tomography (CT) should be considered as part of the initial laboratory evaluation of dementia.
- Structural imaging serves primarily to rule out treatable causes of dementia.
- Structural imaging MRI provide insights regarding the underlying causes of dementia.

General background

In people older than 65 years of age, memory and thinking problems are frequently associated with dementia. However, several brain diseases can also cause memory problems. As a result, doctors perform brain scans, such as computed tomography (CT), and/or magnetic resonance imaging (MRI), to rule out other treatable causes for memory and thinking problems. A CT scan uses X-rays to take pictures of the brain. Using powerful magnets, an MRI can provide more detailed brain pictures. Both the CT and MRI are useful in identifying brain tumours, strokes or other problems that might cause memory and thinking problems.

Brain imaging using head CT or MRI

Structural imaging findings assist in the diagnosis of typical dementia by ruling out the comorbidities of treatable dementias or suggest the presence of comorbidities that may exacerbate dementia symptoms, such as cerebrovascular disease. In addition, specific patterns of brain atrophy, ventricular enlargement and change on the MRI signal may suggest the underlying cause of dementia.

CTs are widely available, less costly, and more convenient for assessing people with claustrophobia, agitation or carriers of pacemakers or ferromagnetic devices. Investigation of individuals with dementia symptoms seldom needs contrast agents. The preferred MRI sequences for dementia assessment are a global T1 sagittal to assess atrophy, T2-weighted and fluid-attenuated inversion recovery (FLAIR) images to detect white matter alterations; conventional T2*-weighted gradient recall-echo or susceptibility-weighted imaging to detect signal alterations derived from microbleeds. Finally, diffusion-weighted Imaging, which provides information regarding water restriction associated with inflammation, is particularly useful for Creutzfeldt-Jakob disease (1).

Reduced cerebral volume or atrophy is invariably described in dementia. While brain loss may be a feature of the ageing brain, the term atrophy implies an underlying pathological process. Structurally, atrophy refers to a wide range of findings, including widening of cerebral sulci, gyri volume or grey matter thickness reduction, or the enlargement of the cerebral ventricles or subarachnoid spaces. Even

Table 1. Methods for semi-quantitative description of brain abnormalities in dementia

	Cortical atrophy	Hippocampus atrophy	Deep white matter abnormalities	Periventricular white matter abnormalities
Range	0–3	0–4	0–3	0–3
Preferred MRI sequence	T1	T1	FLAIR	FLAIR

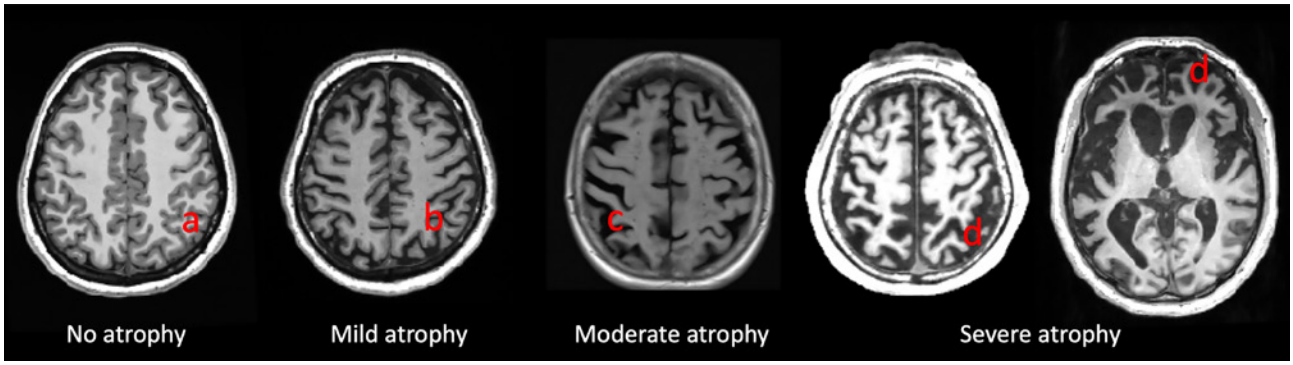


Figure 1. Representation of a series of T1 weighted MRI showing cortical atrophy depicting normal (a), mild (b), moderate (c), and severe (d) cortical atrophy, respectively.

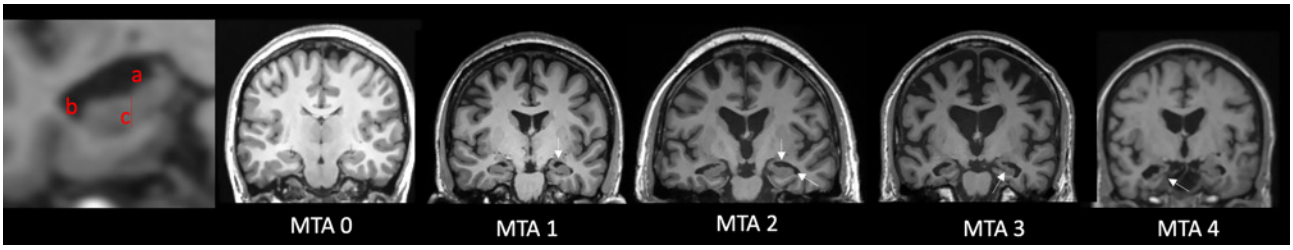


Figure 2. Medial temporal atrophy scores 0–4 indicate medial temporal volume loss. Medial temporal lobe atrophy (MTA) is assessed using a 5-point scale, with scores deduced through assessment of the hippocampal height (c) and width of the choroid fissure (a) and temporal horn (b). For individuals younger than 75 years of age, an MTA score of 2 or more is abnormal, while for subjects older than 75 years of age, an MTA score of 3 or more is abnormal.

though quantitative volumetric measures of global and focal atrophy can be obtained in specialised centres, dementia specialists frequently describe brain atrophy by referring to traditional semi-quantitative visual rating scales (Table 1).

The global cortical atrophy score serves to report mild (opening of sulci), moderate (gyral volume loss), and severe (knife blade) levels of cortical atrophy across cortical regions. The same scale is also useful for reporting various ventricular segments as mild, moderate, and severely enlarged (2,3).

Ventricular enlargement in typical cases is global and proportional to cortical atrophy. When ventricular enlargement seems disproportional to cortical atrophy, one should suspect normal pressure hydrocephalus, particularly in dementia cases associated with incontinence and gait disturbance.

Hippocampal atrophy is part of the repertoire of structural changes observed in typical and atypical dementias. A medial temporal lobe atrophy (MTA) score, also known as Scheltens scale, describes the progression of hippocampal atrophy observed in typical dementia cases based on the coronal T1 weighted MRI reconstructed according to the hippocampal plane. As such, the widening of the choroidal fissure characterises score 1, the widening of the temporal horn characterises score 2, moderate and severe volume loss of hippocampus body characterises scores

3 and 4, respectively. Hippocampal atrophy is associated with a tau load, TDP-43 load, neuronal depletion and other pathophysiological events in the mesial temporal lobe (3,4).

Frontal and temporal lobe atrophy is a hallmark of the frontotemporal dementias, which is a condition associated with multiple pathophysiological processes, including tauopathies (3R, 4R, 3/4R), TDP43 and FUS inclusions. The variability across atrophy patterns seems to be dependent on genetic factors and underlying pathology. Recently, it has been proposed that patterns of brain atrophy observed in frontotemporal dementias and other neurodegenerative conditions follow patterns dictated by physiological brain networks. Methods for assessing frontal lobe atrophy using semi-quantitative visual methods have been summarised elsewhere and are out of the scope of this report (3).

Atrophy in people with the diagnosis of primary progressive aphasia predominates in the left hemisphere. In semantic aphasia, the pattern of atrophy encompasses the anterior ventral and basal temporal lobe, the hippocampus amygdala, and fusiform gyrus. In individuals with non-fluent aphasia, atrophy includes the left inferior frontal, opercular, and insular regions with as well as motor and premotor regions. Atrophy in the basal ganglia, thalamus, and amygdala is frequently observed. The right temporal variant of frontotemporal dementia associated with the behavioural variant of frontotemporal dementia has also been recognised as a distinct syndrome.

Central atrophy – In corticobasal syndrome, atrophy encompass perirolandic regions asymmetrically. Superior frontal, pre-and post- central atrophy are typically accompanied by ipsilateral dilation of the lateral ventricles and basal ganglia atrophy. Corpus callosum atrophy has also been described in corticobasal syndrome (5,6).

Brainstem atrophy and increase signal on T2 – Brainstem atrophy is present in individuals with progressive supranuclear palsy or multiple system atrophy. In progressive supranuclear palsy, an MRI reveals brainstem atrophy, particularly involving the midbrain. Such midbrain atrophy on the midsagittal T1 weighted MRI resembles a hummingbird or a penguin silhouette. On an axial T2-weighted MRI, midbrain atrophy resembles the morning glory flower silhouette. On T1 weighted images, multiple system atrophy individuals show putamen, pons, and middle cerebellar

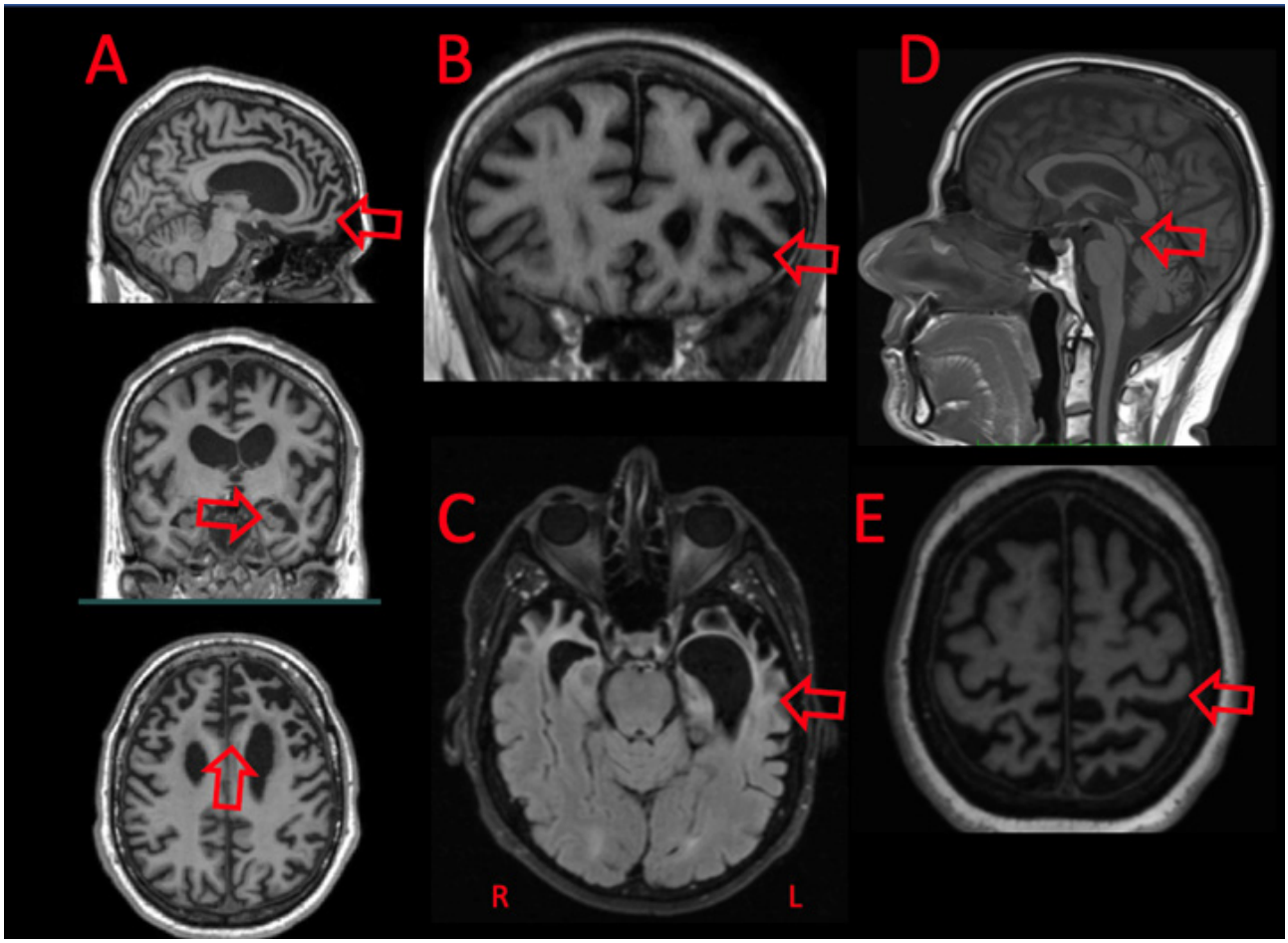


Figure 3. Representative patterns of brain atrophy from a behavioural frontotemporal dementia case (A), non-fluent primary progressive aphasia (B), semantic primary progressive aphasia (C), progressive supranuclear palsy (D) and corticobasal syndrome (E). Arrows represent areas with clinically significant atrophy.

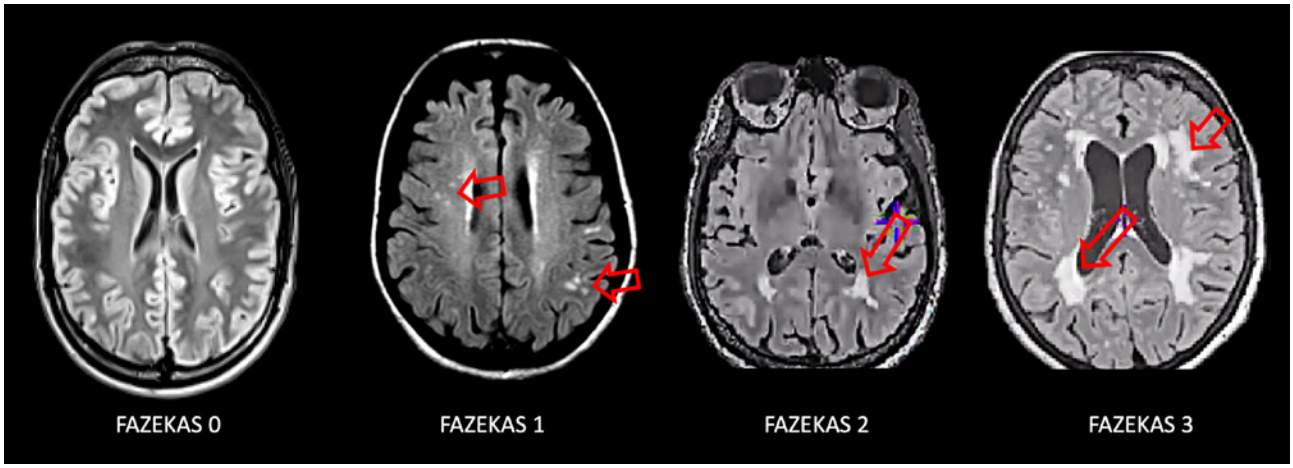


Figure 4. Typical example of Fazekas deep score.

peduncles atrophy. On T2 MRI sequences, the lateral putamen and middle cerebellar peduncles may show hyperintensities. The hyperintense T2 signal in the shape of a cross within the pons of multiple system atrophy patients is called the 'hot cross bun sign'.

T2 and FLAIR hypersignal – Cortical with white matter hyperintensities in T2 and FLAIR can be observed in corticobasal syndrome, posterior cortical atrophy and frontotemporal dementias.

Cerebrovascular disease is a common cause of cognitive impairment and dementia. Imaging manifestations of cerebrovascular disease found in people with dementia include focal areas of infarction or diffuse ischemic changes in the white matter also designates as leukoaraiosis.

T2 weighted imaging and FLAIR MRI have better sensitivity for detecting chronic cerebrovascular abnormalities in dementia. MRI findings associated with vascular cognitive impairment and dementia include cortical and subcortical infarctions and periventricular white matter lesions (see chapter related to cerebrovascular disease) (7).

White matter hyperintensities are lesions on T2-weighted images, mainly in the periventricular regions and in the centrum semiovale. They are the most common abnormalities seen on MRI scans, identified as risk factors for stroke (8). The Fazekas scores provide a semiquantitative reading of the white matter hyperintense lesions attributed to chronic small vessel disease. The Fazekas score is a 4-point score system for assessing periventricular lesions and deep white matter hyperintensities. The absence of a periventricular signal defines score 0, while a periventricular cap of pencil-thin characterises score 1, and a smooth halo illustrates score 2. Periventricular score 3 indicates irregular hyperintensities extending into the deep white matter. The absence of deep periventricular hyperintensities defines the Fazekas score 0, while punctate focal deep hyperintensity characterises score one, and the confluence of hyperintensities illustrates score 2. Large confluent areas of deep white matter hyperintensities describe the score 3.

Lacunes are focal small infarcts with less than 1.5 mm, caused by the atherosclerotic occlusion of deep small vessels. They are the second most common neuroradiological finding associated with vascular brain pathology. On CT scans, lacunar infarcts appear as a small ovoid hypodensity, while on MRI scans, they appear as an ovoid cavity, filled with fluid and hyperintense in T2-weighted images (9,10)

Perivascular spaces, also called Virchow-Robin spaces, are subpial interstitial spaces surrounding the penetrating arteries and arterioles and filled with fluid that follows the course of a vessel through the grey or white matter. Perivascular spaces in the basal ganglia are particularly prominent, with a diameter up to 3–5 mm (11,12).

Gradient echo MRI pulse sequences and susceptibility-weighted imaging show cortical and subcortical microhaemorrhages. They constitute an incidental finding in older individuals. While microhaemorrhages associated with cerebral amyloid angiopathy are observed in cortical areas, those associated with hypertension typically occur in the basal ganglia, thalamus, or pons (13,14).

Diffusion-weighted imaging is mandatory for the care of rapidly progressive dementias. MRI findings in sporadic Creutzfeldt-Jakob disease feature hyperintense signal on DWI, FLAIR, and T2-weighted in the topography of the frontal, parietal and cingulate and insular cortices, head of caudate and putamen. Thalamic hyperintensity resembling a double hockey stick, also called the pulvinar sign, suggests the variant Creutzfeldt-Jakob disease (15–17).

Survey results

Of the 2,327 people with dementia and their carers who completed the survey, neuroimaging with either CT or MRI was an integral part of their dementia patient assessment (Chart 1). However, as indicated by the responses from the 1,111 clinicians, accessibility and costs remain challenges to overcome, particularly in low- and middle-income countries (Chart 2).

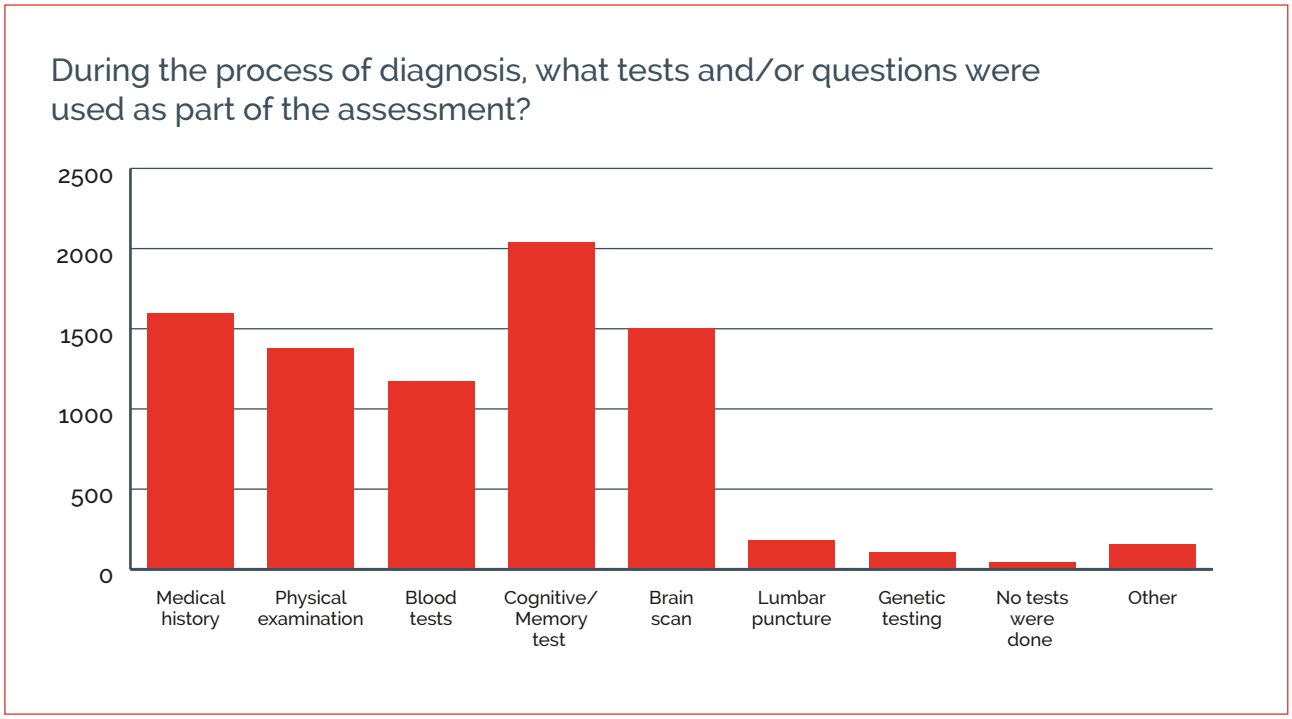


Chart 1. People with dementia and carer responses (multiple answers selected).

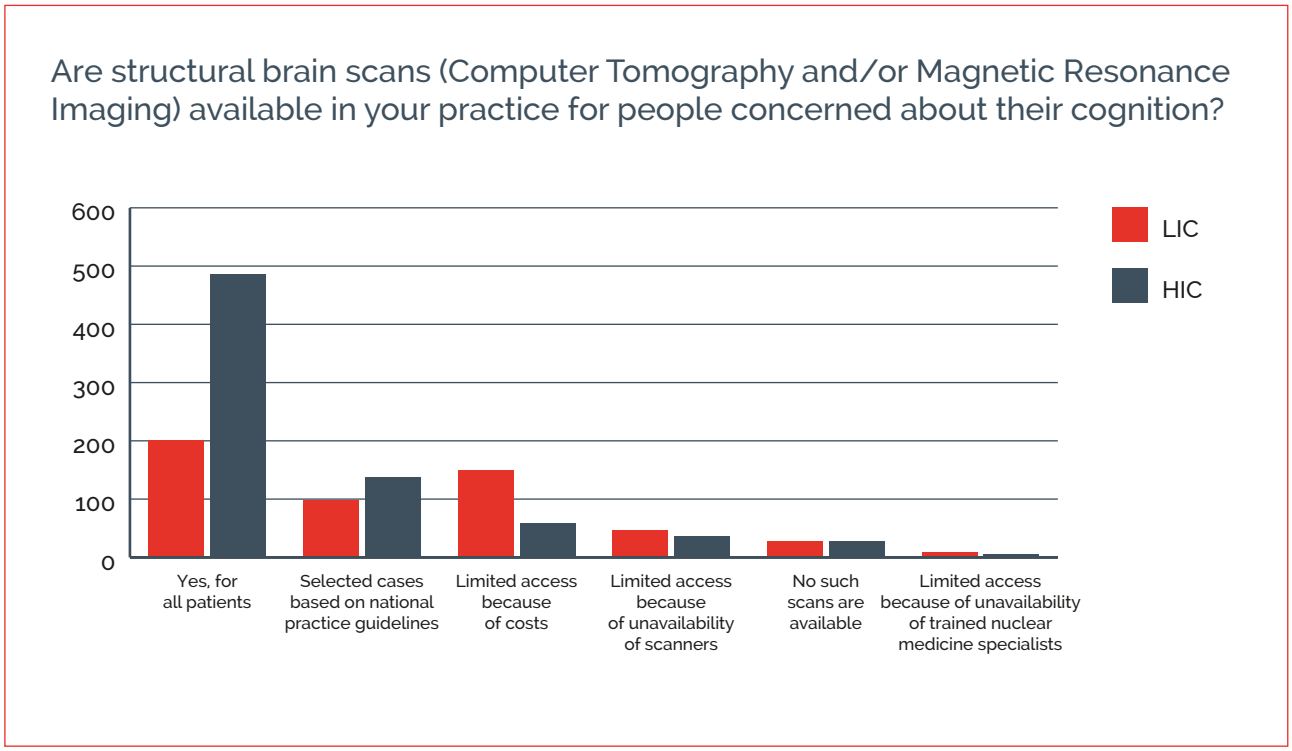


Chart 2. Clinician responses.

Conclusions

As people near the age of 65, instances of memory and thinking problems are often associated with the onset of dementia. Hence the reason doctors order brain scans to confirm such a diagnosis, as well as to rule out other potential causes of the memory or thinking problems experienced by an individual.

Many medical guidelines suggest the superiority of magnetic resonance imaging (MRI) in assessing individuals with dementia. However, neuroimaging with computed tomography or magnetic resonance unequivocally benefits dementia patients with acute onset of cognitive impairment, rapid neurologic deterioration, seizures, or findings on physical examination suggestive of vascular disease, tumour, or other brain focal abnormalities. It should be noted that these tests are costly, and accessibility is not universal.

Additional references

1. Frisoni GB, Fox NC, Jack CR, Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol [Internet]. 2010;6(2):67–77. https://pubmed.ncbi.nlm.nih.gov/20139996
2. Pasquier F, Leys D, Weerts JGE, Mounier-Vehier F, Barkhof F, Scheltens P. Inter-and intraobserver reproducibility of cerebral atrophy assessment on mri scans with hemispheric infarcts. Eur Neurol. 1996;36(5):268–72.
3. Harper L, Barkhof F, Fox NC, Schott JM. Using visual rating to diagnose dementia: A critical evaluation of MRI atrophy scales. J Neurol Neurosurg Psychiatry [Internet]. 2015;86(11):1225–33. https://www.ncbi.nlm.nih.gov/pubmed/25872513
4. Scheltens P, Kuiper M, Ch Wolters E, Barkhof F, Valk J, Weinsten HC, et al. Atrophy of medial temporal lobes on MRI in 'probable' Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry [Internet]. 1992;55(10):967–72. https://dx.doi.org/10.1136/jnnp.55.10.967
5. Di Stasio F, Suppa A, Marsili L, Upadhyay N, Asci F, Bologna M, et al. Corticobasal syndrome: neuroimaging and neurophysiological advances. Eur J Neurol [Internet]. 2019;26(5):701-e52. https://dx.doi.org/10.1111/ene.13928
6. Kouri N, Whitwell JL, Josephs KA, Rademakers R, Dickson DW. Corticobasal degeneration: A pathologically distinct 4R tauopathy. Nat Rev Neurol [Internet]. 2011;7(5):263–72. https://dx.doi.org/10.1038/nrneurol.2011.43
7. Krismer F, Wenning GK. Multiple system atrophy: Insights into a rare and debilitating movement disorder. Nat Rev Neurol [Internet]. 2017;13(4):232–43. https://dx.doi.org/10.1038/nrneurol.2017.26
8. Verhaaren BFJ, Debette S, Bis JC, Smith JA, Ikram MK, Adams HH, et al. Multiethnic Genome-Wide Association Study of Cerebral White Matter Hyperintensities on MRI. Circ Cardiovasc Genet [Internet]. 2015;8(2):398–409. https://dx.doi.org/10.1161/circgenetics.114.000858
9. Ling Y, Chabriat H. Incident cerebral lacunes: A review. J Cereb Blood Flow Metab [Internet]. 2020;40(5):909–21. https://dx.doi.org/10.1177/0271678x20908361
10. Toth P, Tarantini S, Csiszar A, Ungvari Z. Functional vascular contributions to cognitive impairment and dementia: Mechanisms and consequences of cerebral autoregulatory dysfunction, endothelial impairment, and neurovascular uncoupling in aging. Am J Physiol – Hear Circ Physiol [Internet]. 2017;312(1):H1–20. https://dx.doi.org/10.1152/ajpheart.00581.2016
11. Wardlaw JM, Benveniste H, Nedergaard M, Zlokovic B V., Mestre H, Lee H, et al. Perivascular spaces in the brain: anatomy, physiology and pathology. Nat Rev Neurol [Internet]. 2020;16(3):137–53. https://dx.doi.org/10.1038/s41582-020-0312-z
12. Owens T, Bechmann I, Engelhardt B. Perivascular spaces and the two steps to neuroinflammation. J Neuropathol Exp Neurol [Internet]. 2008;67(12):1113–21. https://dx.doi.org/10.1097/nen.0b013e31818f9ca8
13. Yakushiji Y, Wilson D, Ambler G, Charidimou A, Beiser A, Van Buchem MA, et al. Distribution of cerebral microbleeds in the East and West: Individual participant meta-analysis. Neurology [Internet]. 2019;92(10):E1086–97. https://dx.doi.org/10.1212/wnl.0000000000007039
14. Yamada M. Cerebral amyloid angiopathy: Emerging concepts. J Stroke [Internet]. 2015;17(1):17–30. https://dx.doi.org/10.5853/jos.2015.17.1.17
15. Vitali P, MacCagnano E, Caverzasi E, Henry RG, Haman A, Torres-Chae C, et al. Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias. Neurology [Internet]. 2011;76(20):1711–9. https://dx.doi.org/10.1212/wnl.0b013e31821a4439
16. Zeidler M, Sellar RJ, Collier DA, Knight R, Stewart G, Macleod MA, et al. The pulvinar sign on magnetic resonance imaging in variant Creutzfeldt-Jakob disease. Lancet [Internet]. 2000;355(9213):1412–8. https://dx.doi.org/10.1016/s0140-6736(00)02140-1
17. Zanusso G, Monaco S, Pocchiari M, Caughey B. Advanced tests for early and accurate diagnosis of Creutzfeldt-Jakob disease. Nat Rev Neurol [Internet]. 2016;12(7):427. https://www.ncbi.nlm.nih.gov/pubmed/27174240.

Chapter 10
Brain imaging using PET and SPECT

Pedro Rosa-Neto

Key points

- Neuroimaging using positron emission tomography (PET) or single-photon emission computed tomography (SPECT) increases the diagnostic accuracy of Alzheimer's disease and dementia with Lewy bodies.
- Applying appropriate use criteria, PET or SPECT neuroimaging may improve the management of patients by revealing specific brain diseases underlying their dementia.
- There is a high demand for diagnostic imaging tests that can identify other brain diseases causative of dementia.

General background

Positron emission tomography (PET) is a functional imaging technique that uses positron-emitting imaging agents to visualise and quantify a wide range of biochemical processes. In individuals with dementia, PET quantifies abnormal protein accumulation and metabolic dysfunctions affecting blood flow and metabolism. The ability to probe the accumulation of abnormal proteins associated with neurodegeneration in vivo offers unprecedented research and clinical application opportunities. There has been tremendous progress in the last 15 years with regards to Alzheimer's disease PET imaging. It is possible to quantify the load of brain amyloid, or neurofibrillary tangles, glucose hypometabolism imposed by disease pathophysiology using PET. Today, PET imaging agents are available for amyloid, neurofibrillary tangles (commonly designated as tau) and neurodegeneration.

A single-photon emission computed tomography (SPECT) scan allows doctors to measure the integrity of the cells affected by Parkinson's and Lewy body's disease in the brain of living people. Like PET, a SPECT scan is a type of nuclear imaging test that uses a radioactive substance and a special camera to create 3-D pictures. Biomarkers generated by these tests permit doctors to diagnose the cause of dementias.

Amyloid imaging agents are biomarkers for brain amyloid pathology. Vizamyl ([18F]flutemetamol), Amyvid ([18F] flobetapir) and Neuraceq ([18F]florbetaben) have been approved by regulatory agencies as amyloid imaging agents for clinical practice. In vivo post-mortem correlations have shown that images of these PET tracers are highly correlated with neuritic plaques (3). Present appropriate-use criteria provide guidance for the utilisation of

Table 1. Types of brain abnormalities measured by PET and SPECT

Disease Process	Amyloid	Tau	Neuronal injury	Dopamine cells
PET	Yes	Yes	Yes	Yes
SPECT	No	No	Yes	Yes

these diagnostic tests in clinical practice. For example, a negative Aβ-PET scan in a person with dementia will rule out Alzheimer's disease as the underlying aetiology (4,5).

Tau imaging agents are biomarkers for tau pathology. Although there are several PET tau imaging options available to researchers, only Tauvid ([18F]flortaucipir) has been approved by the US Food and Drug Administration for clinical use. Tau imaging serves to diagnose Alzheimer's disease. In contrast with amyloid imaging, the distribution of tau uptake in living patients correlate with clinical symptoms and agrees with the disease staging system proposed by Braak in pathological specimens (6,7).

Brain metabolism measured with [18F]fluodeoxyglucose has been extensive utilised as a clinical tool in neurodegenerative conditions. Abnormal reduction of brain glucose metabolism, or hypometabolism, is a hallmark of neurodegenerative dementias. Hypometabolism from neurons and astrocytes reflects brain synaptic dysfunction. As such, the diagnosis of dementia based on hypometabolism has extensively been utilised to diagnose neurodegenerative conditions (4).

Dopamine nerve terminal imaging provides information regarding the viability of dopaminergic projections in the striatum. 23I-ioflupane is a radioligand that binds to the dopamine transporter located in the presynaptic membrane of dopamine nerve terminals. Images are obtained with SPECT imaging 3 hours after an injection of 123I-ioflupane. In dementia, dopamine transporter imaging can help differentiate Alzheimer's disease from dementia with Lewy bodies (8,9).

Limitation of PET and SPECT imaging agents as dementia biomarkers – The use of PET and SPECT remains limited to a small fraction of people with dementia. Although practical and beneficial in specific clinical circumstances, imaging biomarkers are expensive and not readily accessible or affordable to most healthcare systems worldwide due to the problematic availability of scanners and cyclotrons to produce radiopharmaceuticals.

Table 2. Summary of imaging biomarkers available for degenerative conditions

Methods	Biomarker	Pathophysiologic process		Topographic marker	Neuronal injury
		amyloid	tau		
PET	Amyloid tracer uptake	Yes	No	Yes	No
PET	Tau tracer uptake	No	Yes	Yes	No
PET	Fluorodeoxyglucose	No	No	Yes	Yes
SPECT	Iodinated ioflupane	No	No	Yes	Yes

Survey results

The 1,111 multidisciplinary clinicians who responded, indicated that basic assessments such as history, neurological examination, basic laboratory screening tests, and cognitive assessment are widely used as dementia tests (Chart 1). Due to accessibility limitations and high costs, biomarkers are not always available in many countries and therefore not included in their clinical practice. That said, 70% of the participants are open to using blood biomarkers in their practice. However, these tests are not yet available in many nations. Once supply distribution is more widely offered, it will fill a gap in their practices and result in more efficient testing protocols (Chart 2).

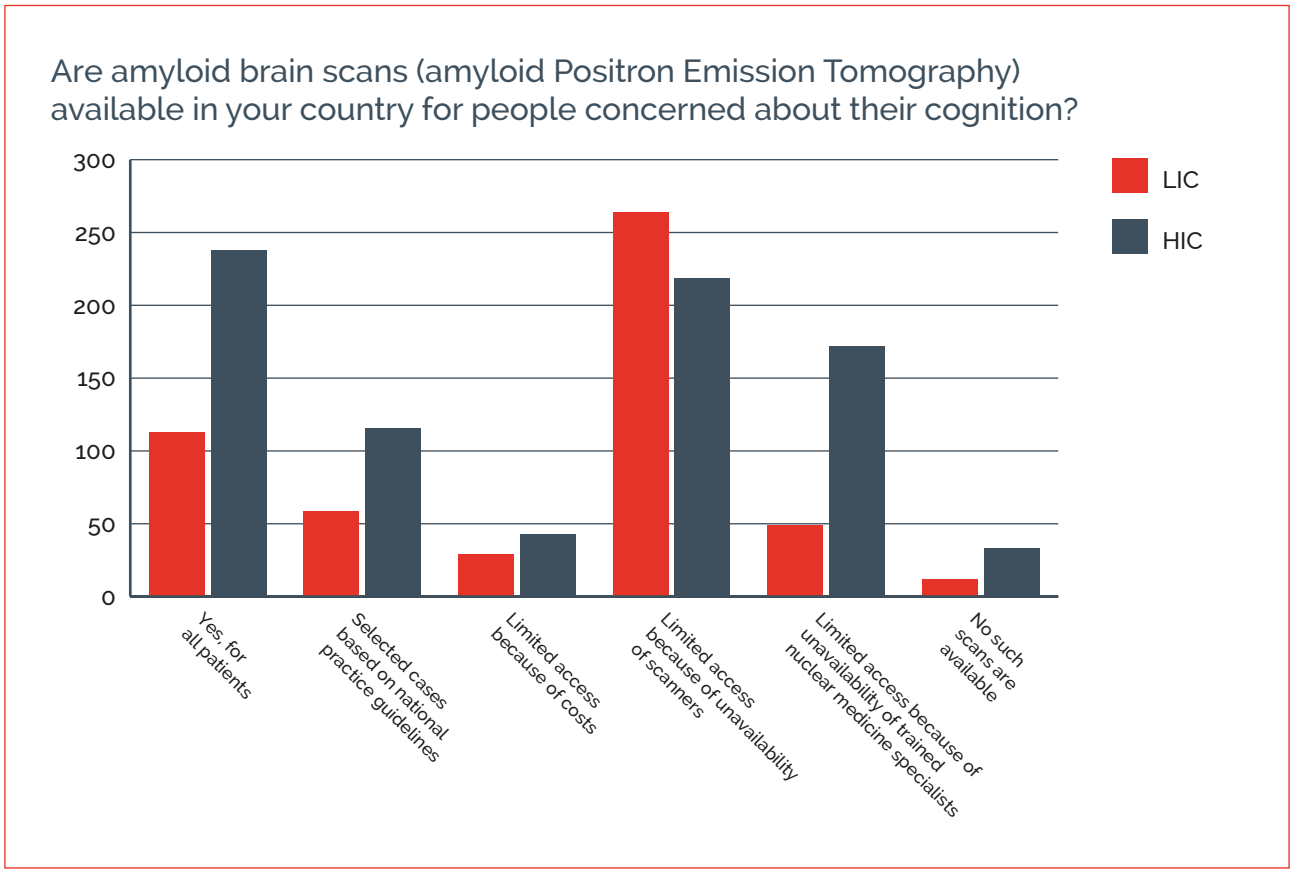


Chart 1. Clinician responses.

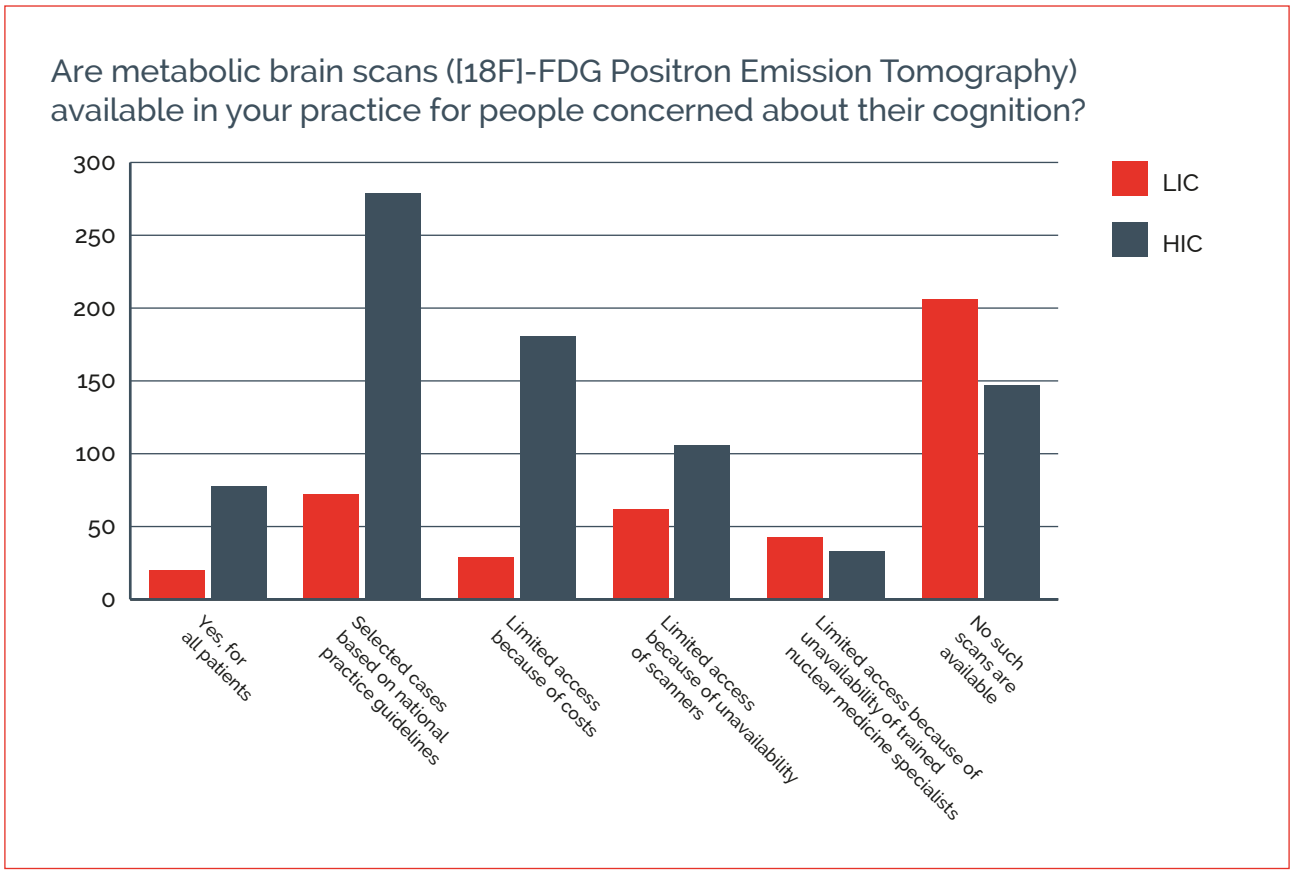


Chart 2. Clinician responses.

Expert essay

Optimal use of anatomic and metabolic brain imaging in the workup of cognitively impaired people

Katherine A. Zukotynski,[1] Pedro Rosa-Neto,[2] Jean-Paul Soucy,[3] Phillip H. Kuo,[4] Sandra E. Black[5]

1 Departments of Radiology and Medicine, McMaster University, Hamilton, CANADA
2 McConnell Brain Imaging Centre, Montreal Neurological Institute, Montreal and McGill Center for Studies in Aging, CANADA
3 McConnell Brain Imaging Centre, Montreal Neurological Institute, CANADA
4 Departments of Medical Imaging, Medicine, and Biomedical Engineering, University of Arizona, UNITED STATES
5 Departments of Neurology, and Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, CANADA

Currently, clinical evaluation by a cognitive specialist remains the mainstay in the workup of someone with suspected dementia, with both anatomic and metabolic imaging continuing to play a central and complementary role. In general, anatomic imaging refers to computed tomography (CT) and magnetic resonance imaging (MRI), while metabolic brain imaging refers to [18F]-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET). In all cases, it is important to recall that the risk associated with imaging is essentially non-existent and that substantial benefit may be derived in clarifying the diagnosis and ultimately improving the individual's diagnosis management. Finally, while the recommendations below are directly derived from those of the recently published Canadian Consensus Conference on the Diagnosis and Treatment of Dementia, these views are shared by several organisations including those devoted to neurology and imaging (1–3).

Structural imaging is recommended in the workup of people with onset of cognitive symptoms within the past two years (irrespective of rate of progression) as well as in those with unexpected and unexplained decline in cognition and/or functional status in the setting of known dementia regardless of age (1). Either a head CT or MRI is appropriate (2), particularly to assess atrophy and exclude space occupying lesions among other issues. While a head CT including coronal reformatting may be helpful to exclude a space occupying lesion, detect vascular lesions and assess hippocampal atrophy, MRI is generally preferred because of its higher sensitivity for vascular lesions, microhaemorrhages and white matter disease, as well as its ability to exclude space occupying lesions and other features with diagnostic and predictive value (4). When available, a 3 Tesla MRI is preferred to a 1.5 Tesla scanner. The sequences acquired should include: a 3D T1 volumetric sequence (with coronal reformatting), a fluid-attenuation inversion recovery (FLAIR) sequence, T2* (or susceptibility)-weighted imaging as well as T2-weighted and diffusion-weighted imaging (1). A proton density (PD) sequence, although not routinely acquired, may be helpful. Intravenous contrast is not administered, unless there is a clinical indication such as suspected neoplastic, infectious or inflammatory disease. Effort should be made to standardise imaging including equipment and sequences, particularly when follow-up imaging is considered. Interpretation should be done by an experienced individual with consideration to including semi-quantitative scales for medial temporal lobe atrophy and global cortical atrophy (that is, Scheltens and Pasquier scales) as well as white matter disease (namely the Fazekas scale) (5–7).

Metabolic imaging with 18F-FDG PET is recommended in the workup of an individual with a confirmed cognitive impairment who has been evaluated by a cognitive disorders specialist and has had structural imaging but whose underlying pathological process remains unclear (1–3). PET may improve diagnostic accuracy and can lead to a change in medication and use of specialised care, in addition to improved quality of life. While several radioactive drugs (radiopharmaceuticals) may be imaged using PET, 18F-FDG, a radioactive glucose analogue is the most ubiquitous. Uptake of 18F-FDG by cells is detected using PET specific; patterns of decreased uptake correlate to various neurodegenerative diseases (Fig. 1). If 18F-FDG PET is unavailable, assessment of regional cerebral blood flow using single photon emission computed tomography (SPECT) may be helpful (1).

Over the last decade, several additional radiopharmaceuticals have been developed that are useful in the workup of someone with dementia (8). The true strength of imaging is that it provides a non-invasive regional representation of disease pathology. For example, there are 11C- and 18F-labelled radiopharmaceuticals available to image cerebral amyloid including: [11C]-PIB as well as [18F]-florbetapir (AmyvidTM), [18F]-flutemetamol (VizamylTM) and [18F]-florbetaben (NeuraCeqTM). While the presence of cerebral amyloid deposition may be seen in cognitively normal subjects, the absence of cerebral amyloid deposition essentially eliminates the possibility of Alzheimer's disease (Fig. 2). Thus, amyloid PET may provide insight on the pathology underlying dementia and possibly change management. To wit, the results of the IDEAS study reported a change in management pre- and post- amyloid PET in 60% of people with mild cognitive impairment (MCI) and 63% with dementia out of 11,409 subjects 65 years of age or older (9). Currently, accessibility and cost are two of the principal issues limiting use of amyloid PET in the workup of someone with dementia; however, when available amyloid PET can be very helpful. Further, if therapy targeting cerebral amyloid plaque proves beneficial in Phase 3 clinical trials, it is likely that amyloid PET will gain wide utilisation for patient selection and serial amyloid PET may become a more ubiquitous marker of therapy response. Also, over the last few years [123I]-Ioflupane (DaTscanTM) SPECT has become available and may be useful to establish a diagnosis of cognitive impairment linked to dementia with Lewy bodies (DLB) (10). Finally, tau PET is a topic of active research which has already reached the clinical stage with the arrival of a first commercially available agent in the U.S., [18F]-flortaucipir (TauvidTM). Its impact on clinical practice will become clearer within the next few years, particularly given the push to characterise people with dementia in terms of amyloid and tau status in conjunction with an assessment of neurodegeneration (8).

In summary, the workup of a subject suspected of presenting with cognitive deterioration includes a clinical evaluation by a cognitive specialist as well as structural imaging, preferably with a 3Tesla MRI and standard sequences. Metabolic imaging is reserved for individuals where the pathology underlying the cognitive decline remains uncertain. Within the last few years, imaging including amyloid and tau PET as well as [123I]-Ioflupane SPECT have become available. Although not yet part of routine clinical practice, their use is increasing and is likely to become more prevalent pending further development of new therapies for dementia that are on the horizon. The same, with some delay, should happen with tau PET imaging.

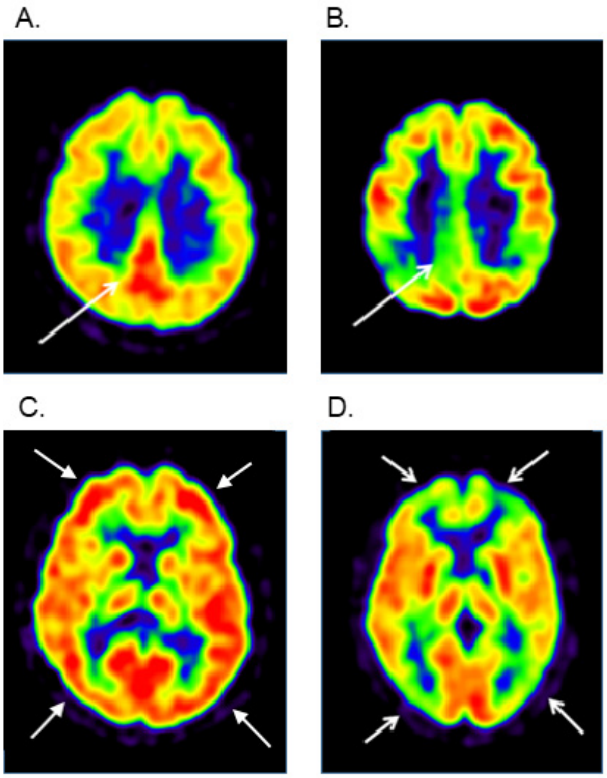


Figure 1. Axial [18F]-fluorodeoxyglucose PET images on the left (A, C) show normal uptake of the radiopharmaceutical. Those on the right (B, D) were obtained from a person with Alzheimer's disease. Arrows point to recognisable differences as being characteristic of the disease.

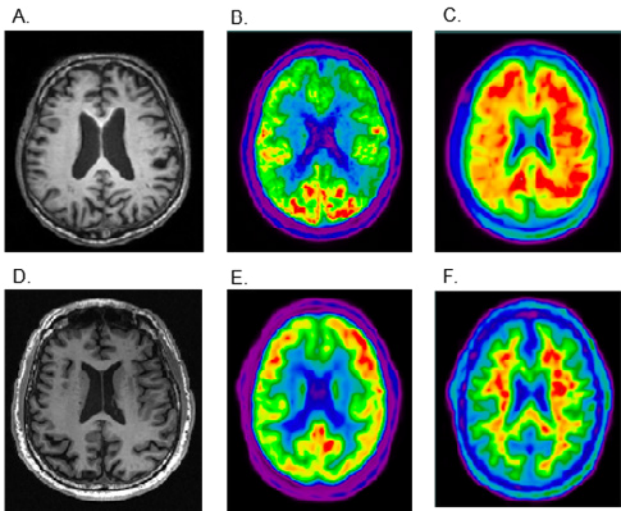


Figure 2. Axial MRI (A,D), [18F]-fluorodeoxyglucose PET (B,E) and [18F]-florbetapir PET (C,F) in two different people; top row: decreased [18F]-fluorodeoxyglucose in the parietal, temporal (not shown), and frontal lobes (B) as well as increased [18F]-florbetapir in the cerebral cortex (C) are characteristic of Alzheimer's disease; bottom row: normal radiopharmaceutical uptake (E, F) (11).

References

1. Brisson M, Brodeur C, Létourneau-Guillon L, Masellis M, Stoessl J, Tamm A, et al. CCCDTD5: Clinical role of neuroimaging and liquid biomarkers in patients with cognitive impairment. Alzheimer's Dement Transl Res Clin Interv. 2020;6(1):1.
2. Moonis G, Subramaniam RM, Trofimova A, Burns J, Bykowski J, Chakraborty S, et al. ACR Appropriateness Criteria® Dementia. J Am Coll Radiol. 2020;17(5):S100–12.
3. Nobili F, Arbizu J, Bouwman F, Drzezga A, Agosta F, Nestor P, et al. European Association of Nuclear Medicine and European Academy of Neurology recommendations for the use of brain 18 F-fluorodeoxyglucose positron emission tomography in neurodegenerative cognitive impairment and dementia: Delphi consensus. Eur J Neurol. 2018;25(10):1201–17.
4. Vernooij MW, Pizzini FB, Schmidt R, Smits M, Yousry TA, Bargallo N, et al. Dementia imaging in clinical practice: a European-wide survey of 193 centres and conclusions by the ESNR working group. Neuroradiology. 2019;61(6):633–42.
5. Scheltens P, Kuiper M, Ch Wolters E, Barkhof F, Valk J, Weinsten HC, et al. Atrophy of medial temporal lobes on MRI in 'probable' Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry [Internet]. 1992;55(10):967–72. https://dx.doi.org/10.1136/jnnp.55.10.967.
6. Pasquier F, Leys D, Weerts JGE, Mounier-Vehier F, Barkhof F, Scheltens P. Inter-and intraobserver reproducibility of cerebral atrophy assessment on mri scans with hemispheric infarcts. Eur Neurol. 1996;36(5):268–72.
7. Fazekas F, Chawluk JB, Alavi A. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. Am J Neuroradiol. 1987;8(3):421–6.
8. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's Dement. 2018;14(4):535–62.
9. Rabinovici GD, Gatsonis C, Apgar C, Chaudhary K, Gareen I, Hanna L, et al. Association of Amyloid Positron Emission Tomography with Subsequent Change in Clinical Management among Medicare Beneficiaries with Mild Cognitive Impairment or Dementia. JAMA – J Am Med Assoc. 2019;321(13):1286–94.
10. McKeith IG, Boeve BF, DIckson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies [Internet]. Vol. 89, Neurology. Neurology; 2017 [cited 2021 Jul 13]. p. 88–100. https://pubmed.ncbi.nlm.nih.gov/28592453/.

Expert essay

The impact of amyloid imaging in the diagnosis of dementias

Gil Rabinovici,[1] Maura Malpetti[1,2]

[1] Memory & Aging Center, Departments of Neurology, Radiology and Biomedical Imaging, Weill Institute for Neuroscience, UCSF, UNITED STATES
[2] Department of Clinical Neurosciences, University of Cambridge, Cambridge, UNITED KINGDOM

The diagnosis of Alzheimer's disease and other dementias on purely clinical grounds is challenging due to the complex relationship between clinical presentation and underlying molecular pathology. In vivo biomarkers that detect key elements of Alzheimer's disease pathophysiology can be used to complement the clinical evaluation and provide direct evidence of the core features that define Alzheimer's disease neuropathology, namely amyloid-β (Aβ) plaques and tau neurofibrillary tangles. Direct visualisation of accumulating Aβ plaques in people living with Alzheimer's disease was first reported by Klunk and colleagues (1), applying the novel positron emission tomography (PET) radiotracer carbon-11 labelled Pittsburgh Compound-B (PIB). PIB is an analogue of thioflavin-T, a dye that has been used to stain amyloid in autopsy samples for over a century. While the short half-life of the carbon-11 radioisotope (20min) limit the use of PIB to research centres, a number of fluorine-18 (110min half-life) labelled radiotracers have subsequently been developed for clinical use, and three (18F-florbetapir, 18F-florbetaben, 18F-flutametamol) have been approved by the United States Food & Drug Administration (FDA), the European Medicines Agency and other regulatory agencies.

Aβ aggregation is an early event in the evolution of Alzheimer's disease, starting decades before symptom onset. On PET, cortical radiotracer uptake is first evident in posterior cingulate-precuneus and prefrontal regions and is later seen throughout large regions of the neocortex (Figure 1). This pattern corresponds to a moderate-frequent density of neuritic plaques on neuropathology. In contrast, people with an absent or low burden of plaques show retention only in the sub-cortical white matter, which reflects non-specific (i.e., not Aβ-related) tracer binding (Figure 1). While the radiotracers are specific for plaques, Aβ is strongly related to tau pathology in Alzheimer's disease, with increased Aβ burden associated with higher Braak stages of neurofibrillary pathology. Braak stages in turn are closely associated with clinical symptoms and decline. Thus, positive amyloid PET can also suggest tau pathology and (in a clinic-based cohort study) has been shown to correspond to intermediate-high overall Alzheimer's disease neuropathological changes. Importantly, the intensity of amyloid PET signal corresponds only weakly with disease stage, and the topography of binding corresponds weakly with neurodegenerative changes and specific cognitive symptoms. This is in contrast with tau PET signal, which correlates closely with disease progression and spatial distribution of neurodegeneration.

Appropriate Use Criteria have been developed to identify people who would most benefit from amyloid PET in their diagnostic work-up (2). These include individuals with objectively confirmed cognitive impairment seen by a dementia specialist, in whom the cause of impairment is uncertain after a comprehensive evaluation (including cognitive testing, basic labs and brain CT/MRI), Alzheimer's disease is a diagnostic consideration and knowledge of amyloid status is expected to alter diagnosis and management. Amyloid PET may be considered for people with progressive unexplained mild cognitive impairment (MCI), atypical/mixed clinical presentations or early age of onset (under the age of 65). In MCI, positive amyloid PET can confirm the presence of prodromal Alzheimer's disease and increases the likelihood that the person will convert to dementia in the coming 2–5 years. In people with dementia, amyloid PET may be most useful in distinguishing Alzheimer's disease from frontotemporal dementia, an early-onset disease that does not involve Aβ neuropathology. Conversely, amyloid PET is not useful for distinguishing Alzheimer's disease from other Aβ-associated conditions, such as dementia with Lewy bodies or cerebral amyloid angiopathy. While the initial Appropriate Use Criteria suggested amyloid PET is inappropriate in older people with a 'typical' (that is, amnestic) Alzheimer's disease presentation, this notion has been challenged by a relatively high rate of negative scans in such people in research studies and clinical trials. Furthermore, it is increasingly recognised that an Alzheimer's disease-like amnestic syndrome can also be caused by other common limbic-predominant pathologies, such as limbic-predominant age-related TDP-43 encephalopathy (3) and primary age-related tauopathy (4). While a negative amyloid PET is always useful in excluding Alzheimer's disease, clinicians should consider the person's age and apolipoprotein E (APOE) genotype in interpreting

the clinical significance of a positive scan. This is because the overall prevalence of amyloid pathology in the general (that is, cognitively unimpaired) population increases with age and in carriers of the APOE4 risk allele. Finally, the presence of amyloid does not exclude another pathology which may be more directly contributing to a person's symptoms.

A number of studies have evaluated the clinical impact of amyloid PET on patient diagnosis and management (5–7). Among these, the Imaging Dementia–Evidence for Amyloid Scanning (IDEAS) study assessed the utility of amyloid PET in over 18,000 Medicare beneficiaries in the US who met Appropriate Use Criteria (5). The study found that amyloid PET was associated with a change in core elements of patient management (use of Alzheimer's disease drugs, use of other drugs that treat dementia or dementia risk factors, counselling about safety and future planning) in over 60% of people. Following PET, the diagnosis changed from Alzheimer's disease to a non- Alzheimer's disease dementia in 25% of cases, and from a non- dementia to Alzheimer's disease in 10%. These results are consistent with those reported in smaller studies (6–7). Future studies will compare health outcomes (rates of hospitalisations, emergency department visits) and overall healthcare utilisation in the IDEAS cohort to a group of matched patients with MCI/dementia who have not had amyloid PET. In lieu of data on long-term health outcomes, many third-party payers have declined to cover amyloid PET, severely restricting people's access to this diagnostic tool.

Despite its central role in Alzheimer's disease diagnosis, amyloid PET is not a stand-alone tool, and needs to be considered in combination with other tests and biomarkers. The information about molecular pathology provided by amyloid PET can be complemented via imaging markers of neurodegeneration, such as MRI (measuring brain atrophy) or 18F-fluorodeoxyglucose (FDG) PET (measuring glucose metabolism). The combination of amyloid PET and MRI or FDG improves the prediction of conversion from MCI to dementia due to Alzheimer's disease compared to either modality alone (8–9) and improves prediction of a neuropathological diagnosis of Alzheimer's disease (9). Beyond imaging, cerebrospinal fluid measures of Aβ42 or the ratio of Aβ42/Aβ40 are concordant with amyloid PET in classifying individual amyloid status in most cases (~80–90%). CSF markers may be more sensitive than amyloid imaging in early stages of the disease, reflecting changes in soluble Aβ species that precede detectable aggregation into plaques (10). In the future, emerging plasma markers of Aβ will facilitate broad access to amyloid biomarkers in clinical care and

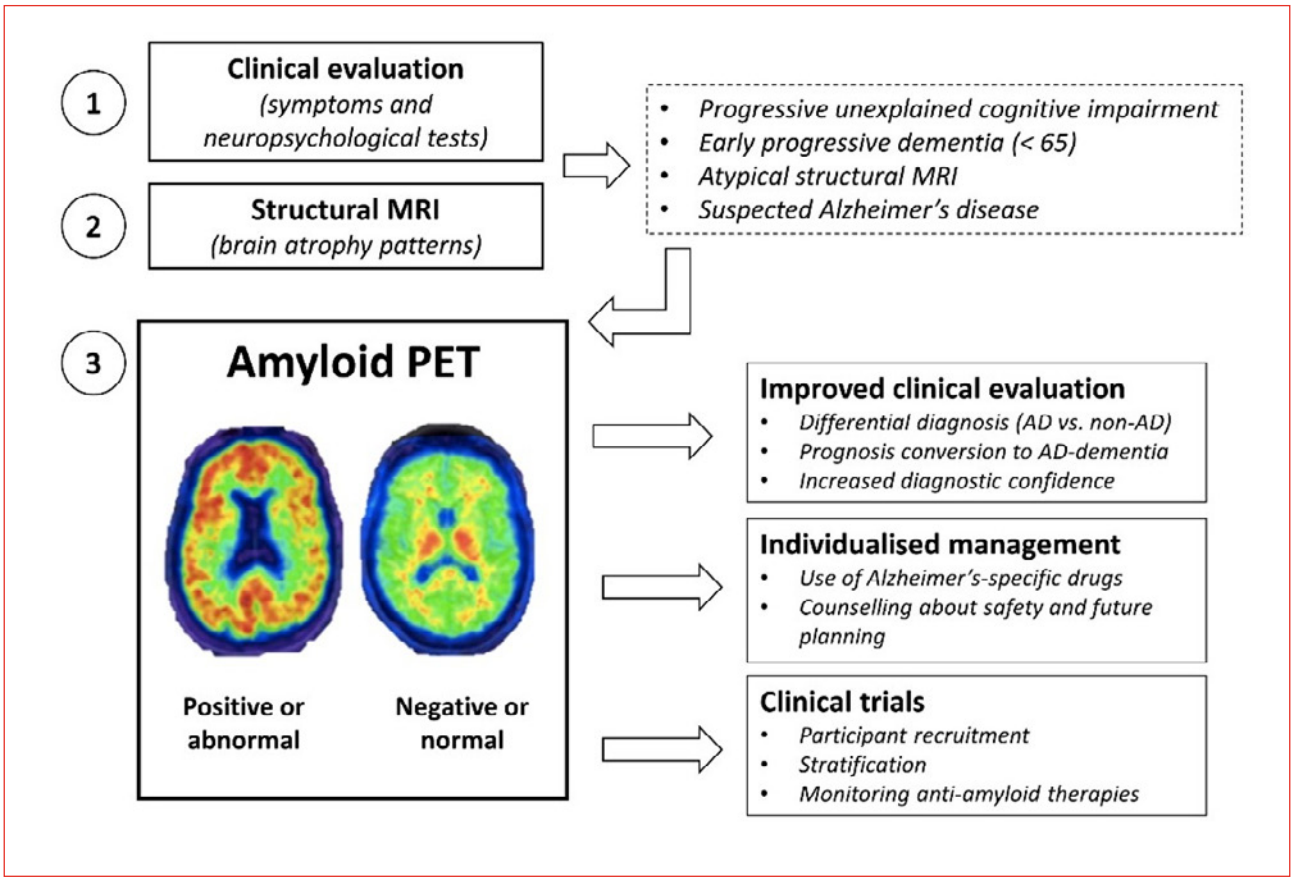


Figure 1. Flowchart of amyloid PET usage in dementia diagnosis, and its impact on clinical evaluation, dementia management and clinical trials. A positive amyloid PET scan (left) shows cortical radiotracer uptake in cortical brain regions, early in posterior cingulate-precuneus and prefrontal regions, while a negative scan (right) shows retention in the sub-cortical white matter, which reflects non-specific tracer binding.

research. However, compared to CSF or plasma, PET provides a better marker for overall brain amyloid burden and a more sensitive measure of longitudinal change.

In addition to its other uses, amyloid PET has played a critical role in Alzheimer's disease drug development. In clinical trials, amyloid PET has been used for subject selection (enabling early identification of pathology) and to measure target engagement for drugs designed to remove plaques. Very recently, the FDA approved the Aβ-targeting monoclonal antibody aducanumab for the treatment of Alzheimer's disease, on the grounds that it robustly lowered amyloid PET signal, which was considered a surrogate outcome measure. While the clinical efficacy of the drug remains controversial in light of conflicting trial results, this approval heralds a new era of molecular-specific therapies for Alzheimer's disease. Identifying people who might benefit from these treatments will require broad access to amyloid PET and other biomarkers of Aβ deposition, and will provide great incentive for an early, biomarker-supported diagnosis of Alzheimer's disease.

References

1. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging Brain Amyloid in Alzheimer's Disease with Pittsburgh Compound-B. Ann Neurol 2004;55:306–19. https://doi.org/10.1002/ana.20009.
2. Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, et al. Appropriate use criteria for Amyloid PET: A report of the Amyloid imaging task force the society of nuclear medicine and molecular imaging and the Alzheimer's association. J Nucl Med 2013;54:476–90. https://doi.org/10.2967/jnumed.113.120618.
3. Nelson PT, Dickson DW, Trojanowski JQ, Jack CR, Boyle PA, Arfanakis K, et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): Consensus working group report. Brain 2019;142:1503–27. https://doi.org/10.1093/brain/awz099.
4. Crary JF, Trojanowski JQ, Schneider JA, Abisambra JF, Abner EL, Alafuzoff I, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. Acta Neuropathol 2014;128:755–66. https://doi.org/10.1007/s00401-014-1349-0.
5. Rabinovici GD, Gatsonis C, Apgar C, Chaudhary K, Gareen I, Hanna L, et al. Association of Amyloid Positron Emission Tomography with Subsequent Change in Clinical Management among Medicare Beneficiaries with Mild Cognitive Impairment or Dementia. JAMA – J Am Med Assoc 2019;321:1286–94. https://doi.org/10.1001/jama.2019.2000.
6. Pontecorvo MJ, Siderowf A, Dubois B, Doraiswamy PM, Frisoni GB, Grundman M, et al. Effectiveness of Florbetapir PET Imaging in Changing Patient Management. Dement Geriatr Cogn Disord 2017;44:129–43. https://doi.org/10.1159/000478007.
7. De Wilde A, Van Der Flier WM, Pelkmans W, Bouwman F, Verwer J, Groot C, et al. Association of amyloid positron emission tomography with changes in diagnosis and patient treatment in an unselected memory clinic cohort: The ABIDE project. JAMA Neurol 2018;75:1062–70. https://doi.org/10.1001/jamaneurol.2018.1346.
8. Wolk DA, Sadowsky C, Safirstein B, Rinne JO, Duara R, Perry R, et al. Use of flutemetamol F18-labeled positron emission tomography and other biomarkers to assess risk of clinical progression in patients with amnestic mild cognitive impairment. JAMA Neurol 2018;75:1114–23. https://doi.org/10.1001/jamaneurol.2018.0894.
9. Lesman-Segev OH, La Joie R, Iaccarino L, Lobach I, Rosen HJ, Seo SW, et al. Diagnostic Accuracy of Amyloid versus 18F-Fluorodeoxyglucose Positron Emission Tomography in Autopsy-Confirmed Dementia. Ann Neurol 2021;89:389–401. https://doi.org/10.1002/ana.25968.
10. Schindler SE, Bollinger JG, Ovod V, Mawuenyega KG, Li Y, Gordon BA, et al. High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis. Neurology 2019;93:E1647–59. https://doi.org/10.1212/WNL.0000000000008081.

Expert essay

The role of Iodine-123 ioflupane (DaTscan©) SPECT imaging in dementia: what family physicians should know

Jean-Paul Soucy

McConnell Brain Imaging Centre, Montreal Neurological Institute, CANADA

Iodine-123 ioflupane (123I-ioflupane, DaTscan©) is a radiopharmaceutical which can be used in combination with Single Photon Emission Tomography (SPECT) in Nuclear Medicine studies in assessing a series of suspected neurodegenerative conditions. Currently, its most frequent application by far is in the field of movement disorders (Parkinson's disease, other parkinsonian syndromes, essential tremor, etc.) (1). Here, the focus will be on the use of this agent in subjects with neurocognitive deterioration, specifically for differentiating Alzheimer's disease from Lewy bodies diseases (this includes dementia with Lewy bodies, and Parkinson's disease with dementia).

Ioflupane is a molecule, which is closely related to cocaine, and both share a number of chemical and pharmacological properties. In particular, they can bind with high affinity to the membrane transporter for dopamine (DAT) found on the surface of dopaminergic (DA) cells (2), especially at synaptic terminals. Under normal conditions, the number of DAT expressed by those cells is relatively constant, and measurements of the quantity of radioactivity found in the brain after injection of 123I-ioflupane with SPECT can serve as an in vivo, non-invasive proxy for the regional concentrations of functional DA terminals.

Loss of DA cells from the *substantia nigra* in the mesencephalon has long been known as one of the defining observations made in LBD (3). Lewy bodies, largely composed of a pre-synaptic protein called a-synuclein, are associated with progressive loss of the cells harbouring them and are found in multiple monoaminergic neurons of the brainstem in affected people, especially DA ones (as well as in cholinergic neurons). The brain regions which, in humans, contain the largest number of DA terminals, are the basal ganglia, and 123I-ioflupane SPECT studies specifically assess uptake of the tracer in those nuclei. Subjects presenting with clinical manifestations of a Lewy body dementia overwhelmingly show already significant loss of DA terminals in the basal ganglia by the time they seek medical attention, which is depicted with very high sensitivity by the test, to the extent that a normal study essentially rules out the presence of a Lewy body dementia. In addition, a well characterised down regulation of the expression of DAT by DA cells in Lewy body dementia (4) increases the sensitivity of the test by further reducing uptake beyond the actual numerical loss of DA terminals bearing DAT.

The test is remarkably safe, with the odds of side effects being extremely low, and involving systematically mild reactions (5). Except for pregnancy (rare in the class of subjects studied) or a history of a previous unexpected reaction to the product, there are no contraindications to its use; in particular, allergies to iodine-containing contrast agents *are not* a contraindication. Preparation for the test is minimal. Approximately one hour before injection, the person will receive a small quantity of non-radioactive iodine such (as Lugol solution or other sources of stable iodine) to block uptake by the thyroid of any radioactive iodine-123, which might be released by ioflupane (standard quality control of the agent ensures that this would be limited to very small amounts in the first place). It is also important to make sure the patient is not taking medication that can interfere with binding of the radiopharmaceutical to DAT, a list of which can be found in the CANM guidelines for Dopamine Imaging in Movement Disorders. (1). The individual should be advised that they need to schedule approximately four hours at the imaging facility, most of which (three hours) is required because of a relatively long uptake period for this molecule after its IV administration. Acquisition of data will last around 30 minutes spent in a SPECT scanner, which only exceptionally induces claustrophobia as those cameras are much more 'open' than an MR scanner for instance.

Visual inspection of the images obtained with SPECT is the recommended approach for diagnosis. Because, as already mentioned, people with clinical manifestations linked to Lewy body dementia already have lost a large portion of their dopaminergic terminals, this is generally quite straightforward. Some borderline cases may benefit from one of several quantification approaches (6), but obtaining high-quality quantification is technically demanding and is often not performed.

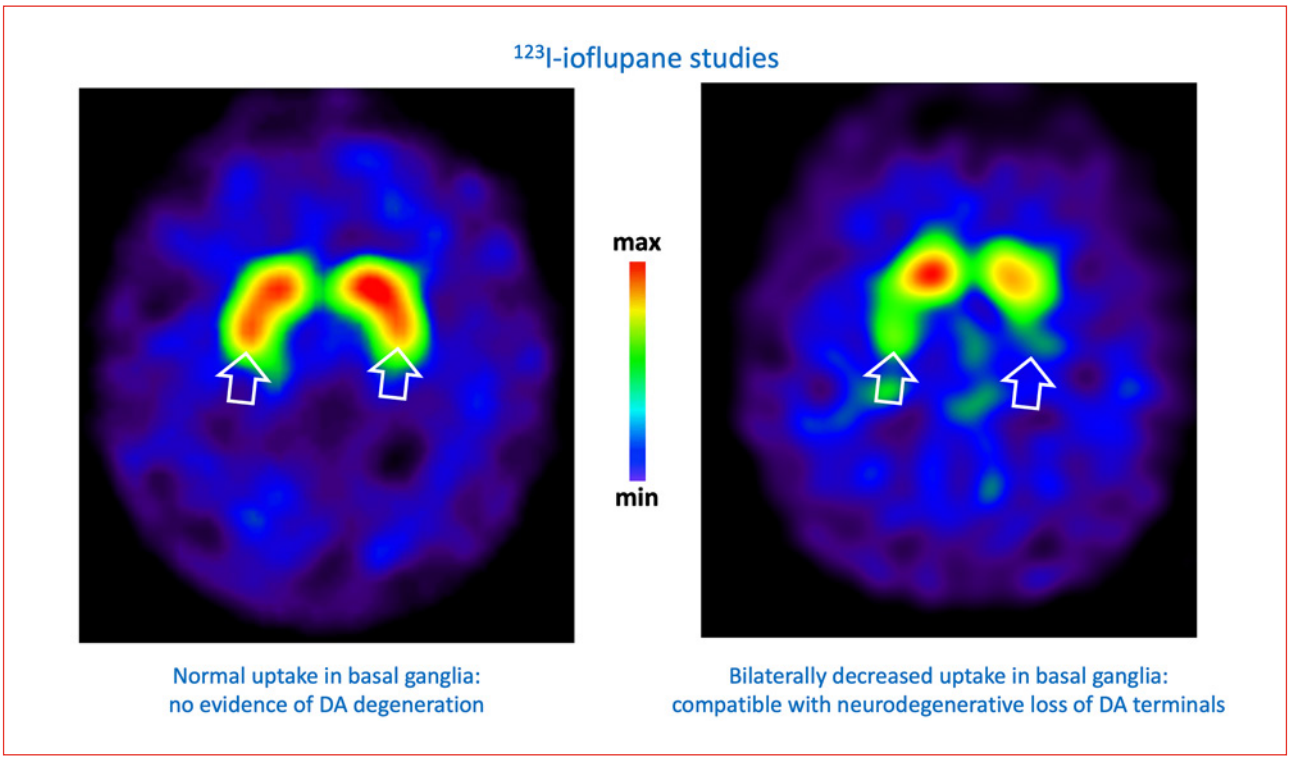


Figure 1. Comparative 123I-ioflupane SPECT imaging after injection illustrating how it identifies suspected dementia with Lewy bodies.

Distinguishing cognitive impairment linked to Alzheimer's disease from that associated to Lewy body dementia (here designating both dementia with Lewy bodies and Parkinson's disease dementia) is an indication to use 123I-ioflupane SPECT imaging which is not approved in all jurisdictions. European authorities have allowed its use under such circumstances, whereas in North America, the use of the product is only authorised for the evaluation of movement disorders, although it is largely used off-label in people with cognitive impairment. Its performance in establishing the correct diagnosis when questions remain after standard evaluation has been obtained (an evolving concept with the arrival of new imaging and liquid biomarkers) is now well recognised (7); and has led to its inclusion in general recommendations for the evaluation of subjects with cognitive impairment by various organisations (8). Diagnostic accuracy in separating LBD-linked cognitive impairment from Alzheimer's disease is reported to be between 88% and 96%.

Therefore, it is now largely accepted that 123I-ioflupane SPECT imaging, in addition to having an established status as an excellent approach to establish the nature of movement disorders of uncertain aetiology, is a powerful tool for the identification of Lewy body dementia as a cause of cognitive impairment in complex cases where that diagnosis is a clinical possibility.

References

1. Fasano A, Gnanakumar R, Rigby H, Ross A, Soucy J-P, Tamm A. CANM guidelines for Dopamine Imaging in Movement. Disorders [Internet]. Ruban Gnanakumar, Heather Rigby, Andrew Ross, Jean-Paul Soucy, Alex Tamm: Alfonso Fasano; 2020. https://canm-acmn.ca/resources/Documents/Guidelines_Resources/CANM_Guidelines_for_Dopamine_Imaging_in_Movement_Disorders__FINAL-2.pdf.
2. Booij J, Andringa G, Rijks LJM, Vermeulen RJ, De Bruin K, Boer GJ, et al. [123I]FP-CIT binds to the dopamine transporter as assessed by biodistribution studies in rats and SPECT studies in MPTP-lesioned monkeys. Synapse. 1997;27(3):183–90.
3. Niznik HB, Fogel EF, Fassos FF, Seeman P. The Dopamine Transporter Is Absent in Parkinsonian Putamen and Reduced in the Caudate Nucleus. J Neurochem. 1991;56(1):192–8.
4. Afonso-Oramas D, Cruz-Muros I, Barroso-Chinea P, de la Rosa DÁ, Castro-Hernández J, Salas-Hernández J, et al. The dopamine transporter is differentially regulated after dopaminergic lesion. Neurobiol Dis. 2010;40(3):518–30.
5. Grosset DG, Tatsch K, Oertel WH, Tolosa E, Bajaj N, Kupsch A, et al. Safety analysis of 10 clinical trials and for 13 years after first approval of ioflupane 123I injection (datscan). J Nucl Med. 2014;55(8):1281–7.
6. Morbelli S, Esposito G, Arbizu J, Barthel H, Boellaard R, Bohnen NI, et al. EANM practice guideline/SNMMI procedure standard for dopaminergic imaging in Parkinsonian syndromes 1.0. Eur J Nucl Med Mol Imaging. 2020;47(8):1885–912.
7. Oliveira FPM, Walker Z, Walker RWH, Attems J, Castanheira JC, Silva Â, et al. 123 I-FP-CIT SPECT in dementia with Lewy bodies, Parkinson's disease and Alzheimer's disease: A new quantitative analysis of autopsy confirmed cases. J Neurol Neurosurg Psychiatry. 2021;92(6):662–7.
8. Brisson M, Brodeur C, Létourneau-Guillon L, Masellis M, Stoessl J, Tamm A, et al. CCCDTD5: Clinical role of neuroimaging and liquid biomarkers in patients with cognitive impairment. Alzheimer's Dement Transl Res Clin Interv. 2020;6(1):1.

Expert essay

Tau PET for the diagnosis and staging of Alzheimer's disease

Tharick A. Pacoal, Annie Cohen, Victor L. Villemagne

Department of Psychiatry, University of Pittsburgh, PA, UNITED STATES

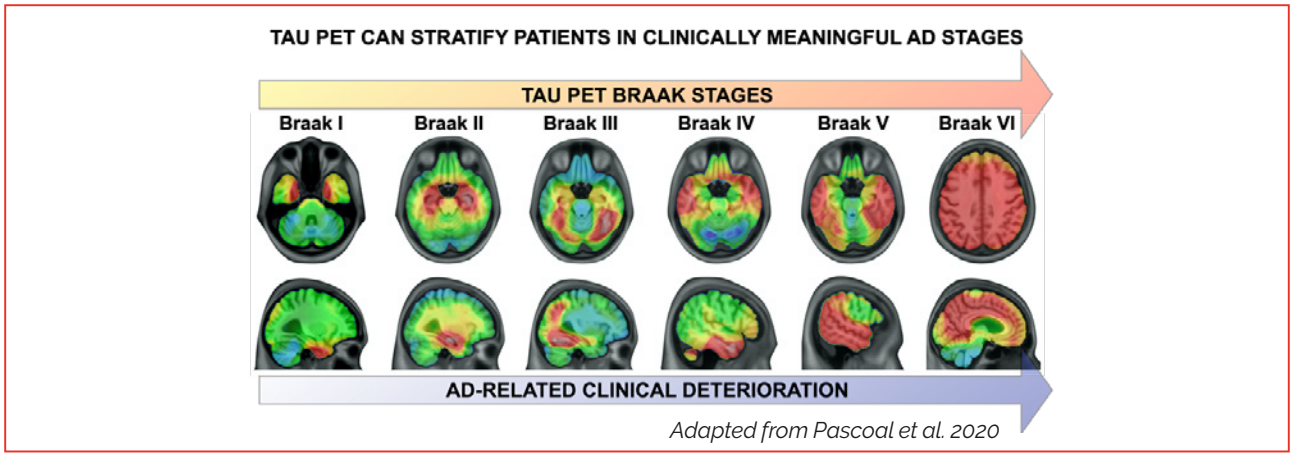
The neuropathological signatures of Alzheimer's disease are brain deposits of amyloid-β plaques and hyperphosphorylated tau protein in the form of neurofibrillary tangles (1). The quantification of these pathological processes in the brain of living patients is critical to identifying individuals with underlying Alzheimer's disease pathophysiology, which can provide a more accurate diagnosis of Alzheimer's disease for research and clinical settings. Biomarkers derived from PET (Positron Emission Tomography) imaging, unlike biomarkers measured in blood or CSF (cerebrospinal fluid), offer the unique opportunity to visualise the distribution of the pathology in the human brain. Klunk and colleagues reported the first results showing direct visualisation of Alzheimer's disease pathophysiology in the living human brain with the amyloid-β PET tracer Pittsburgh Compound-B (PIB) more than 15 years ago (2). Since then, several studies have confirmed that amyloid-β PET tracers are valuable tools for identifying Alzheimer's disease pathophysiology (3), which culminated in the United States Food and Drug Administration (FDA) approval of Aβ PET compounds for clinical use.

More recently, the field of Alzheimer's disease is increasingly focused on tau PET biomarkers because changes in tau pathology are more closely related to the development of clinical symptoms and post-mortem studies suggest that tau accumulation follows a temporal stereotypical pattern known as Braak stages, suggesting that identifying these stages can help define how far the person is in the course of the disease (4). Several post-mortem studies support that these so-called Braak stages of tau accumulation are closely related to other aspects of Alzheimer's disease pathophysiology, such as amyloid-b deposition, neuronal injury, and cognitive impairment (4). Thus, Braak staging was incorporated in the neuropathological diagnosis criteria of Alzheimer's disease (5). Based on the above-mentioned post-mortem observations, it has been postulated that in vivo Braak staging obtained with tau PET has the potential to stratify patients according to their brain patterns of tau accumulation, offering evidence on the patients' tau pathology and disease stage, which could provide valuable information to clinicians to track Alzheimer's disease progression.

Indeed, tau PET tracers have shown high performance for separate individuals with cognitive impairment due to Alzheimer's disease from other causes of dementia (>85–95%) (6). In addition, several lines of evidence suggest that tau PET can significantly add diagnostic value to amyloid-β PET if used in clinical settings (7). Recognising the potential clinical applicability of tau PET, the US FDA has recently approved the tau PET tracer Tauvid (flortaucipir) for clinical use. To date, Tauvid is the first and only FDA-approved tau tracer to clinically estimate the density and distribution of tau tangles pathology in the brain of adult individuals with cognitive impairment in whom Alzheimer's disease is suspected as a possible aetiology.

Recently, second-generation tau PET tracers (e.g., MK-6240, PI-2620, GTP1, RO948, JNJ-067) have been developed to provide better visualisation of tau pathology (12–16), minimising off-target binding to brain pathologies other than tau and increasing the sensitivity to detect low concentrations of tau tangles pathology.

Studies using the second-generation tau PET tracer MK-6240, which has a high sensitivity to detect tau tangles pathology (~6 times higher than the first-generation tau tracers such as the Tauvid), have shown that tau PET tracers are capable of entirely recapitulating the post-mortem stages proposed by Braak and colleagues (4,6,8). These studies suggest that the stratification of patients into seven Braak-like classes of tau accumulation (Braak 0-VI) can provide invaluable clinical information overlooked by dichotomisation techniques (merely indicating tau positivity or tau negativity). These studies have demonstrated that, in the absence of any other biomarker in clinical practice, patients with a tau PET Braak stage 0 (indicating the absence of tau pathology) could be associated with a very low risk of presenting brain amyloid-β pathology, neurodegeneration, and cognitive impairment, individuals classified as tau PET Braak stage IV or greater with a very high risk of presenting underlying neurodegeneration, and tau PET Braak stages V or VI with likely imminent development of dementia symptoms (6) (Figure). These results highlight that in vivo Braak staging using the novel high-sensitivity tau PET tracers can provide a more comprehensive evaluation of the



Adapted from Pascoal et al. 2020

clinical significance of underlying tau deposition as compared to mere dichotomisation into tau positive and negative classes.

Tau PET tracers are also important to the enrichment and monitoring of clinical trials designed to test novel pharmacological interventions to treat Alzheimer's disease. Years of research on fluid biomarkers (phosphorylated-tau or amyloid-β in CSF and now in the blood) and amyloid-β PET studies have shown severe limitations of these markers for longitudinal quantification of Alzheimer's disease-related changes at the level of the individual (9). Unlike other available markers of Alzheimer's disease pathophysiology, individuals with cognitive impairment assessed with tau PET show rates of longitudinal tau accumulation at 12–24 months suitable for use as a surrogate marker in clinical trials (10,11). Thus, in addition to its use for diagnosis and staging Alzheimer's disease pathophysiology, tau PET offers a tool capable of testing the effects of drug therapies in reducing the longitudinal progression of Alzheimer's disease pathophysiology over typical clinical trial periods (12–24 months).

References

1. Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. Lancet Neurol 2013;12:207–16. https://doi.org/10.1016/S1474-4422(12)70291-0.
2. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging Brain Amyloid in Alzheimer's Disease with Pittsburgh Compound-B. Ann Neurol 2004;55:306–19. https://doi.org/10.1002/ana.20009.
3. Rabinovici GD, Gatsonis C, Apgar C, Chaudhary K, Gareen I, Hanna L, et al. Association of Amyloid Positron Emission Tomography with Subsequent Change in Clinical Management among Medicare Beneficiaries with Mild Cognitive Impairment or Dementia. JAMA – J Am Med Assoc 2019;321:1286–94. https://doi.org/10.1001/jama.2019.2000.
4. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991;82(4):239–59.
5. Montine TJ, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Dickson DW, et al. National institute on aging-Alzheimer's association guidelines for the neuropathologic assessment of Alzheimer's disease: A practical approach. Acta Neuropathol 2012;123:1–11. https://doi.org/10.1007/s00401-011-0910-3.
6. Pascoal TA, Therriault J, Benedet AL, Savard M, Lussier FZ, Chamoun M, et al. 18F-MK-6240 PET for early and late detection of neurofibrillary tangles. vol. 143. Brain; 2020. https://doi.org/10.1093/brain/awaa180.
7. Ossenkoppele R, Rabinovici GD, Smith R, Cho H, Scholl M, Strandberg O, et al. Discriminative accuracy of [18F]flortaucipir positron emission tomography for Alzheimer disease vs other neurodegenerative disorders. JAMA – J Am Med Assoc 2018;320:1151–62. https://doi.org/10.1001/jama.2018.12917.
8. Pascoal TA, Shin M, Kang MS, Chamoun M, Chartrand D, Mathotaarachchi S, et al. In vivo quantification of neurofibrillary tangles with [18 F]MK-6240. Alzheimer's Res Ther 2018. https://doi.org/10.1186/s13195-018-0402-y.
9. Toledo JB, Xie SX, Trojanowski JQ, Shaw LM. Longitudinal change in CSF Tau and Aβ biomarkers for up to 48 months in ADNI. Acta Neuropathol 2013;126:659–70. https://doi.org/10.1007/s00401-013-1151-4.
10. Jack CR, Wiste HJ, Schwarz CG, Lowe VJ, Senjem ML, Vemuri P, et al. Longitudinal tau PET in ageing and Alzheimer's disease. Brain 2018;141:1517–28. https://doi.org/10.1093/brain/awy059.
11. Pascoal TA, others. Longitudinal [18F]MK-6240 tau tangles accumulation follows Braak stages. Brain (in Press 2021).
12. Sanabria Bohórquez S, Marik J, Ogasawara A, Tinianow JN, Gill HS, Barret O, et al. [18F]GTP1 (Genentech Tau Probe 1), a radioligand for detecting neurofibrillary tangle tau pathology in Alzheimer's disease. Eur J Nucl Med Mol Imaging 2019;46:2077–89. https://doi.org/10.1007/s00259-019-04399-0.
13. Mormino EC, Toueg TN, Azevedo C, Castillo JB, Guo W, Nadiadwala A, et al. Tau PET imaging with 18F-PI-2620 in aging and neurodegenerative diseases. Eur J Nucl Med Mol Imaging 2021;48:2233–44. https://doi.org/10.1007/s00259-020-04923-7.
14. Leuzy A, Smith R, Ossenkoppele R, Santillo A, Borroni E, Klein G, et al. Diagnostic performance of RO948 F 18 tau positron emission tomography in the differentiation of alzheimer disease from other neurodegenerative disorders. JAMA Neurol 2020;77:955–65. https://doi.org/10.1001/jamaneurol.2020.0989.
15. Brendel M, Barthel H, Van Eimeren T, Marek K, Beyer L, Song M, et al. Assessment of 18F-PI-2620 as a Biomarker in Progressive Supranuclear Palsy. JAMA Neurol 2020;77:1408–19. https://doi.org/10.1001/jamaneurol.2020.2526.
16. Baker SL, Provost K, Thomas W, Whitman AJ, Janabi M, Schmidt ME, et al. Evaluation of [18F]-JNJ-64326067-AAA tau PET tracer in humans. J Cereb Blood Flow Metab 2021;2716. https://doi.org/10.1177/0271678X211031035.

Conclusions

When an individual presents with suspected signs or symptoms of cognitive decline, clinicians will perform the basic dementia assessments such as medical history, neurological examination, basic laboratory screening tests, and cognitive assessment.

Other tools, such as PET and SPECT techniques, that visualise and quantify an extensive list of biochemical processes have undergone much progress in the last fifteen years. However, the availability of PET and SPECT screening methods to diagnose the underlying causes of dementia remains limited worldwide due to cost and accessibility, even in high-income countries.

Although PET can identify Alzheimer's disease pathophysiology, substantial progress has also been achieved for other neurodegenerative conditions.

Additional references

1. Jack CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol [Internet]. 2010;9(1):119–28. https://dx.doi.org/10.1016/s1474-4422(09)70299-6
2. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's Dement. 2018;14(4):535–62.
3. Clark CM, Schneider JA, Bedell BJ, Beach TG, Bilker WB, Mintun MA, et al. Use of florbetapir-PET for imaging β-amyloid pathology. JAMA – J Am Med Assoc [Internet]. 2011;305(3):275–83. https://dx.doi.org/10.1001/jama.2010.2008
4. Chételat G, Arbizu J, Barthel H, Garibotto V, Law I, Morbelli S, et al. Amyloid-PET and 18F-FDG-PET in the diagnostic investigation of Alzheimer's disease and other dementias. Lancet Neurol [Internet]. 2020;19(11):951–62. https://dx.doi.org/10.1016/s1474-4422(20)30314-8
5. Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, et al. Appropriate use criteria for Amyloid PET: A report of the Amyloid imaging task force the society of nuclear medicine and molecular imaging and the Alzheimer's association. J Nucl Med. 2013;54(3):476–90.
6. Villemagne VL, Doré V, Burnham SC, Masters CL, Rowe CC. Imaging tau and amyloid-β proteinopathies in Alzheimer disease and other conditions. Nat Rev Neurol [Internet]. 2018;14(4):225–36. https://dx.doi.org/10.1038/nrneurol.2018.9
7. Leuzy A, Chiotis K, Lemoine L, Gillberg PG, Almkvist O, Rodriguez-Vieitez E, et al. Tau PET imaging in neurodegenerative tauopathies–still a challenge. Mol Psychiatry [Internet]. 2019;24(8):1112–34. https://dx.doi.org/10.1038/s41380-018-0342-8
8. Minguez-Castellanos A, Chamorro CE, Escamilla-Sevilla F, Ortega-Moreno A, Rebollo AC, Gomez-Rio M, et al. Do α-synuclein aggregates in autonomic plexuses predate Lewy body disorders?: A cohort study. Neurology [Internet]. 2007;68(23):2012–8. https://dx.doi.org/10.1212/01.wnl.0000264429.59379.d9
9. Djang DSW, Janssen MJR, Bohnen N, Booij J, Henderson TA, Herholz K, et al. SNM practice guideline for dopamine transporter imaging with 123I-ioflupane SPECT 1.0. J Nucl Med [Internet]. 2012;53(1):154–63. https://dx.doi.org/10.2967/jnumed.111.100784.

Chapter 11
Spinal fluid

Pedro Rosa-Neto, Eduardo Zimmer

Key points

- Lumbar puncture (cerebrospinal fluid or CSF) is a safe and acceptable procedure towards a specific diagnosis in people with dementia of uncertain aetiology.
- Cerebrospinal fluid analysis biomarkers constitute an affordable alternative to imaging biomarkers, with excellent diagnostic properties.
- There is a need for cerebrospinal fluid biomarkers specific for dementias of causes other than Alzheimer's disease.
- Accessibility to cerebrospinal fluid analytical infrastructure remains unavailable in the vast majority of low- and middle-income countries.

General background

Cerebrospinal fluid (CSF) is a clear fluid that protects and supplies nutrients and clears metabolic waste from the brain and spinal cord. Every day, the brain produces nearly half a litre of cerebrospinal fluid, which carries proteins associated with neurodegenerative conditions. The CSF obtained via lumbar puncture is a safe and cost-efficient way to identify the presence of a pathological process in the brain.

> **The CSF obtained via lumbar puncture is a safe and cost-efficient way to identify the presence of a pathological process in the brain.**

Cerebrospinal fluid profile provides information regarding the underlying cause of dementia

In the field of dementia, biomarkers are defined as objective measures of biological or pathogenic processes obtained in living individuals (1). Measures of amyloid or neurofibrillary tangles are biomarkers of brain protein aggregation and reflect the core brain pathology underlying Alzheimer's disease. Unfortunately, apart from Alzheimer's disease, there are no biomarkers specific for other neurodegenerative conditions. Biomarkers of neurodegeneration designate tests (that is, structural MRI, PET-FDG, Nfl and total-tau in the CSF) assess brain damage secondary to Alzheimer's disease or other neurodegenerative dementias. Brain atrophy, reduction of metabolism, release of tau protein in the CSF are measures of brain damage present in all dementias (2). Biomarkers of neurodegeneration can be obtained using MRI, PET, cerebrospinal fluid or blood. Regarding their origin, they are designated as imaging or fluid biomarkers. It is expected that researchers will develop biomarkers able to identify protein aggregates such as alpha-synuclein, 3-R or 4R tau, TDP-43.

The cerebrospinal fluid is an optimal source for Alzheimer's disease biomarkers due to its direct contact with the brain's extracellular space. This physical contiguity between the brain and CSF is advantageous to obtain information regarding abnormal brain processes (3).

As dementia can be caused by various diseases, the goal of cerebrospinal fluid biomarkers in clinical practice is to diagnose Alzheimer's disease in people with dementia

(4). Indeed, one might claim that cerebrospinal fluid biomarkers have an advantage over their PET counterparts by providing a measure of brain amyloid pathology (Aβ42), and t-tau (neurodegeneration), and p-tau (neurofibrillary tangles) in a single test. In fact, cerebrospinal fluid information is sufficient to meet the requirements for the 2018 operational definitions of Alzheimer's disease.

Fluid biomarkers analysis improves the diagnostic of the underlying cause of dementia using a more affordable technology as compared to PET scans. The role of fluid biomarkers in patient care is an evolving field in the face of recent developments of biomarkers for other neurodegenerative conditions (5).

Although cerebrospinal fluid biomarkers are well-established clinic diagnostic tests in some European countries, they are not routine clinical practice elsewhere. The major obstacle impeding CSF dissemination is the availability of an appropriated laboratory infrastructure for analysis.

The most studied biomarkers for dementia are the monomeric form of amyloid beta 42 (Aβ42), the total tau (t-tau), and the tau phosphorylated at threonine 181 (p-tau-181) (see Table 1).

Amyloid isoforms

Aβ42 is one of the most abundant amyloid species in the CSF. It is produced during normal cell metabolism and is secreted into the extracellular space. As Aβ42 is retained in amyloid plaques in the brain of people with Alzheimer's disease, CSF Aβ42 in Alzheimer's disease is decreased to approximately 50% of control levels. Although methodology to quantify Aβ species is mature, cerebrospinal fluid handling from collection to the analysis may be complex due to the Aβ42 physicochemical properties. The ratio between Aβ42/40 has been proposed as a robust measure of amyloidosis, however its use remain restricted to selective clinical centres (3,6).

Phosphorylated tau isoforms

Tau is a neuronal protein part of the skeleton of the brain cells with a large number of phosphorylation sites. Hyperphosphorylation of tau constitutes an important molecular abnormality of Alzheimer's disease. In fact, neurofibrillary tangles are composed by the aggregation of hyperphosphorylated tau. P-tau CSF analysis targets specific to certain phosphorylation sites, namely the 181 (p-tau181) or 217 (p-tau-217) were recently recognised for their excellent diagnostic performance of Alzheimer's disease. Studies using these assays have consistently revealed a robust increase in CSF P-tau in Alzheimer's disease but not in t=other dementia conditions. All phospho-tau isoforms are considered as core biomarkers of Alzheimer's disease (7–9).

Total tau protein

Total tau measured in the CSF belongs to a pool of cytoskeleton proteins secreted to the extracellular space. In the CSF, total tau provides a metric of brain integrity, independent of specific neuronal insult. Cerebrospinal fluid t-tau in Alzheimer's disease might reach 300% of control levels. Total tau is considered a biomarker of neurodegeneration (10).

Several consensus recommendations have been published to provide guidance in the utilisation of cerebrospinal fluid in dementia or predementia cases. In summary, these biomarker tests seem particularly useful in the diagnostic workup of individuals of atypical cases, early-onset dementia and rapid progressive cases (11–13).

Limitations regarding the use of cerebrospinal fluid in dementia diagnosis

The dissemination of cerebrospinal fluid biomarkers is hampered by several factors. First, lumbar punctures remain a complex procedure to be conducted as routine in primary care. Second, handling of CSF samples requires some degree of expertise. Third, analytical infrastructure remains confined at expert centres. Fourth, the absence of cerebrospinal fluid biomarkers for diagnosis of other dementia diseases constitutes an important diagnostic limitation.

Table 1. Clinically relevant cerebrospinal fluid biomarkers for Alzheimer's disease

Pathophysiology	Biomarker	Key References
Amyloid pathology (biomarker of)	AB1–42 (AB 42/40 ratio)	(14) (7) (8) (6)
Tau pathology (core Alzheimer's disease biomarker)	p-tau-181, p-tau-217	
Neurodegeneration (not specific)	t-tau, NfL	

Survey results

The 1,111 multidisciplinary clinicians who responded to the survey revealed that only 35% of clinicians use lumbar punctures to assist in the diagnosis of dementia in selected cases based on national practice guidelines, while 5% of clinicians do this in all patients (Chart 1). These lumbar punctures are mostly performed by neurologists (Chart 2). These responses support the idea that although lumbar punctures constitute an acceptable method for assessing people with dementia (Chapter 11), they are currently underutilised.

Lumbar puncture and cerebrospinal fluid seem to offer an affordable alternative for imaging biomarkers. However, there are limitations regarding the accessibility of CSF infrastructure for the analysis of cerebrospinal fluid.

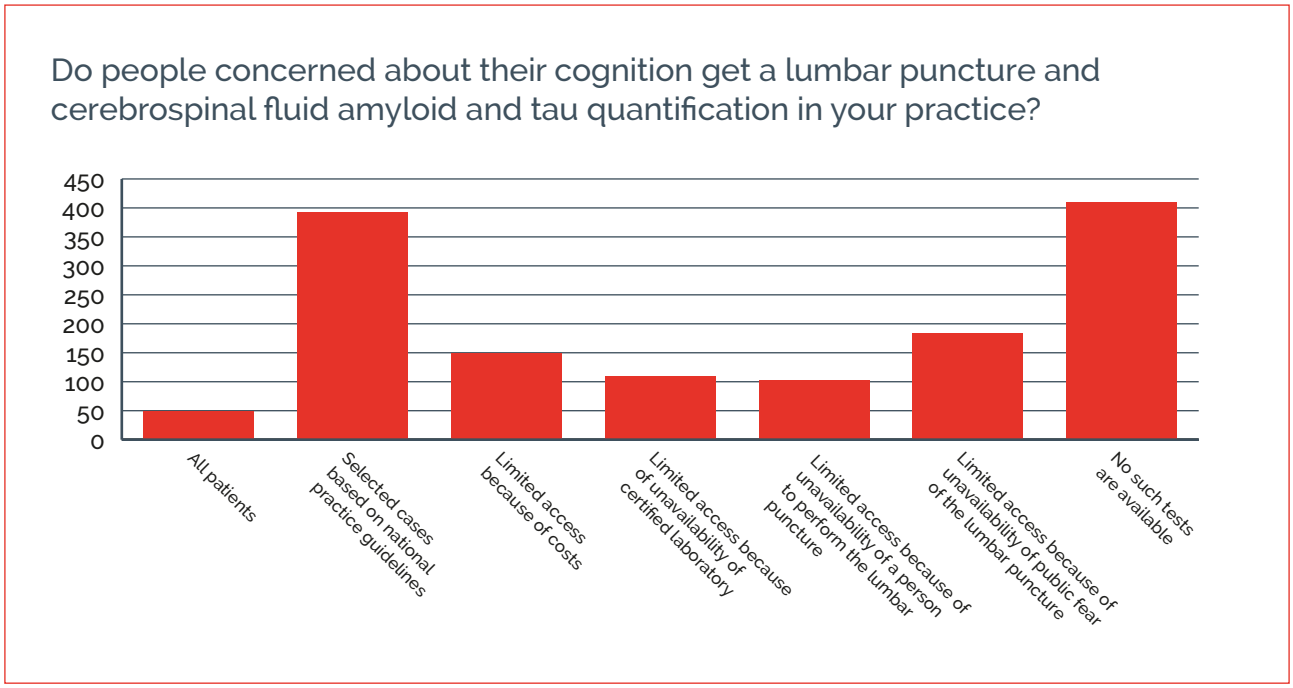


Chart 1. Clinician responses.

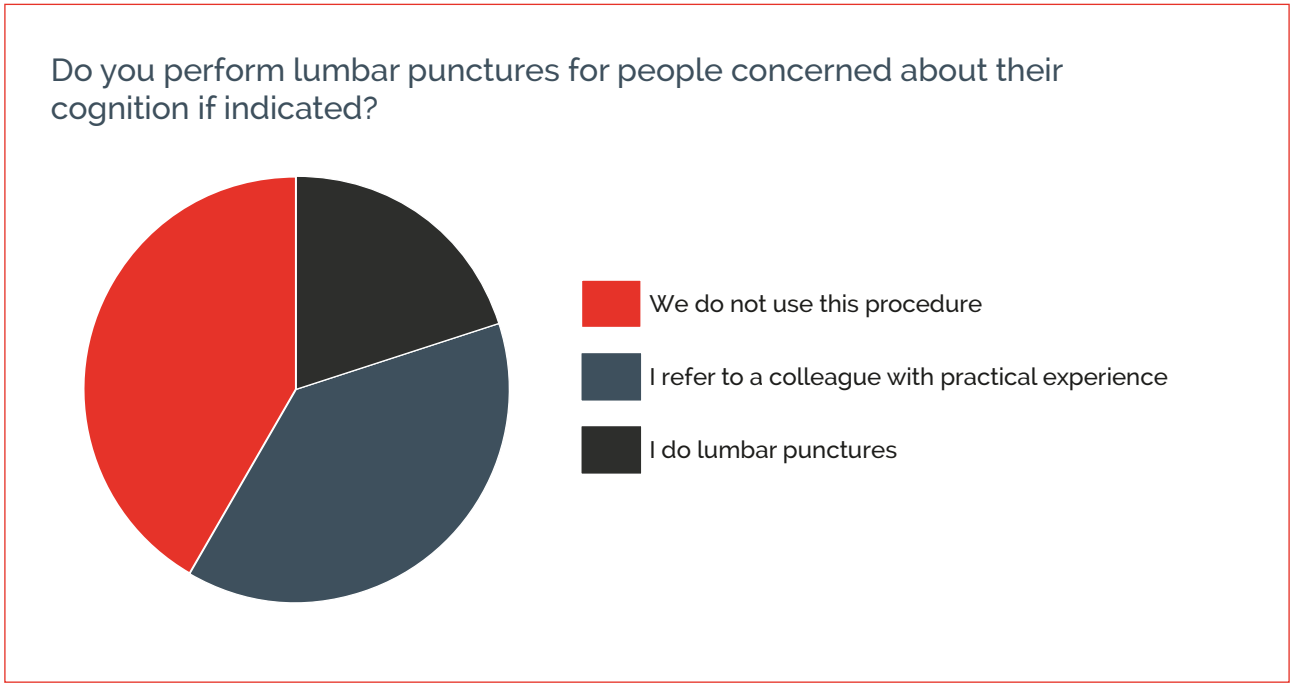


Chart 2. Clinician responses.

Expert essay

How to reassure people in need of a lumbar puncture

Paolo Vitali

McGill University Research Centre for Studies in Aging, CANADA

Lumbar puncture is a unique medical procedure to collect samples of cerebrospinal fluid (CSF) surrounding brain and spinal cord. It represents a relatively non-invasive way to gain direct access to the central nervous system, compared to other more aggressive surgical techniques such as brain biopsy or external ventricular drain. Given its proximity to the central nervous system structures, CSF analysis provides vital information about pathophysiological processes underlying neurological disorders, such as infectious, inflammatory, autoimmune, and neoplastic diseases.

There is no denying that the prospect of a lumbar puncture procedure is very stressful for most people. One way to mitigate the anxiety related to the technique is to keep the individual informed every step of the way throughout the procedure, explaining in simple terms why and how the lumbar puncture is performed, detailing whether there is any associated discomfort or risk, and how to go about minimising the possible minor side effects.

Below is a review of the important features of a lumbar puncture, all with the aim to reassure people who will undergo the procedure.

What to expect?

The procedure lasts approximately 15 minutes and basically consists of inserting a small atraumatic needle into the lower back, similar to the epidural procedure for pregnant women during labour. Before the lumbar puncture itself, people are asked to lie down comfortably on their side or sit with their back arched. The back is then cleansed with antiseptics to prevent infections. Subsequently, a local anaesthesia, (like a dental anaesthesia) is provided. The anaesthesia will numb most of the discomfort experienced from the insertion of the spinal needle. During the lumbar puncture, a needle will be inserted, under aseptic conditions, between two of the bones in the back into a fluid-filled space. The needle enters a space below the actual spinal cord. The lower back is generally considered the safest site to perform a lumbar puncture. Once the needle attains the fluid space, the spinal fluid will be removed for testing. After the lumbar puncture, the person will be asked to drink water or juice and rest in a bed for at least one hour. The amount of spinal fluid removed is naturally replaced by the body after approximately one hour. People are generally invited to avoid driving after a lumbar puncture. The next day, a follow-up call is made to verify that everything is fine and answer questions.

Why perform a lumbar puncture in patients with memory changes?

In memory clinics, lumbar puncture is largely performed by trained physicians to investigate in cognitively impaired patients the presence of abnormal proteins in the CSF, which are generally associated with underlying neurodegenerative conditions. Detection of abnormal values of amyloid beta, tau and phospho-tau in CSF can help diagnose Alzheimer's disease. In Canada, CSF analysis is not recommended routinely, but it can be considered in symptomatic patients with diagnostic uncertainty and onset at an early age (<65) to rule out Alzheimer's disease pathophysiology. CSF analysis can also be considered in patients with atypical cognitive deficits such as predominance of language, visuospatial, dysexecutive, or behavioural features to rule out Alzheimer's disease pathophysiology (2). A CSF-based diagnosis will eliminate diagnostic incertitude and help people receive more adequate treatments and appropriate referral to clinical trials if available.

Will it be painful?

Contrary to what is commonly believed, due to the anaesthetic most people do not feel any discomfort during a lumbar puncture, except for some pressure in the back. In most memory clinics, especially where research lumbar punctures are performed, physicians are required to complete a lumbar puncture certificate to guarantee that the standard operational procedures respected. Complying with evidence-based guidelines contributes to reduced discomfort and complication rates. It has been proven that the use of atraumatic (small) needles with an introducer, not more than four lumbar puncture attempts, passive withdrawal of

CSF (instead of active withdrawal using a syringe), collection of up to 30 mL of CSF, and the lateral recumbent position minimise complaints and complications (3).

Which are the risks?

Lumbar puncture is considered a safe procedure. Post-lumbar puncture complaints are generally mild and severe complications are extremely rare (< 0.01%) (4). Per procedure, nerve root irritation by the needle – occasioning intermittent electric shocks down in one leg – is relatively common, but not dangerous nor associated to any complication. After the procedure, lower back pain may be experienced, which is essentially related to the number of attempts and failures. For the experienced physician, this amount is low. Post lumbar puncture headache is the most frequent complication and occurs in 9% of cases (4). Classically, this happens over the subsequent three days when sitting or standing and subsides when lying down. To prevent this, people are asked to rest at for least one hour after the LP and drink plenty of water (or coffee, which stimulates CSF production). Over the next 24 hours, people are also instructed to refrain from strenuous physical activities. If typical post lumbar puncture headache symptoms arise, the individual is advised to lie down and continue to stay well hydrated. Simple analgesics can help. If the pain persists for a couple of days, a simple procedure, called epidural blood patch, is performed at the emergency department and provides immediate relief. This is done by withdrawing an individual's own blood and injecting it back into the lumbar puncture site where there may be some leaking spinal fluid. This relieves the pressure and seals the leak. Generally, only 0.3% of people need a blood patch procedure. (4).

It should be noted that individuals under the age of 40 typically have higher instances of post lumbar puncture headaches, while conversely, those experiencing cognitive complaints seem to have a protective barrier. (4).

References

1. Rosa-Neto P, Gauthier S. Standard operational procedures (SOP) to perform Cerebral Spinal Fluid Sampling at the Douglas Hospital n.d.
2. Ismail Z, Black SE, Camicioli R, Chertkow H, Herrmann N, Laforce R, et al. Recommendations of the 5th Canadian Consensus Conference on the diagnosis and treatment of dementia. Alzheimer's Dement 2020;16:1182–95. https://doi.org/10.1002/alz.12105.
3. Engelborghs S, Niemantsverdriet E, Struyfs H, Blennow K, Brouns R, Comabella M, et al. Consensus guidelines for lumbar puncture in patients with neurological diseases. Alzheimer's Dement Diagnosis, Assess Dis Monit 2017;8:111–26. https://doi.org/10.1016/j.dadm.2017.04.007.
4. Duits FH, Martinez-Lage P, Paquet C, Engelborghs S, Lleó A, Hausner L, et al. Performance and complications of lumbar puncture in memory clinics: Results of the multicenter lumbar puncture feasibility study. Alzheimer's Dement 2016;12:154–63. https://doi.org/10.1016/j.jalz.2015.08.003.
5. Amorim JA, Gomes De Barros M V., Valença MM. Post-dural (post-lumbar) puncture headache: Risk factors and clinical features. Cephalalgia 2012;32:916–23. https://doi.org/10.1177/0333102412453951.

Expert essay

CSF biomarkers for Alzheimer's disease

Henrik Zetterberg, Kaj Blennow

Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, SWEDEN

The development of Alzheimer's disease fluid biomarkers started with using cerebrospinal fluid (CSF) as the matrix, which was logical based on the proximity of CSF to the brain, and the secretion (at that time called 'shedding') of brain proteins from neurons and other cell types to the extracellular space, which is continuous with the CSF. CSF can easily be collected by lumbar puncture (1).

Based on the knowledge of Alzheimer's disease pathophysiology, methods for the quantification of CSF levels of 'total' tau (T-tau), phosphorylated tau (P-tau) and amyloid b (Aβ42 and Aβ42/40 ratio) were developed. These proteins are often referred to as the 'core' Alzheimer's disease CSF biomarkers. The typical changes in Alzheimer's disease, namely the increased CSF levels of T-tau (reflecting neurodegeneration) and P-tau (a marker for tangles and tau pathology) together with decreased Aβ42 and Aβ42/40 ratio (reflecting brain amyloidosis and plaques), are often called the 'Alzheimer CSF profile'.

A very large number of clinical studies consistently show that these core Alzheimer's disease CSF biomarkers reflect key parts of Alzheimer's disease pathophysiology and have high diagnostic value, also in the early disease stages (2) to identify MCI individuals with 'prodromal Alzheimer's disease' that will progress to Alzheimer's disease at long-term clinical follow up, and to differentiate from both stable MCI cases and MCI people developing other dementias (3). Notably, a wealth of studies have also shown high agreement between CSF Aβ42 (and Aβ42/40 ratio) and amyloid PET positivity, with concordance figures of 90% or higher (4), which is in the same range as the concordance between different expert readers classifying amyloid PET scans as either positive or negative for brain amyloidosis (5). In other words, amyloid PET and CSF biomarkers can be used interchangeably in the clinic, leaving the clinician, together with the individual, the option to decide based on costs, expertise, availability, and risk estimations (radiation exposure vs. post lumbar puncture headache).

It should be noted that CSF T-tau and P-tau correlate closely within Alzheimer's disease and control populations (6), but the correlation is lost in diseases with marked neuronal damage but no tangles or tau pathology, such as acute stroke and Creutzfeldt-Jakob disease (7–9), supporting CSF T-tau as a neurodegeneration biomarker and that CSF P-tau reflects Alzheimer-type tau pathology. For unknown reasons, CSF P-tau seems specifically increased in Alzheimer's disease, and normal in other tauopathies, such as progressive supranuclear palsy and frontotemporal dementia.

Recent developments to standardise the core Alzheimer's disease CSF biomarkers include uniform procedures for the collection of CSF by lumbar puncture and so-called pre-analytical procedures, for example, the use of specific test tubes (to avoid unspecified loss of the protein biomarkers) for CSF collection (10), and the development methods for measurement of these Alzheimer's disease CSF biomarkers on fully automated lab analysers. As an example, the Aβ1–42 method on the Cobas Elecsys platform shows excellent performance and very low between-day variability (11), and the methods for T-tau and P-tau have even higher performance (12). These improvements are important to have exact and consistent readouts for the CSF Alzheimer's disease biomarkers in the clinical routine setting.

CSF biomarkers reflecting other pathogenic mechanisms in Alzheimer's disease include biomarkers for synaptic degeneration, which is an early phenomenon in Alzheimer's disease (13, 14) that is linked to cognitive symptoms (15, 16). One example is the post-synaptic protein neurogranin, that is found in the cortex and hippocampus, brain regions heavily affected in Alzheimer's disease (17, 18), and plays a role in memory formation (19, 20). Increased CSF neurogranin concentration is found in Alzheimer's disease dementia also in the early prodromal phase of disease (21), and high CSF neurogranin predicts future rate of neuronal degeneration (22). Interestingly, high CSF neurogranin is seemingly specific to Alzheimer's disease, while levels are normal in other neurodegenerative disorders such as frontotemporal dementia and progressive supranuclear palsy (23, 24).

In summary, the core CSF Alzheimer's disease biomarkers show very high diagnostic utility, are clinically well validated, and are available today on fully automated instruments that have excellent analytical performance. In many countries all over the world, these biomarkers now have a central place as diagnostic tests in routine clinical practice.

References

1. Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. Nature reviews Neurology. 2010;6(3):131-44.
2. Olsson B, Lautner R, Andreasson U, Ohrfelt A, Portelius E, Bjerke M, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet neurology. 2016;15(7):673-84.
3. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet neurology. 2006;5(3):228-34.
4. Blennow K, Mattsson N, Scholl M, Hansson O, Zetterberg H. Amyloid biomarkers in Alzheimer's disease. Trends in pharmacological sciences. 2015;36(5):297-309.
5. Hansson O, Seibyl J, Stomrud E, Zetterberg H, Trojanowski JQ, Bittner T, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-beta PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimers Dement. 2018.
6. Sjogren M, Davidsson P, Tullberg M, Minthon L, Wallin A, Wikkelso C, et al. Both total and phosphorylated tau are increased in Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2001;70(5):624-30.
7. Hesse C, Rosengren L, Andreasen N, Davidsson P, Vanderstichele H, Vanmechelen E, et al. Transient increase in total tau but not phospho-tau in human cerebrospinal fluid after acute stroke. Neuroscience letters. 2001;297(3):187-90.
8. Riemenschneider M, Wagenpfeil S, Vanderstichele H, Otto M, Wiltfang J, Kretzschmar H, et al. Phospho-tau/total tau ratio in cerebrospinal fluid discriminates Creutzfeldt-Jakob disease from other dementias. Mol Psychiatry. 2003;8(3):343-7.
9. Skillback T, Rosen C, Asztely F, Mattsson N, Blennow K, Zetterberg H. Diagnostic performance of cerebrospinal fluid total tau and phosphorylated tau in Creutzfeldt-Jakob disease: results from the Swedish Mortality Registry. JAMA Neurol. 2014;71(4):476-83.
10. Hansson O, Batrla R, Brix B, Carrillo MC, Corradini V, Edelmayer RM, et al. The Alzheimer's Association international guidelines for handling of cerebrospinal fluid for routine clinical measurements of amyloid beta and tau. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2021.
11. Bittner T, Zetterberg H, Teunissen CE, Ostlund RE, Jr., Militello M, Andreasson U, et al. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of beta-amyloid (1-42) in human cerebrospinal fluid. Alzheimers Dement. 2016;12(5):517-26.
12. Hansson O, Seibyl J, Stomrud E, Zetterberg H, Trojanowski JQ, Bittner T, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-beta PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimer's & dementia: the journal of the Alzheimer's Association. 2018;14(11):1470-81.
13. Masliah E, Mallory M, Alford M, DeTeresa R, Hansen LA, McKeel DW, Jr., et al. Altered expression of synaptic proteins occurs early during progression of Alzheimer's disease. Neurology. 2001;56(1):127-9.
14. Scheff SW, Price DA, Schmitt FA, DeKosky ST, Mufson EJ. Synaptic alterations in CA1 in mild Alzheimer disease and mild cognitive impairment. Neurology. 2007;68(18):1501-8.
15. Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, et al. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol. 1991;30(4):572-80.
16. DeKosky ST, Scheff SW. Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity. Annals of neurology. 1990;27(5):457-64.
17. Represa A, Deloulme JC, Sensenbrenner M, Ben-Ari Y, Baudier J. Neurogranin: immunocytochemical localization of a brain-specific protein kinase C substrate. J Neurosci. 1990;10(12):3782-92.
18. Guadano-Ferraz A, Vinuela A, Oeding G, Bernal J, Rausell E. RC3/neurogranin is expressed in pyramidal neurons of motor and somatosensory cortex in normal and denervated monkeys. J Comp Neurol. 2005;493(4):554-70.
19. Huang KP, Huang FL, Jager T, Li J, Reymann KG, Balschun D. Neurogranin/RC3 enhances long-term potentiation and learning by promoting calcium-mediated signaling. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2004;24(47):10660-9.
20. Wu J, Li J, Huang KP, Huang FL. Attenuation of protein kinase C and cAMP-dependent protein kinase signal transduction in the neurogranin knockout mouse. The Journal of biological chemistry. 2002;277(22):19498-505.
21. Kvartsberg H, Duits FH, Ingelsson M, Andreasen N, Ohrfelt A, Andersson K, et al. Cerebrospinal fluid levels of the synaptic protein neurogranin correlates with cognitive decline in prodromal Alzheimer's disease. Alzheimers Dement. 2015;11(10):1180-90.
22. Portelius E, Zetterberg H, Skillback T, Tornqvist U, Andreasson U, Trojanowski JQ, et al. Cerebrospinal fluid neurogranin: relation to cognition and neurodegeneration in Alzheimer's disease. Brain : a journal of neurology. 2015;138(Pt 11):3373-85.
23. Wellington H, Paterson RW, Portelius E, Tornqvist U, Magdalinou N, Fox NC, et al. Increased CSF neurogranin concentration is specific to Alzheimer disease. Neurology. 2016;86(9):829-35.
24. Portelius E, Olsson B, Hoglund K, Cullen NC, Kvartsberg H, Andreasson U, et al. Cerebrospinal fluid neurogranin concentration in neurodegeneration: relation to clinical phenotypes and neuropathology. Acta neuropathologica. 2018;136(3):363-76.

Conclusions

Cerebrospinal fluid biomarkers provide reliable and clinically relevant diagnostic information in dementia cases of diagnostic uncertainly. Due to its lower cost, cerebrospinal fluid biomarker might constitute a viable diagnostic method in low- and middle-income countries. Importantly, the scalability of cerebrospinal fluid biomarkers seems a sustainable option for assessing patient eligibility for the upcoming disease-modifying interventions. Cerebrospinal fluid biomarker research developments bring hope for the diagnosis of non-Alzheimer's disease neurodegenerative processes underlying dementia.

Additional references

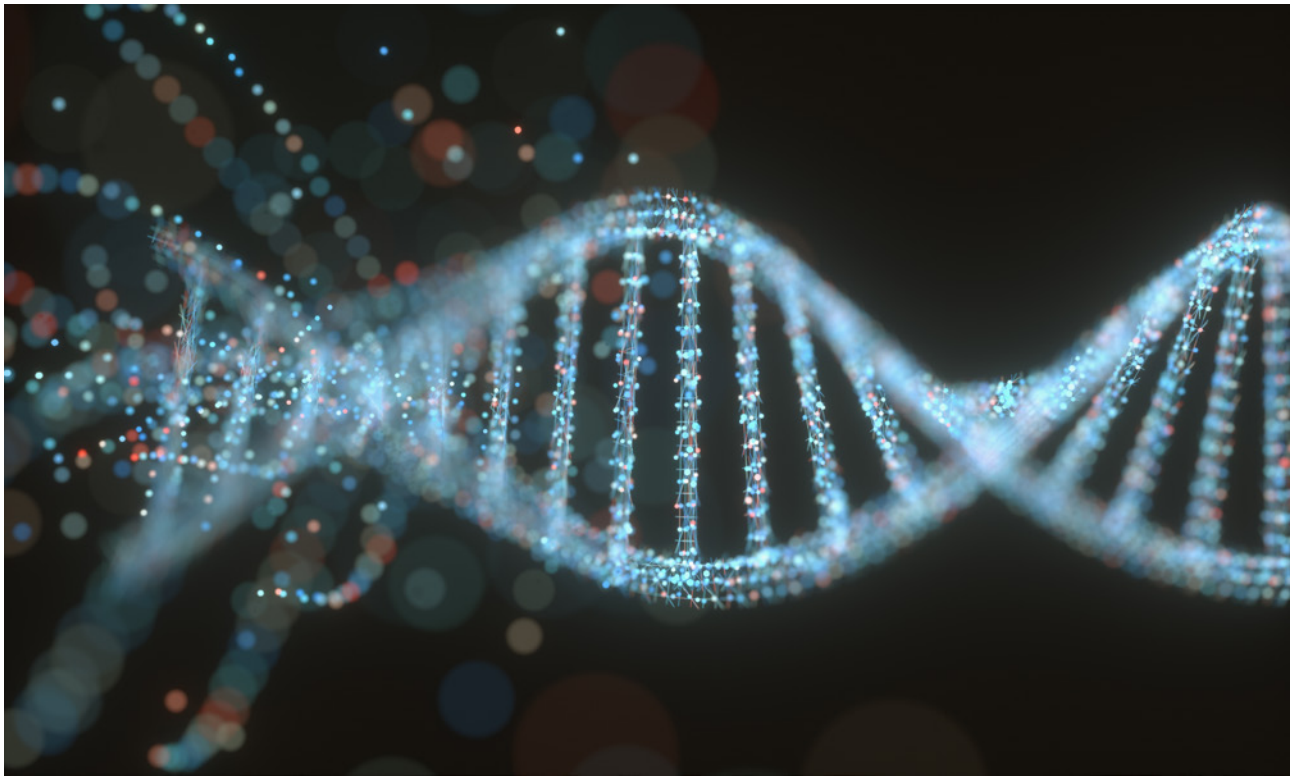
1. Atkinson AJ, Colburn WA, DeGruttola VG, DeMets DL, Downing GJ, Hoth DF, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69:89–95. https://doi.org/10.1067/mcp.2001.113989.
2. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's Dement 2018;14:535–62. https://doi.org/10.1016/j.jalz.2018.02.018.
3. Blennow K, Zetterberg H, Fagan AM. Fluid biomarkers in Alzheimer disease. Cold Spring Harb Perspect Med 2012;2:9. https://doi.org/10.1101/cshperspect.a006221.
4. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement 2011;7:263–9. https://doi.org/10.1016/j.jalz.2011.03.005.
5. Hansson O. Biomarkers for neurodegenerative diseases. Nat Med 2021;27:954–63. https://doi.org/10.1038/s41591-021-01382-x.
6. Hansson O, Lehmann S, Otto M, Zetterberg H, Lewczuk P. Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's Disease. Alzheimer's Res Ther 2019;11:1–15. https://doi.org/10.1186/s13195-019-0485-0.
7. Mattsson N, Zetterberg H, Hansson O, Andreasen N, Parnetti L, Jonsson M, et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. JAMA – J Am Med Assoc 2009;302:385–93. https://doi.org/10.1001/jama.2009.1064.
8. Janelidze S, Stomrud E, Smith R, Palmqvist S, Mattsson N, Airey DC, et al. Cerebrospinal fluid p-tau217 performs better than p-tau181 as a biomarker of Alzheimer's disease. Nat Commun 2020;11:1. https://doi.org/10.1038/s41467-020-15436-0.
9. Ritchie C, Smailagic N, Noel-Storr AH, Ukoumunne O, Ladds EC, Martin S. CSF tau and the CSF tau/ABeta ratio for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev 2017;2017. https://doi.org/10.1002/14651858.CD010803.pub2.
10. Leuzy A, Cullen NC, Mattsson-Carlgren N, Hansson O. Current advances in plasma and cerebrospinal fluid biomarkers in Alzheimer's disease. Curr Opin Neurol 2021;34:266–74. https://doi.org/10.1097/WCO.0000000000000904.
11. Simonsen AH, Herukka SK, Andreasen N, Baldeiras I, Bjerke M, Blennow K, et al. Recommendations for CSF AD biomarkers in the diagnostic evaluation of dementia. Alzheimer's Dement 2017;13:274–84. https://doi.org/10.1016/j.jalz.2016.09.008.
12. Ismail Z, Black SE, Camicioli R, Chertkow H, Herrmann N, Laforce R, et al. Recommendations of the 5th Canadian Consensus Conference on the diagnosis and treatment of dementia. Alzheimer's Dement 2020;16:1182–95. https://doi.org/10.1002/alz.12105.
13. Hort J, O'Brien JT, Gainotti G, Pirttila T, Popescu BO, Rektorova I, et al. EFNS guidelines for the diagnosis and management of Alzheimer's disease. Eur J Neurol 2010;17:1236–48. https://doi.org/10.1111/j.1468-1331.2010.03040.x.
14. Ashton NJ, Janelidze S, Al Khleifat A, Leuzy A, van der Ende EL, Karikari TK, et al. A multicentre validation study of the diagnostic value of plasma neurofilament light. Nat Commun 2021;12. https://doi.org/10.1038/s41467-021-23620-z.

Chapter 12
Genetic testing

Pedro Rosa-Neto

Key points

- A structured genetic assessment is required if there is a suspicion of familial type of dementia.
- Genetic assessments should be conducted by a specialised team able to manage all the medical, ethical and social complexities associated with genetic testing.
- Although APOE4 is the major genetic risk factor for Alzheimer's disease, APOE4 genotyping is not currently recommended in routine clinical practice.
- Access to genetic assessment constitutes a major challenge in low- and middle-income countries.



General background

The risk of developing dementias such as Alzheimer's disease, Lewy body or frontotemporal dementias may be dependent on certain genes. These genes can either cause, protect or increase the risk of developing dementia. When several members of a family have been previously affected by dementia, an individual should be carefully assessed by healthcare professionals to determine whether a genetic component runs in their family and may increase their chances of developing the condition. As such, doctors will select the appropriate tests to order, interpret the findings, and share the results with the individuals concerned.

> **When several members of a family have been previously affected by dementia, an individual should be carefully assessed by healthcare professionals to determine whether a genetic component runs in their family and may increase their chances of developing the condition.**

Survey results

17% of the multidisciplinary clinicians who participated in the survey indicated that they have access to genetic testing in accordance with national guidelines while 39% indicated that genetic testing is performed based on clinical grounds. While genetic testing is not available to 35% of the participants, 33% had limited access. Low- and middle-income countries have less accessibility (Chart 1).

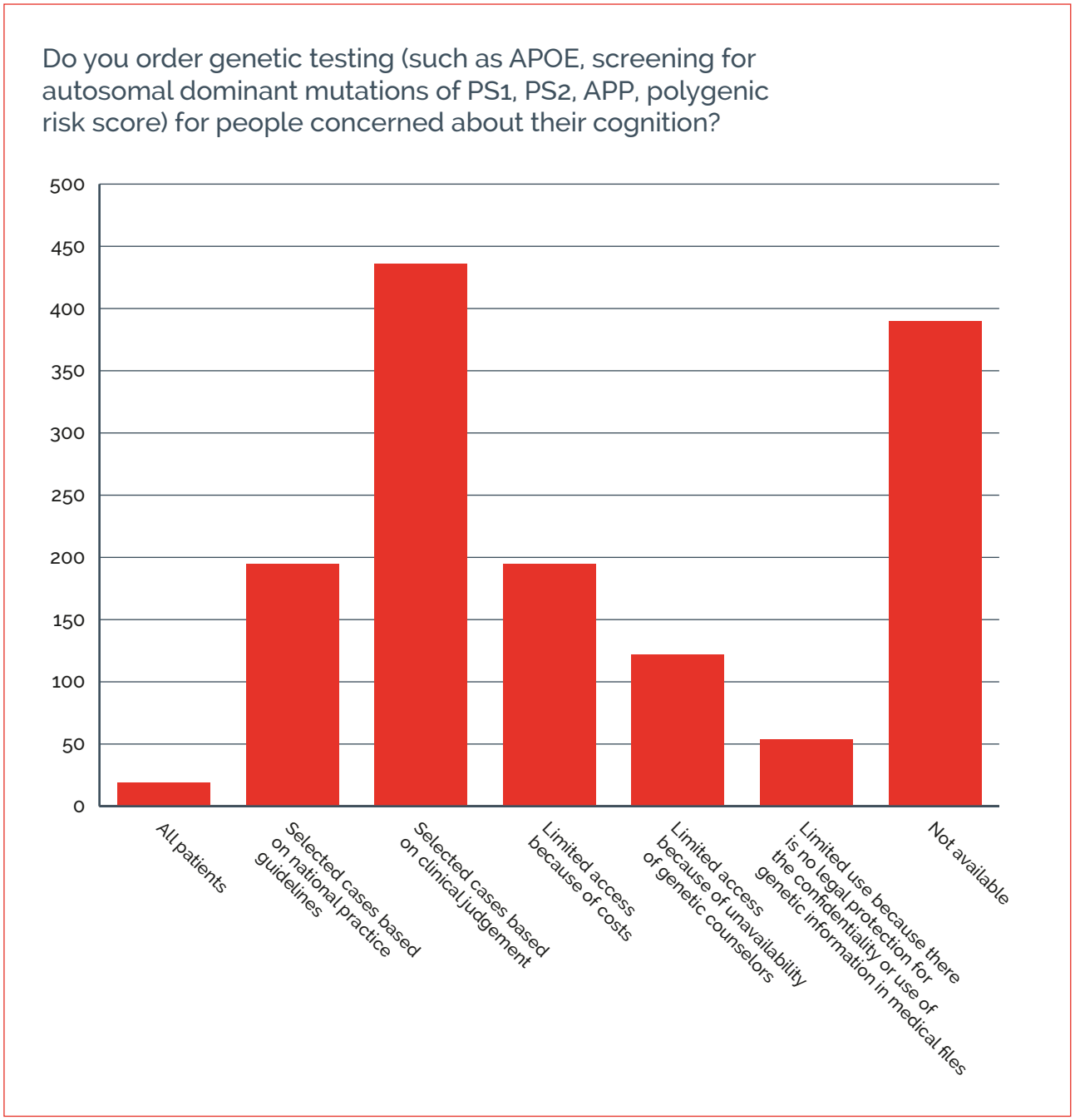


Chart 1. Clinician responses.

Genetic testing

The risk associated with developing dementia is often discussed with the children of people with dementia or members from families with a high rate of dementia. However, only in specific cases, do genetic assessments becomes an important consideration for the person and their family members. Genetic assessment searches for defects in genes that causes brain accumulation of amyloid, tau, alpha-synuclein, transactive response DNA binding protein 43 kD (TDP-43) and other pathogenic proteins. When well indicated, genetic testing offers a precise molecular diagnosis and guides family members to determine their own personal risk, provides a basis for reproductive choices and offers options for clinical trials (1).

When is genetic assessment of dementia patients needed?

Most dementia cases are caused by illnesses in which a certain pool of genes might confer vulnerability to disease pathophysiology. However, in a small percentage of cases, dementias are caused by rare mutations, or copy number variants, or repeat expansions. While some of these cases may be recessive, others show an autosomal dominant pattern. At primary care, family history plays an important role in identifying those individuals with a high number of affected family members, particularly at a young age. While recording the family history, one should take into consideration multiple phenotypes within a family (namely, frontotemporal dementia and motoneuron diseases or progressive aphasia). Families with a high frequency of young-onset or atypical dementias should be assessed by a multidisciplinary team capable of handling the complexities associated with the diagnostic procedures, disclosure, counselling, and management of these families. Such an assessment should include cognitive testing, neurological examination and a multi-generation family history able to estimate the likelihood of an autosomal dominant trait (that is, the Goldman criteria) (2).

Genes associated with sporadic Alzheimer's disease

By far, the most important genetic risk factor for dementia due to Alzheimer's disease is the apolipoprotein ε4 gene. The apolipoprotein gene, located on chromosome 19, has three polymorphisms called ε2, ε3, and ε4. They code for a protein involved in brain cholesterol, which plays a role in brain repair. Carriers of the ε4 allele have a higher risk of developing dementia due to Alzheimer's disease. This common variant is present in up to 30% of the population. In fact, 40–65% of people with dementia due to Alzheimer's disease have at least one ε4 allele. The risk associated with a single ε4 allele is especially prominent in women and increases in double ε4 carriers. However, it is important to emphasise that carrying the ε4 genotype is neither necessary nor sufficient to cause dementia. For this reason, apolipoprotein ε testing is not clinically useful. Interestingly, the ε4 allele is not associated with risk for frontotemporal dementia, dementia with Lewy bodies, or Creutzfeldt-Jakob disease (3–5).

Research conducted in Alzheimer's disease using genome-wide association designs identify a wide range of common gene variants involved in lipid metabolism endocytosis, vesicle recycling and neuroinflammatory responses. It has been proposed that the risk of developing dementia is higher in carriers with certain polygenic gene signatures (6–8).

Down syndrome

Down syndrome (trisomy 21) is a common form of young-onset dementia. Adults with Down syndrome, after the age of 40, consistently show a progressive cognitive decline and dementia superimposed on their baseline cognitive limitations. They accumulate amyloid, neurofibrillary tangles and cell depletion similarly to sporadic Alzheimer's disease. Due to the trisomy of the chromosome 21, these individuals carry an extra copy of the amyloid precursor protein, which is believed to be responsible for dementia in adults with Down syndrome (9, 10).

Genes associated with autosomal dominant Alzheimer's disease

Three causative genes have been associated with autosomal dominant familial Alzheimer's disease. Mutations in the APP, presenilin-1 (PS-1; chromosome 14) and presenilin-2 (PS-2; chromosome 1) code for proteins involved on Aβ42 production pathways, which is a toxic component of amyloid plaques. PS-1 mutations account for most autosomal dominant cases. Autosomal dominant Alzheimer's disease has an earlier dementia onset and progresses more rapidly than sporadic cases. Depending on the location, mutations phenotypes might vary from typical dementia to more complex presentations, featuring motor symptoms or behavioural abnormalities. Individuals with a high number of affected family members with young-onset should undergo specialised clinical assessment and genetic testing for rare variants. Research conducted within the Colombian PS-1 E280A kindred, and the Dominantly Inherited Alzheimer Network (DIAN) have tremendously advanced the understanding of Alzheimer's disease based on research conducted in autosomal dominant families. A brief summary of these genes is listed in Table 1 (11–22).

Protective genes in Alzheimer's disease

Interestingly, there are genes that provide resilience to dementia. For example, the Icelandic APP coding mutation (A673T) protects against Alzheimer's disease and cognitive decline in the elderly. APOE2 allele has one of the strongest genetic protective effects according to genome-wide association meta-analyses. The rare apolipoprotein ε3 mutation called Christchurch, when in homozygosis, seems to protect against dementia despite the presence of a PS1 mutation. A genetic variant in the PLCG2 gene reduces the risk of Alzheimer's disease and other neurodegenerative conditions (23–26).

Genes associated with frontotemporal dementia

Frontotemporal dementia cases require a careful assessment of family history. Up to 50% of frontotemporal dementia patients have a positive family history of dementia or psychiatric conditions. Careful clinical assessments identify an autosomal dominant pattern in up to 15% of cases. Indeed, individuals with the association between behavioural variant frontotemporal and motor neuron disease, are most likely to carry genetic alterations. Frequent causal genes associated with frontotemporal dementia are summarised in Table 1. MAPT and progranulin mutations in addition to the C09orf72 hexanucleotide are the three genetic abnormalities responsible for 15% of familial frontotemporal dementia cases (2, 27, 28). Mutations in the MAP-T gene or progranulin gene mutations located in chromosome 17 will cause protein aggregations within the neurons leading to cell death and dementia. In chromosome 9, a six-nucleotide repeat expansion on the C9ORF72 gene is the most common genetic cause of familial FTD and familial amyotrophic lateral sclerosis (ALS) (29–31).

Other genes associated with dementia

Many people with genetic diseases may present dementia as part of their clinical phenotype. Apart from the Alzheimer's disease related conditions, family prion diseases, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), Huntington's disease, Wilson's disease, dentatorubropallidoluysian atrophy, Niemann Pick type C, spinocerebellar ataxias are examples of genetic conditions frequently associated with dementia (32).

Table 1. Genetic abnormalities associated with neurodegenerative dementias

Genes	Name	Chromosome	Mutations	Repeats	Dementia type
PS1	Presenilin 2	14	326		Alzheimer's disease
Ps2	Presenilin 2	1	68		Alzheimer's disease
APP	Amyloid precursor protein	21	69		Alzheimer's disease
MAPT	Microtubule associated protein tau	17	63		Frontotemporal dementia
GRN	Pro-granulin gene	17	114		Frontotemporal dementia
C9ORF72		9		>30	Frontotemporal dementia
VCP	Valosin-containing protein	9	15		Frontotemporal dementia
FUS	Fuse in Sarcoma	16	2		Familial ALS

Expert essay

Genetics of Alzheimer's disease: diagnostic, research, and ethical considerations

David Wallon[1,2]

[1] Normandie Univ, UNIROUEN, Inserm U1245, Rouen, FRANCE
[2] Department of Neurology and CNR-MAJ, CHU Rouen, Normandy Center for Genomic and Personalized Medicine, Rouen, FRANCE

The last 30 years paved the way and cemented the immense role genetics play in our understanding of Alzheimer's disease. Two different aspects should be distinguished. The autosomal dominant inheritance, which is extremely rare but has a complete risk of inducing illness before the age of 65 for all carriers of a causative mutation. In parallel, there are many genetic risk factors that can lead to a high but not complete risk, such as the e4 genotype of the APOE gene, common in the general population, or others that are much less frequent, such as the TREM2, SORL1 or ABCA7 genes. Finally, more than twenty frequent polymorphisms have been found to be related to Alzheimer's disease but weakly associated with its occurrence.

The so-called 'hereditary' or autosomal dominant forms of Alzheimer's disease

For a minority of people, representing less than 1%, Alzheimer's disease is due to a causal mutation in one of these three genes: APP, PSEN1 or PSEN21. These mutations lead to an early-onset of Alzheimer's disease beginning before the age of 65 with affected relatives from generation to generation and both men and women. This explains why these mutations are typically found in families with early-onset Alzheimer's disease. About 80% of them are linked to a mutation within PSEN1, APP or PSEN2 (1). Any individual carrying one of these mutations will develop symptoms before 65 and approximately at the same age of their own parent. Historically, APP was the first gene to be identified (2) but PSEN1 represents the major gene in proportion of families (43%). Since 2006, increases in APP copy number or APP duplications have been reported as causative with a clinical phenotype close to point mutations of the same gene (3). Mutations and duplications of APP represent 9% and 7% respectively. Finally, the third gene identified to date is PSEN2, but it concerns only a small minority of families (6%) (1). The phenotypes described are mostly typical forms with memory disorders (80% of cases). Depending on the gene, the ages of onset range, on average, from 43 years for PSEN1 to 53 years for PSEN2 (4,5) but in some rare cases, some were reported with a very young age of onset as 24 years old. Several atypical situations are also encountered, particularly for certain PSEN1 or APP mutations (4–6): behavioural modifications (9% of patients) and non-cognitive manifestations such as early epileptic seizures (7), spastic paraparesis for 9% (1,6). Sporadic cases are also reported harbouring a mutation in one of these three genes. One explanation is the occurrence of a *de novo* mutation (8). This underlines why it is preferable to talk about autosomal dominant forms rather than 'familial'. Some countries, such as France, have published criteria for the genetic diagnosis based on this clinical data. Indeed, a genetic analysis should be proposed in people with early-onset Alzheimer's disease, beginning at 65 years of age or before, if there is at least one other relative with a family history with early-onset Alzheimer's disease. For sporadic cases, people with an age of onset before 51 years should also qualify for a molecular diagnosis (9).

Genetic risk factors

Apart from these rare situations, the other forms of Alzheimer's disease, whether early or late, familial or sporadic, are part of a complex framework with significant genetic heterogeneity. The explanatory part related to either genetic or environmental components has been highly debated but twin studies have demonstrated the important genetic component (10). The APOE gene coding for apoliprotein E (APOE) has been identified since the end of the 1980s and in particular the impact of the e4 allele found in about 21% of the general population (11). The increased risk of Alzheimer's disease related to the presence of this allele was moderate to high, depending on whether the individual was carrying one or two e4 alleles. Subsequently, technological developments have, since 2000, allowed further genetic research. Indeed, thanks to DNA chip techniques capable of searching for the presence of genetic variations in large international cohorts of patients, these genome-wide association studies compare the DNA of tens of thousands of patients and controls to identify frequent variants (12). Several dozen genetic

polymorphisms, for instance linked to PICALM or BIN1, have been identified as being associated with Alzheimer's disease, but with a risk considered to be low. That risk has therefore a limited interest in the management of patients but allows to study some mechanisms of the disease.

In parallel to these genome-wide association studies, next generation sequencing (NGS) appeared in the late 2000s. The goal of these methods is to uncover all the variants present in the genome of each individual. Applied to Alzheimer's disease research, that technique makes it possible to identify all the variants present on the coding parts of our 20,000 genes by whole-exome sequencing (WES) and to identify those present in patients and absent in healthy controls, or conversely. This method, without any presumption about the gene to be identified, offers the advantage of being able to look at variants regardless of their frequency, even low (<1% of the general population) or very low (<0.1%) frequencies. These strategies allow researchers to manage a huge amount of data and to establish specific methods to restrict the number of potential candidates related with Alzheimer's disease. While the frequent variants did not clinically contribute to the genetic component, the application of these sequencing techniques to rare variants allowed for the identification of several risk factors that confer at least a moderate risk for Alzheimer's disease. Rare variants identified within TREM2, SORL1, and ABCA7 genes are known to explain between 1.1% and 1.5% of early-onset Alzheimer's disease heritability each, as compared to 9.12% for APOE4 (13).

Clinical and ethical consequences

Distinguishing between genetic variants within causative genes for the 'hereditary' forms, or just risk factors, is not only a question of classification. This has consequences in terms of research and clinical practice for individuals and their families. Indeed, the causative mutations of PSEN1, PSEN2 and APP are responsible for an almost complete probability of becoming ill before the age of 65. This point justifies providing well-defined information to families for which first-degree relatives are at high risk (in practice, 50% for each individual) of carrying the same mutation and therefore becoming ill. This information is most often provided, as in France or Canada, by the genetic counsellor. If the multidisciplinary process is completed, the person requesting it will be able to obtain a presymptomatic diagnosis, in other words, to know their genetic status before the onset of Alzheimer's disease symptoms. These rare forms of the disease have allowed for the implementation of research protocols specifically dedicated to improving our knowledge of the disease. Since 2013, it has been possible to include asymptomatic relatives to receive experimental treatment aimed at preventing or delaying the onset of Alzheimer's disease, such as the DIAN-TU protocol (14). Unfortunately, the primary criteria, based on clinical efficacy was not met, but the study is being pursued with an open label extension to get more information on a long-term impact of the treatment (15).

The situation of genetic risk factors is quite different. Indeed, by definition, a risk factor is neither necessary nor sufficient for the disease but only modifies the risk at a given age. In other words, the risk associated with carrying 2 APOE4 alleles cannot justify a presymptomatic diagnosis, even if the attributed risk is high. That situation could change in the next few years if preventive therapeutic research protocols based on the presence of a risk factor are positive. A programme led by the Banner Alzheimer Institute is aiming to meet this objective with specific ethical procedure regarding APOE genotype disclosure (16). In the meantime, the problem remains the same for all risk factors, whether they are rare or frequent. None can justify a presymptomatic diagnosis, but it is important to continue investigations in these families to determine a potential additive or even synergistic effect of these variations in a given individual. To meet that goal, several research teams are working on determining polygenic scores or age-related risk curves (12,17). This personalisation of the risk for Alzheimer's disease should overcome the significant genetic heterogeneity and to propose an effective and personalised therapeutic strategy, particularly critical for prevention.

References

1. Lanoiselée HM, Nicolas G, Wallon D, Rovelet-Lecrux A, Lacour M, Rousseau S, et al. APP, PSEN1, and PSEN2 mutations in early-onset Alzheimer disease: A genetic screening study of familial and sporadic cases. PLoS Med 2017;14. https://doi.org/10.1371/journal.pmed.1002270.
2. Levy E, Carman MD, Fernandez-Madrid IJ, Power MD, Lieberburg I, Van Duinen SG, et al. Mutation of the Alzheimer's disease amyloid gene in hereditary cerebral hemorrhage, Dutch type. Science (80-) 1990;248:1124–6. https://doi.org/10.1126/science.2111584.
3. Rovelet-Lecrux A, Hannequin D, Raux G, Le Meur N, Laquerrière A, Vital A, et al. APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy. Nat Genet 2006;38:24–6. https://doi.org/10.1038/ng1718.
4. Wallon D, Rousseau S, Rovelet-Lecrux A, Quillard-Muraine M, Guyant-Maréchal L, Martinaud O, et al. The french series of autosomal dominant early onset alzheimer's disease cases: Mutation spectrum and cerebrospinal fluid biomarkers. J Alzheimer's Dis 2012;30:847–56. https://doi.org/10.3233/JAD-2012-120172.
5. Tang M, Ryman DC, McDade E, Jasielec MS, Buckles VD, Cairns NJ, et al. Neurological manifestations of autosomal dominant familial Alzheimer's disease: a comparison of the published literature with the Dominantly Inherited Alzheimer Network observational study (DIAN-OBS). Lancet Neurol 2016;15:1317–25. https://doi.org/10.1016/S1474-4422(16)30229-0.
6. Ryan NS, Nicholas JM, Weston PSJ, Liang Y, Lashley T, Guerreiro R, et al. Clinical phenotype and genetic associations in autosomal dominant familial Alzheimer's disease: a case series. Lancet Neurol 2016;15:1326–35. https://doi.org/10.1016/S1474-4422(16)30193-4.
7. Zarea A, Charbonnier C, Rovelet-Lecrux A, Nicolas G, Rousseau S, Borden A, et al. Seizures in dominantly inherited Alzheimer disease. Neurology 2016;87:912–9. https://doi.org/10.1212/WNL.0000000000003048.
8. Lacour M, Quenez O, Rovelet-Lecrux A, Salomon B, Rousseau S, Richard AC, et al. Causative Mutations and Genetic Risk Factors in Sporadic Early Onset Alzheimer's Disease before 51 Years. J Alzheimer's Dis 2019;71:227–43. https://doi.org/10.3233/JAD-190193.
9. Nicolas G, Wallon D, Charbonnier C, Quenez O, Rousseau S, Richard AC, et al. Screening of dementia genes by whole-exome sequencing in early-onset Alzheimer disease: Input and lessons. Eur J Hum Genet 2016;24:710–6. https://doi.org/10.1038/ejhg.2015.173.
10. Gatz M, Reynolds CA, Fratiglioni L, Johansson B, Mortimer JA, Berg S, et al. Role of genes and environments for explaining Alzheimer disease. Arch Gen Psychiatry 2006;63:168–74. https://doi.org/10.1001/archpsyc.63.2.168.
11. Schellenberg GD, Deeb SS, Boehnke M, Bryant EM, Martin GM, Lampe TH, et al. Association of an apolipoprotein CII allele with familial dementia of the alzheimer type. J Neurogenet 1987;4:97–108. https://doi.org/10.3109/01677068709102337.
12. de Rojas I, Moreno-Grau S, Tesi N, Grenier-Boley B, Andrade V, Jansen IE, et al. Common variants in Alzheimer's disease and risk stratification by polygenic risk scores. Nat Commun 2021;12. https://doi.org/10.1038/s41467-021-22491-8.
13. Bellenguez C, Charbonnier C, Grenier-Boley B, Quenez O, Le Guennec K, Nicolas G, et al. Contribution to Alzheimer's disease risk of rare variants in TREM2, SORL1, and ABCA7 in 1779 cases and 1273 controls. Neurobiol Aging 2017;59:220.e1-220.e9. https://doi.org/10.1016/j.neurobiolaging.2017.07.001.
14. Bateman RJ, Benzinger TL, Berry S, Clifford DB, Duggan C, Fagan AM, et al. The DIAN-TU Next Generation Alzheimer's prevention trial: Adaptive design and disease progression model. Alzheimer's Dement 2017;13:8–19. https://doi.org/10.1016/j.jalz.2016.07.005.
15. Salloway S, Farlow M, McDade E, Clifford DB, Wang G, Llibre-Guerra JJ, et al. A trial of gantenerumab or solanezumab in dominantly inherited Alzheimer's disease. Nat Med 2021. https://doi.org/10.1038/s41591-021-01369-8.
16. Langlois CM, Bradbury A, Wood EM, Roberts JS, Kim SYH, Riviere ME, et al. Alzheimer's Prevention Initiative Generation Program: Development of an APOE genetic counseling and disclosure process in the context of clinical trials. Alzheimer's Dement Transl Res Clin Interv 2019;5:705–16. https://doi.org/10.1016/j.trci.2019.09.013.
17. Genin E, Hannequin D, Wallon D, Sleegers K, Hiltunen M, Combarros O, et al. APOE and Alzheimer disease: A major gene with semi-dominant inheritance. Mol Psychiatry 2011;16:903–7. https://doi.org/10.1038/mp.2011.52.

Expert essay

Autosomal dominant Alzheimer's disease

Yue Cui, Liyong Wu

Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, CHINA

'As that person, I find myself learning the art of losing every day. Losing my bearings, losing objects, losing sleep. But mostly, losing memories.' It's a classic line from the movie *Still Alice*, about a linguistics professor who struggles to maintain her mind and self after being diagnosed with familial early-onset Alzheimer's disease, in autosomal dominant form of inheritance. The movie, based on a true story, can help us understand autosomal dominant Alzheimer's disease (ADAD), a rare, characteristic, and clinically significant form of Alzheimer's disease (AD) more clearly.

As depicted on screen, autosomal dominant Alzheimer's disease is characterised by early-onset cognitive impairment (typically occurring from the ages of 30 to 50), fairly consistent within a family and principally caused by highly penetrant pathogenic mutations in the amyloid precursor protein gene (APP), presenilin 1 gene (PSEN1) and presenilin 2 gene (PSEN2) (1). To date, 326 PSEN1, 68 PSEN2, and 69 APP mutations have been identified,[i] as well as new mutations constantly being discovered in Alzheimer's disease with a positive or negative family history (2). Dissimilar to the previously held view that all individuals with autosomal dominant Alzheimer's disease have an explicit positive family history, cases of individuals with autosomal dominant Alzheimer's disease whose cause is identified as de novo mutation with a negative family history has increased in recent years, and a diagnostic approach of young-onset dementia with negative family history have been proposed (3). Although this occurrence only accounts for 10% to 15% of familial early-onset Alzheimer's disease and <1% of all Alzheimer's disease cases, autosomal dominant Alzheimer's disease represents an ideal population to explore pathogenesis, prevention and treatment of Alzheimer's disease, widely approached by researchers as an independent area of study.

In 2008, the Dominantly Inherited Alzheimer Network (DIAN)[ii] an international research organisation focused on autosomal dominant Alzheimer's disease was established. DIAN, led by Randall Bateman at the Washington University School of Medicine, and represented by several institutions around the world, is dedicated to clinical trials and observational study, as well as working directly with individuals and families who are impacted by autosomal dominant Alzheimer's disease. Participation by individuals with autosomal dominant Alzheimer's disease and their families will contribute to the global understanding of how it can be prevented, diagnosed and treated by registering with the DIAN Expanded Registry, as well as help researchers pursue avenues to prevent or minimise its medical and social impact. Among many prominent research achievements based on DIAN, the latest discovery of novel disease trajectories for autosomal dominant Alzheimer's disease through Machine learning models will contribute to targeted treatment of autosomal dominant Alzheimer's disease individuals in particular (4).

With the exception of the Dominantly Inherited Alzheimer Network study, research into the world's largest single-mutation autosomal dominant Alzheimer's disease kindred, a family in Antioquia, Colombia with the E280A (Glu280Ala) mutation in the Presenilin1 gene, also provided great insight into this disease (5). The autosomal dominant Alzheimer's disease kindred were first reported in 1997, including approximately 6,000 living members and an estimated 1,200 mutation carriers now. There have been dozens of original articles published based on this Colombia cohort, and the latest comprehensive review unifies the knowledge gained from the past three decades, showing significant abnormalities in plasma, cerebrospinal fluid, brain structure and function as well as evidence of Alzheimer's disease pathology in as early as three and a half decades before the median age of onset of Alzheimer's disease-related cognitive decline (6) (Figure 1). We believe more research disclosures will be made from this unique kindred model.

As a hereditary disease, the diversity of autosomal dominant Alzheimer's disease among different ethnic groups needs to be fully appreciated. Although most of the large-scale autosomal dominant Alzheimer's disease studies were conducted with Caucasians, some significant original studies have recently been published in Asia, indicating the heterogeneity in the pathogenesis of Alzheimer's disease between

i https://www.alzforum.org/mutations
ii https://dian.wustl.edu/

different ethnicities. In 2002, the Chinese Familial Alzheimer's Disease Network (CFAN)[iii] was established by director Jianping Jia, Xuanwu Hospital, Capital Medical University. They recruited 404 familial Alzheimer's disease pedigrees from among 1,330 individuals from 69 medical centres in 26 provinces and regions of China, becoming the largest familial Alzheimer's disease registration website to date. Through follow-up studies conducted for the past 17 years, a relatively low detection rate of PSENs/APP mutations in Chinese familial Alzheimer's disease than other ethnic groups was found, suggesting the involvement of other factors such as APOE4, recessive inheritance, incomplete penetrance and de novo mutation in Chinese familial Alzheimer's disease (7).

Although more and more research advancements in pathogenesis and treatment of Alzheimer's disease have been made, it would appear there is still an insurmountable gap between delaying the course of the disease and a complete cure. No matter where people are located or their ethnic background, individuals with autosomal dominant Alzheimer's disease places an even greater emotional and economic burden on families and society as a whole than typical Alzheimer's disease. For these individuals and their families, reconciling the impact of the disease with learning how to have a beneficial post diagnosis journey are the most important thing. 'I have people I love dearly. I have things I want to do with my life. I rail against myself for not being able to remember things. But I still have moments in the day of pure happiness and joy. And please, do not think I am suffering, I am not suffering, I am struggling. Struggling to be part of things, to stay connected to whom I once was. So 'live in the moment', I tell myself.' says Alice towards the end of the movie. We sincerely hope that every person with autosomal dominant Alzheimer's disease and their families continue this struggle, as do the clinicians and researchers who remain dedicated to struggle to do what they can to prevent and treat Alzheimer's disease.

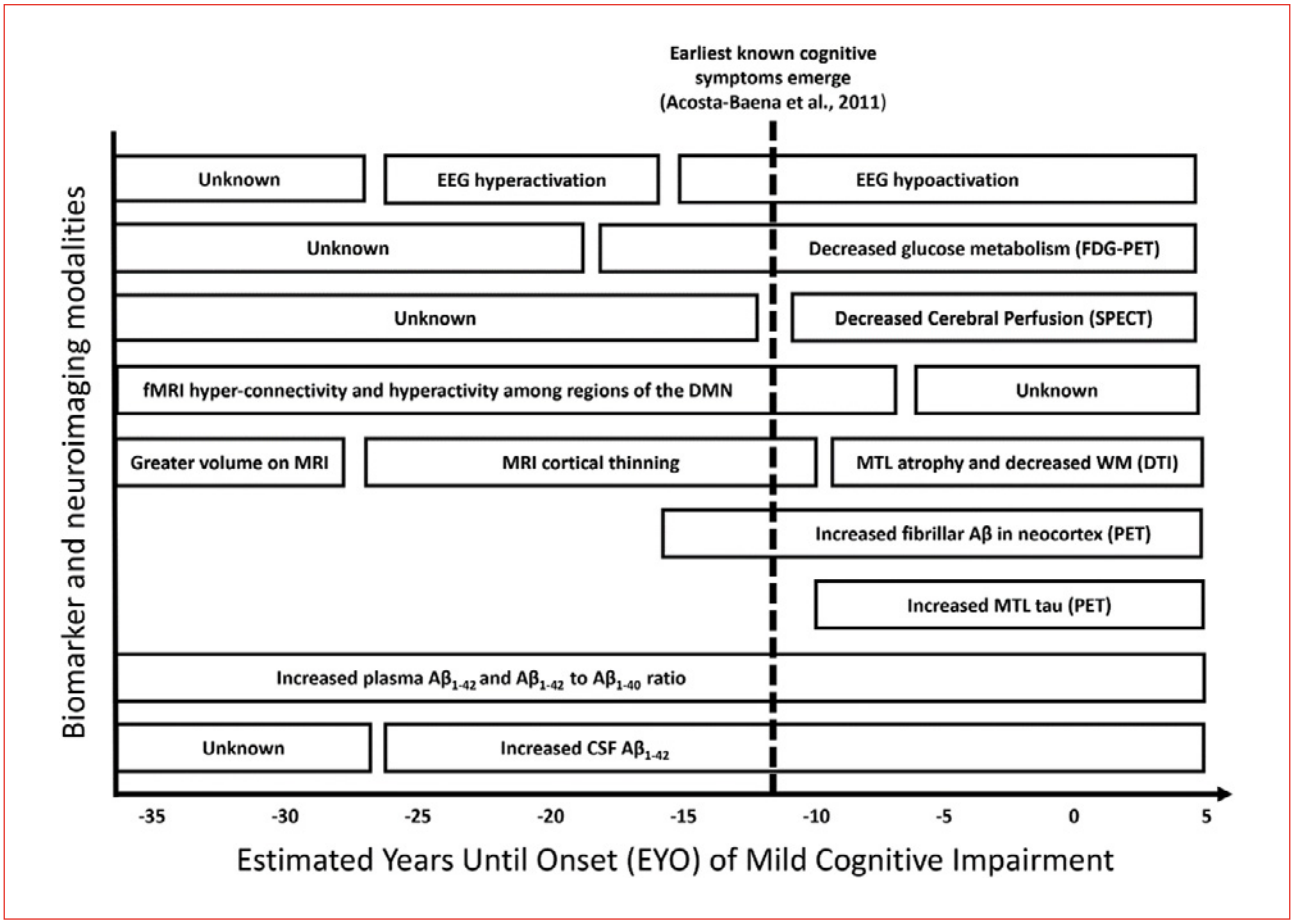


Figure 1. Hypothetical Model of Progression of Biological Markers of PSEN1 E280A Autosomal Dominant Alzheimer's Disease Relative to Earliest Known Signal of Cognitive Decline.

iii https://www.clinicaltrials.gov/, NCT03657732

References

1. Alonso Vilatela ME, López-López M, Yescas-Gómez P. Genetics of Alzheimer's disease. *Archives of medical research*. Nov 2012;43(8):622-31. doi:10.1016/j.arcmed.2012.10.017
2. Li XY, Cui Y, Jing D, et al. Novel PSEN1 and PSEN2 Mutations Identified in Sporadic Early-onset Alzheimer Disease and Posterior Cortical Atrophy. *Alzheimer disease and associated disorders*. May 11 2021;doi:10.1097/wad.0000000000000438
3. Liu J, Wang Q, Jing D, et al. Diagnostic Approach of Early-Onset Dementia with Negative Family History: Implications from Two Cases of Early-Onset Alzheimer's Disease with De Novo PSEN1 Mutation. *Journal of Alzheimer's disease : JAD*. 2019;68(2):551-558. doi:10.3233/jad-181108
4. Luckett PH, McCullough A, Gordon BA, et al. Modeling autosomal dominant Alzheimer's disease with machine learning. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. Jan 21 2021;doi:10.1002/alz.12259
5. Lopera F, Ardilla A, Martínez A, et al. Clinical features of early-onset Alzheimer disease in a large kindred with an E280A presenilin-1 mutation. *Jama*. Mar 12 1997;277(10):793-9.
6. Fuller JT, Cronin-Golomb A, Gatchel JR, et al. Biological and Cognitive Markers of Presenilin1 E280A Autosomal Dominant Alzheimer's Disease: A Comprehensive Review of the Colombian Kindred. *The journal of prevention of Alzheimer's disease*. 2019;6(2):112-120. doi:10.14283/jpad.2019.6
7. Jia L, Fu Y, Shen L, et al. PSEN1, PSEN2, and APP mutations in 404 Chinese pedigrees with familial Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. Jan 2020;16(1):178-191. doi:10.1002/alz.12005

Expert essay

The genetic feature of frontotemporal dementia in China

Li Liu, Liyong Wu

Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China.

Frontotemporal degeneration (FTD) is one of the most common forms of dementia in individuals under the age of 65, following Alzheimer's disease and is characterised by a broad range of different clinical phenotypes. These include progressive changes in personality, behaviour and/or language resulting from underlying neurodegeneration of the frontal and temporal lobes of the cerebral cortex. As these character changes increasingly progress and manifest in inappropriate emotional and behavioural displays in public, its diagnosis remains difficult, with individuals being erroneously diagnosed with psychiatric disorders. People with frontotemporal degeneration may also develop motor deficits, either amyotrophic lateral sclerosis (FTD-ALS) or parkinsonism, in the latter case often with specific features of a corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP). Frontotemporal degeneration is a highly heritable disorder but almost uniquely within the neurodegenerative disease spectrum, it is neither purely genetic (like Huntington's disease) nor a mainly sporadic condition (like Alzheimer's disease). It was once thought that the prevalence of variants (4.9–7.7%) was comparatively lower in the Chinese frontotemporal degeneration population (1–4). More recently, individuals diagnosed with bvFTD, which is the most common subtype of frontotemporal degeneration, present with a family history of dementia or other neurodegenerative diseases (28.6% of cases). It has been estimated that 27.9% of frontotemporal degeneration is inherited in an autosomal dominant manner (5). All of these factors highlight the importance of genetics in the aetiology of frontotemporal degeneration in China.

Gene

So far, thirty-eight rare variants in genes of MAPT, GRN, C9orf72, CHCHD10, VCP, FUS and TBK1 were identified in Chinese frontotemporal degeneration populations. The majority of the heritability of frontotemporal degeneration is accounted for by autosomal dominant mutations in three genes: microtubule-associated protein tau (MAPT), progranulin (GRN) and chromosome 9 open reading frame 72 (C9orf72). MAPT (3.9–20.9%) seems to be the most common Chinese cause of genetic frontotemporal degeneration, while the frequency of C9orf72 repeat expansions were comparatively low (1–7). To date, 11 pathogenic variants in MAPT and 4 pathogenic variants in GRN have been currently described in Chinese individuals, most of which are missense mutations (1). N279K and P301L mutations in exon 10 of the MAPT gene are common pathogenic mutations resulting in frontotemporal degeneration in China [1]. C9ORF72 repeat expansion is rare in Chinese FTD-ALS individuals, 1.2–2.1% in frontotemporal degeneration individuals, and 0.8% in ALS patients (1,6–10). In contrast to the relative scarcity of C9ORF72 hexanucleotide expansions, pathogenic mutations in CHCHD10 may be quite common, accounting for 7.7% of frontotemporal degeneration cases in the reported Chinese cohort (3,11,12). Although 12 pathogenic variants in CHCHD10 have been identified, the pathogenic nature of them remains unclear. Further studies are needed for a reliable estimate of pathogenic CHCHD10 mutation prevalence in Chinese frontotemporal degeneration populations. Additional rare genetic causes of frontotemporal degeneration, including 8 pathogenic variants in VCP, TBK1, FUS, ANXA11 and CHCHD2 were also reported in the years following the discoveries of pathogenic variation in MAPT, GRN and C9ORF72. However, these mutations collectively account for only a fraction (<2%) of Chinese patients with FTD (1,13–19).

Phenotype

The most common clinical presentation of all genetic forms is behavioural variant frontotemporal dementia (bvFTD), but all phenotypes within the frontotemporal degeneration spectrum are observed in Chinese frontotemporal degeneration individuals. A variety of phenotypes with MAPT mutation were observed, which to some extent, was associated with mutation location (2–4,21). There were eleven variants reported in Chinese frontotemporal degeneration populations, including N279K, P301L, G389R, R5H, D177V, H299Y, V337M, N296N R5C, D54N and P513A [1]. Early parkinsonism is the common manifestation in individuals with N279K mutation [20]. P301L MAPT mutation mainly presented with cognitive and behavioural manifestations. Interestingly, one of four affected individuals in the pedigree with P301L mutation presented with parkinsonism and demonstrated the phenotypic variability

associated with the P301L mutation in individuals with the same MAPT mutation, even within the same family (5). Furthermore, the G389R mutation in exon 13 of the MAPT gene was also detected in individuals with bvFTD or frontotemporal dementia with parkinsonism and presented with early-onset dementia and rapid progression (22). MAPT mutation carriers may have a prominent semantic impairment but this is presents only rarely, nor other forms of PPA. In contrast, GRN mutations can present as a PPA syndrome and bvFTD (1). Unlike the other two major genetic groups, C9orf72 repeat expansions can cause FTD-ALS, FTD or ALS alone (1,6–10). Similarly, frontotemporal dementia with parkinsonism can occur in affected individuals of a family with C9orf72 repeat expansions but is uncommon in China (6). To date, eight variants of the CHCHD10 gene were detected in Chinese frontotemporal degeneration individuals, including A21A, H22Y, P23L, P24L, A32D, V57E, P23S, and P89L. All variants were reported only in the Chinese population and located in CHCHD10 exon 2 except P89L. CHCHD10 mutations can cause SD, bvFTD, FTD-ALS and ALS alone (1,3,11,12). Two mutations (G97E and T127A) in the VCP gene were identified in Chinese families associated with Paget disease of bone and frontotemporal dementia (IBMPFD) and drontotemporal degeneration, respectively (13). Five variants (I334T, R444X, E653fs, and L688Rfs'14) in the TBK1 gene and six variants (c.174–2A>G, D40G, V128M, S229R, R302C and G491R) in the ANXA11 gene had been reported in Chinese individuals, which may be obligated to the ALS-FTD spectrum (1,14–17,19).

Much has been learned about genetic frontotemporal degeneration in the past decade, with the majority of autosomal dominant frontotemporal degeneration now accounting for a large proportion of that. However, most frontotemporal degeneration genetics studies have primarily focused on populations of European ancestry. There is much work to be done in improving the understanding of genetic profile associated with frontotemporal degeneration in China.

References

1. Jiang Y, Jiao B, Xiao X, Shen L. Genetics of frontotemporal dementia in China. Amyotroph Lateral Scler Frontotemporal Degener. 2021:1-15.
2. Shi Z, Liu S, Xiang L, Wang Y, Liu M, Liu S, Han T, Zhou Y, Wang J, Cai L, et al. Frontotemporal dementia-related gene mutations in clinical dementia patients from a Chinese population. J Hum Genet. 2016;61:1003-8.
3. Che XQ, Zhao QH, Huang Y, Li X, Ren RJ, Chen SD, Wang G, Guo QH. Genetic Features of MAPT, GRN, C9orf72 and CHCHD10 Gene Mutations in Chinese Patients with Frontotemporal Dementia. Curr Alzheimer Res. 2017;14:1102-1108.
4. Tang M, Gu X, Wei J, Jiao B, Zhou L, Zhou Y, Weng L, Yan X, Tang B, Xu J, et al. Analyses MAPT, GRN, and C9orf72 mutations in Chinese patients with frontotemporal dementia. Neurobiol Aging. 2016;46:235 e11-5.
5. Liu L, Cui B, Chu M, Cui Y, Jing DL, Li D. The Frequency of Genetic Mutations Associated with Behavioral 2 Variant Frontotemporal Dementia in Chinese Han Patients. Front Aging Neurosci. (accepted)
6. Jiao B, Tang B, Liu X, Yan X, Zhou L, Yang Y, et al. Identification of C9orf72 repeat expansions in patients with amyotrophic lateral sclerosis and frontotemporal dementia in mainland China. Neurobiol Aging. 2014;35: 936.e19–22.
7. He J, Tang L, Benyamin B, Shah S, Hemani G, Liu R, et al. C9orf72 hexanucleotide repeat expansions in Chinese sporadic amyotrophic lateral sclerosis. Neurobiol Aging. 2015;36:2660.e1–8.
8. Tsai CP, Soong BW, Tu PH, Lin KP, Fuh JL, Tsai PC, et al. A hexanucleotide repeat expansion in C9ORF72 causes familial and sporadic ALS in Taiwan. Neurobiol Aging. 2012;33:2232.e11–18.
9. Chen Y, Lin Z, Chen X, Cao B, Wei Q, Ou R, et al. Large C9orf72 repeat expansions are seen in Chinese patients with sporadic amyotrophic lateral sclerosis. Neurobiol Aging. 2016;38:217.e15–22.
10. Liu F, Liu Q, Lu CX, Cui B, Guo XN, Wang RR, et al. Identification of a novel loss-of-function C9orf72 splice site mutation in a patient with amyotrophic lateral sclerosis. Neurobiol Aging. 2016;47:219.e1–5.
11. Shen S, He J, Tang L, Zhang N, Fan D. CHCHD10 mutations in patients with amyotrophic lateral sclerosis in Mainland China. Neurobiol Aging. 2017;54:214.e7–10.
12. Zhou Q, Chen Y, Wei Q, Cao B, Wu Y, Zhao B, et al. Mutation screening of the CHCHD10 gene in chinese patients with amyotrophic lateral sclerosis. Mol Neurobiol. 2017;54:3189–94.
13. Gu JM, Ke YH, Yue H, Liu YJ, Zhang Z, Zhang H, et al. A novel VCP mutation as the cause of atypical IBMPFD in a Chinese family. Bone 2013;52:9–16.
14. Shu S, Li XL, Liu Q, Liu F, Cui B, Liu MS, et al. Screening of the TBK1 gene in familial and sporadic amyotrophic lateral sclerosis patients of Chinese origin. Amyotroph Lateral Scler Frontotemporal Degener. 2016; 17:605–7
15. Yu H, Yu W, Luo SS, Yang YJ, Liu FT, Zhang Y, et al. Association of the TBK1 mutation p.Ile334Thr with frontotemporal dementia and literature review. Mol Genet Genomic Med. 2019;7:e547
16. Tsai PC, Liu YC, Lin KP, Liu YT, Liao YC, Hsiao CT, et al. Mutational analysis of TBK1 in Taiwanese patients with amyotrophic lateral sclerosis. Neurobiol Aging. 2016; 40:191.e11–16
17. Jiao B, Sun Q, Yuan Z, Wang J, Zhou L, Yan X, et al. Rare TBK1 variants in patients with frontotemporal dementia and amyotrophic lateral sclerosis in a Chinese cohort. Transl Neurodegener. 2018;7:31.
18. Che XQ, Zhao QH, Huang Y, Li X, Ren RJ, Chen SD, et al. Mutation screening of the CHCHD2 gene for Alzheimer's disease and frontotemporal dementia in Chinese mainland population. J Alzheimers Dis. 2018;61: 1283–8.
19. Zhang K, Liu Q, Liu K, Shen D, Tai H, Shu S, et al. ANXA11 mutations prevail in Chinese ALS patients with and without cognitive dementia. Neurol Genet. Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology; 2018;4:e237.
20. Wu L, Liu J, Feng X, Dong J, Qin W, Liu Y, et al. 11CCFT-PET in presymptomatic FTDP-17: a potential biomarker predicting onset. J Alzheimers Dis. 2018;61: 613–8.
21. Mao C, Dong L, Li J, Huang X, Lei D, Wang J, et al. Phenotype Heterogeneity and Genotype Correlation of MAPT Mutations in a Chinese PUMCH Cohort. J Mol Neurosci. 2021;71:1015-1022.
22. Sun L, Chen K, Li X, Xiao S. Rapidly progressive frontotemporal dementia associated with MAPT mutation G389R. J Alzheimer's Dis. 2017;55:777–85.

Conclusions

There are a small percentage of individuals who carry gene defects that contribute to the development of dementia. These genes can either cause, protect or increase the risk of developing dementia. Therefore having extensive knowledge of their family's medical history becomes a crucial component to an individual seeking answers. This is especially true when they present with atypical, young-onset or rapidly progressive symptoms. If a potential link is established, a physician will order tests to look for brain accumulation of amyloid, tangles, alpha-synuclein, transactive response DNA binding protein 43 kD (TDP-43) and other pathogenic proteins to indicate the presence of dementia.

By delving deeper into potential causes, genetic testing offers a precise molecular diagnosis. If confirmed, healthcare professionals can provide information, guidance, and support in order to help make choices in their personal lives, related to their own personal risks, having children, and planning for the future.

As explored in the two essays from China, autosomal dominant Alzheimer's disease can be a particular burdensome form of the condition as it tends to affect people between the ages of 30 and 50. The hereditary component of this form of the disease merits further study across different ethnic cultures to assess the heterogeneity in the pathogenesis of Alzheimer's disease. Frontotemporal degeneration (FTD) is yet another classification of dementia that strikes individuals at a younger age, usually under 65, with genetic factors. Though recent studies have advanced the understanding of frontotemporal dementia, these have primarily focused on individuals of European lineage. This means there is still a long way to go in order to enhance the knowledge of genetic profile associated with frontotemporal degeneration in China.

It must be pointed out that having a risk factor is not necessarily an absolute determinant about whether one will develop the condition. The advances made in genetic testing over the past 30 years have simply added to the dementia diagnostic toolbox in estimating its likelihood and the probabilities at a given age.

Additional references

1. Crook A, Jacobs C, Newton-John T, Richardson E, McEwen A. Patient and Relative Experiences and Decision-making About Genetic Testing and Counselling for Familial ALS and FTD: A Systematic Scoping Review. Alzheimer Dis Assoc Disord. 2021. https://www.ncbi.nlm.nih.gov/pubmed/34054018.
2. Koriath CAM, Kenny J, Ryan NS, Rohrer JD, Schott JM, Houlden H, et al. Genetic testing in dementia – utility and clinical strategies. Nat Rev Neurol. 2021;17(1):23-36. https://www.ncbi.nlm.nih.gov/pubmed/33168964.
3. Long JM, Holtzman DM. Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. Cell. 2019;179(2):312-39. https://www.ncbi.nlm.nih.gov/pubmed/31564456.
4. Serrano-Pozo A, Das S, Hyman BT. APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. The Lancet Neurology. 2021;20(1):68-80.
5. Farrer LA. Statement on Use of Apolipoprotein E Testing for Alzheimer Disease. JAMA: The Journal of the American Medical Association. 1995;274(20).
6. Okbay A, Beauchamp JP, Fontana MA, Lee JJ, Pers TH, Rietveld CA, et al. Genome-wide association study identifies 74 loci associated with educational attainment. Nature. 2016;533(7604):539-42. https://www.ncbi.nlm.nih.gov/pubmed/27225129.
7. Wingo AP, Liu Y, Gerasimov ES, Gockley J, Logsdon BA, Duong DM, et al. Integrating human brain proteomes with genome-wide association data implicates new proteins in Alzheimer's disease pathogenesis. Nat Genet. 2021;53(2):143-6. https://www.ncbi.nlm.nih.gov/pubmed/33510477
8. Jansen IE, Savage JE, Watanabe K, Bryois J, Williams DM, Steinberg S, et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. Nat Genet. 2019;51(3):404-13. https://www.ncbi.nlm.nih.gov/pubmed/30617256.
9. Antonarakis SE, Skotko BG, Rafii MS, Strydom A, Pape SE, Bianchi DW, et al. Down syndrome. Nat Rev Dis Primers. 2020;6(1):9. https://www.ncbi.nlm.nih.gov/pubmed/32029743
10. Wiseman FK, Al-Janabi T, Hardy J, Karmiloff-Smith A, Nizetic D, Tybulewicz VL, et al. A genetic cause of Alzheimer disease: mechanistic insights from Down syndrome. Nat Rev Neurosci. 2015;16(9):564-74. https://www.ncbi.nlm.nih.gov/pubmed/26243569.
11. Janssen JC, Beck JA, Campbell TA, Dickinson A, Fox NC, Harvey RJ, et al. Early onset familial Alzheimer's disease: Mutation frequency in 31 families. Neurology. 2003;60(2):235-9. https://www.ncbi.nlm.nih.gov/pubmed/12552037.
12. Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med. 2012;367(9):795-804. https://www.ncbi.nlm.nih.gov/pubmed/22784036.
13. Dube U, Del-Aguila JL, Li Z, Budde JP, Jiang S, Hsu S, et al. An atlas of cortical circular RNA expression in Alzheimer disease brains demonstrates clinical and pathological associations. Nat Neurosci. 2019;22(11):1903-12. https://www.ncbi.nlm.nih.gov/pubmed/31591557.
14. Lee S, Viqar F, Zimmerman ME, Narkhede A, Tosto G, Benzinger TL, et al. White matter hyperintensities are a core feature of Alzheimer's disease: Evidence from the dominantly inherited Alzheimer network. Ann Neurol. 2016;79(6):929-39. https://www.ncbi.nlm.nih.gov/pubmed/27016429
15. Tang M, Ryman DC, McDade E, Jasielec MS, Buckles VD, Cairns NJ, et al. Neurological manifestations of autosomal dominant familial Alzheimer's disease: a comparison of the published literature with the Dominantly Inherited Alzheimer Network observational study (DIAN-OBS). Lancet Neurol. 2016;15(13):1317-25. https://www.ncbi.nlm.nih.gov/pubmed/27777020.
16. Campion D, Dumanchin C, Hannequin D, Dubois B, Belliard S, Puel M, et al. Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. Am J Hum Genet. 1999;65(3):664-70. https://www.ncbi.nlm.nih.gov/pubmed/10441572.
17. Ryman DC, Acosta-Baena N, Aisen PS, Bird T, Danek A, Fox NC, et al. Symptom onset in autosomal dominant Alzheimer disease: a systematic review and meta-analysis. Neurology. 2014;83(3):253-60. https://www.ncbi.nlm.nih.gov/pubmed/24928124.
18. Wang F, Gordon BA, Ryman DC, Ma S, Xiong C, Hassenstab J, et al. Cerebral amyloidosis associated with cognitive decline in autosomal dominant Alzheimer disease. Neurology. 2015;85(9):790-8. https://www.ncbi.nlm.nih.gov/pubmed/26245925.
19. Bateman RJ, Aisen PS, De Strooper B, Fox NC, Lemere CA, Ringman JM, et al. Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. Alzheimers Res Ther. 2011;3(1):1. https://www.ncbi.nlm.nih.gov/pubmed/21211070.
20. Reiman EM, Quiroz YT, Fleisher AS, Chen K, Velez-Pardo C, Jimenez-Del-Rio M, et al. Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal dominant Alzheimer's disease in the presenilin 1 E280A kindred: a case-control study. The Lancet Neurology. 2012;11(12):1048-56.
21. Lemere CA, Lopera F, Kosik KS, Lendon CL, Ossa J, Saido TC, et al. The E280A presenilin 1 Alzheimer mutation produces increased A beta 42 deposition and severe cerebellar pathology. Nat Med. 1996;2(10):1146-50. https://www.ncbi.nlm.nih.gov/pubmed/8837617.
22. Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature. 1991;349(6311):704-6. https://www.ncbi.nlm.nih.gov/pubmed/1671712.
23. van der Lee SJ, Conway OJ, Jansen I, Carrasquillo MM, Kleineidam L, van den Akker E, et al. A nonsynonymous mutation in PLCG2 reduces the risk of Alzheimer's disease, dementia with Lewy bodies and frontotemporal dementia, and increases the likelihood of longevity. Acta Neuropathol. 2019;138(2):237-50. https://www.ncbi.nlm.nih.gov/pubmed/31131421.
24. Zalocusky KA, Nelson MR, Huang Y. An Alzheimer's-disease-protective APOE mutation. Nat Med. 2019;25(11):1648-9. https://www.ncbi.nlm.nih.gov/pubmed/31686033.
25. Arboleda-Velasquez JF, Lopera F, O'Hare M, Delgado-Tirado S, Marino C, Chmielewska N, et al. Resistance to autosomal dominant Alzheimer's disease in an APOE3 Christchurch homozygote: a case report. Nat Med. 2019;25(11):1680-3. https://www.ncbi.nlm.nih.gov/pubmed/31686034
26. Jonsson T, Atwal JK, Steinberg S, Snaedal J, Jonsson PV, Bjornsson S, et al. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature. 2012;488(7409):96-9. https://www.ncbi.nlm.nih.gov/pubmed/22801501.
27. Goldman JS, Farmer JM, Wood EM, Johnson JK, Boxer A, Neuhaus J, et al. Comparison of family histories in FTLD subtypes and related tauopathies. Neurology. 2005;65(11):1817-9. https://www.ncbi.nlm.nih.gov/pubmed/16344531.
28. Rohrer JD, Guerreiro R, Vandrovcova J, Uphill J, Reiman D, Beck J, et al. The heritability and genetics of frontotemporal lobar degeneration. Neurology. 2009;73(18):1451-6. https://www.ncbi.nlm.nih.gov/pubmed/19884572.
29. Hinz FI, Geschwind DH. Molecular Genetics of Neurodegenerative Dementias. Cold Spring Harb Perspect Biol. 2017;9(4). https://www.ncbi.nlm.nih.gov/pubmed/27940516.
30. Ferrari R, Manzoni C, Hardy J. Genetics and molecular mechanisms of frontotemporal lobar degeneration: an update and future avenues. Neurobiol Aging. 2019;78:98-110. https://www.ncbi.nlm.nih.gov/pubmed/30925302.
31. Greaves CV, Rohrer JD. An update on genetic frontotemporal dementia. J Neurol. 2019;266(8):2075-86. https://www.ncbi.nlm.nih.gov/pubmed/31119452.
32. Bras J, Gibbons E, Guerreiro R. Genetics of synucleins in neurodegenerative diseases. Acta Neuropathol. 2021;141(4):471-90. https://www.ncbi.nlm.nih.gov/pubmed/32740728.

Chapter 13
Diagnostic tests: novel biomarkers

Pedro Rosa-Neto, Stijn Servaes

Key points

- Blood biomarkers for p-tau181, p-tau217 and p-tau231 reflecting brain tau and Aβ pathology have been developed and validated in research and are being assessed through the appropriate channels for commercialisation and general clinical use.
- Novel biomarkers of non-Alzheimer's disease pathology are needed for research and clinical care.

Background for clinicians

The scientific community is developing cost-effective tests (or biomarkers) to diagnose the cause of dementia. It is expected that these tests will allow physicians to precisely identify and monitor the accumulation of abnormal proteins in the brain using affordable blood tests. This will pave the way for forthcoming therapies designed to remove the accumulation of proteins that can cause dementia.

> **Biomarkers are expected to advance clinical care by providing information regarding the underlying causes of dementias.**

Why are new biomarkers needed?

Biomarkers are expected to advance clinical care by providing information regarding the underlying causes of dementias. Today, biomarkers estimate brain concentrations of amyloid plaques and neurofibrillary tangles which are the hallmarks of Alzheimer's disease. However, there is a need to expand the biomarker repertoire to other proteinopathies involving aggregation of alpha-synuclein, transactive response DNA binding protein 43 kD (TDP-43), and tau aggregates involved in Picks's disease (3R-tau), or tauopathies like progressive supranuclear palsy (4R-tau), among others.

The global accessibility to these biomarkers will open unprecedented opportunities for personalised dementia prevention. As most biomarkers involve expensive infrastructure such as positron emission tomography (PET) scanners, cyclotrons or cerebrospinal fluid facilities, affordable blood biomarkers are needed to disseminate advances in early diagnostic and therapy to low- and middle-income countries.

Table 1 summarises examples of this new generation of biomarkers

Biomarker	
NfL	Neurofilament light chain
p-tau-181	Hyperphosphorylated tau
p-tau-217	Hyperphosphorylated tau
p-tau-231	Hyperphosphorylated tau
GFAP	Inflammation
YLK40	Inflammation
sTREM2	Inflammation

Blood based biomarkers

This new generation of biomarkers results from technological advances in mass spectroscopy and the introduction of high sensitivity immunoassays such as the single-molecule array (SIMOA), which is many orders of magnitude more sensitive than conventional immunoassays.

These technological advances allow detection, in peripheral blood, of the accumulation of amyloid and neurofibrillary tangles in the brain. In addition, the same techniques allow for quantifying downstream effects such as inflammatory responses, neuronal injury, and synaptic depletion.

Plasma fragments of amyloid-beta species quantified, thanks to innovations in immunoprecipitation and high-resolution mass spectrometry techniques, permit detection of brain amyloidosis based on the plasma concentrations of amyloid-beta species. Although these techniques are accurate and constitute significant progress in the field, they are neither affordable nor mature for large-scale utilisation. (1,2).

Plasma species of tau phosphorylated are considered biomarkers of tau pathology. Recently, species of tau phosphorylated on the epitopes 181, 217 and 231 have been measured in plasma using the SIMOA technology. Preliminary studies conducted in observational cohorts have shown excellent performance to identify individuals with pathologic load of neurofibrillary tangles in the brain, with specificity to Alzheimer's disease. As these phosphorylated tau species are also highly associated with pathological levels of amyloid, they constitute an excellent biomarker for Alzheimer's disease pathophysiology (3–7).

Neurofilament light (NFL) is an axonal protein sensitive to a wide range of neuronal insults. Although this biomarker of neuronal injury is not specific for any disease process, it is particularly increased in frontotemporal dementia when compared to Alzheimer's disease. Serum NFL correlates closely with CSF levels, suggesting that blood measurements reflect brain alterations. NFL increases with ageing and in familial Alzheimer's disease, blood NFL levels increase before its clinical onset. A recent multicentre validation supports the use of this biomarker as a screening test for neurodegeneration (8,9).

Biomarkers for non-Alzheimer's disease dementias constitute an important gap in the diagnosis of neurodegenerative conditions. Although quantification of alpha-synuclein remains challenging, progress has been achieved on the detection of pathological alpha-synuclein. Real-time quaking-induced conversion (RT-QuIC), which has been used in the diagnosis of Creutzfeldt-Jakob disease, has shown the ability to detect pathological forms of α-synuclein in CSF with high accuracy (10–12). A growing body of literature suggests that tau imaging agents such as PET with the tracers PI2620 and PBB3 detects 4R aggregates (13–15).

Research on biomarkers for neuroinflammation suggests potential clinical applications to help in the differential diagnosis of dementia. Preliminary results indicate that neuroinflammation biomarkers provide signatures of brain inflammatory responses secondary to the accumulation of abnormal protein aggregates. Changes in YLK40 and sTREM2 mean activation of microglial brain cells, while GFAP indicates astrocyte activation (16–22). Although several PET imaging agents can quantify neuroinflammation responses, they are exclusively used in research.

Biomarkers of synaptic depletion are being developed to quantify cerebrospinal fluid as synapse dysfunction constitutes a common target in all neurodegenerative conditions. However, such biomarkers remain in the early phase of development (23–25).

Survey results

The survey indicates that clinicians foresee an increase in the number of patients seeking a dementia diagnosis and that options such blood tests would facilitate their practice in combination with cognitive assessment and their own clinician judgement or national guidelines.

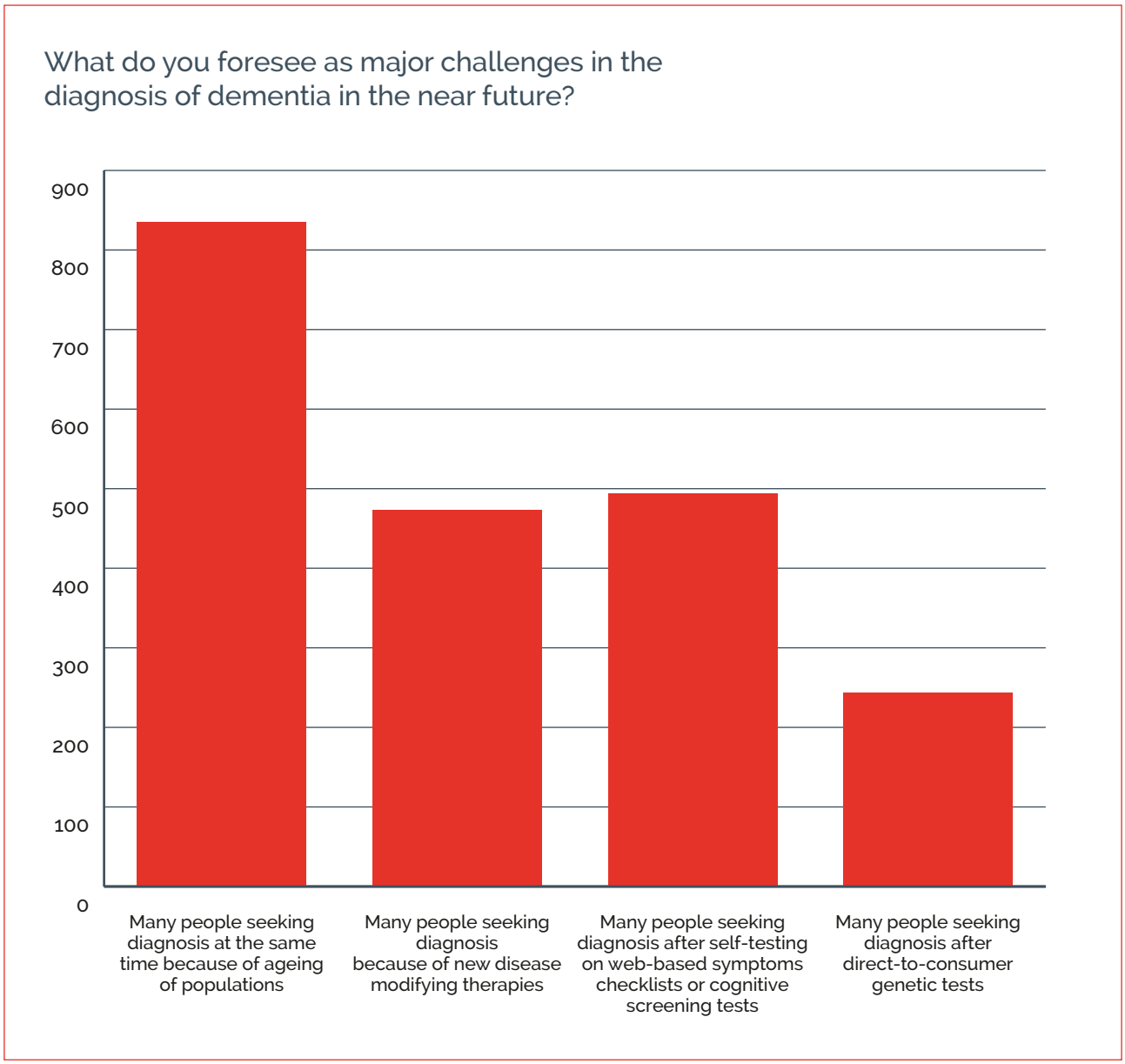


Chart 1. Clinician responses (multiple answers selected).

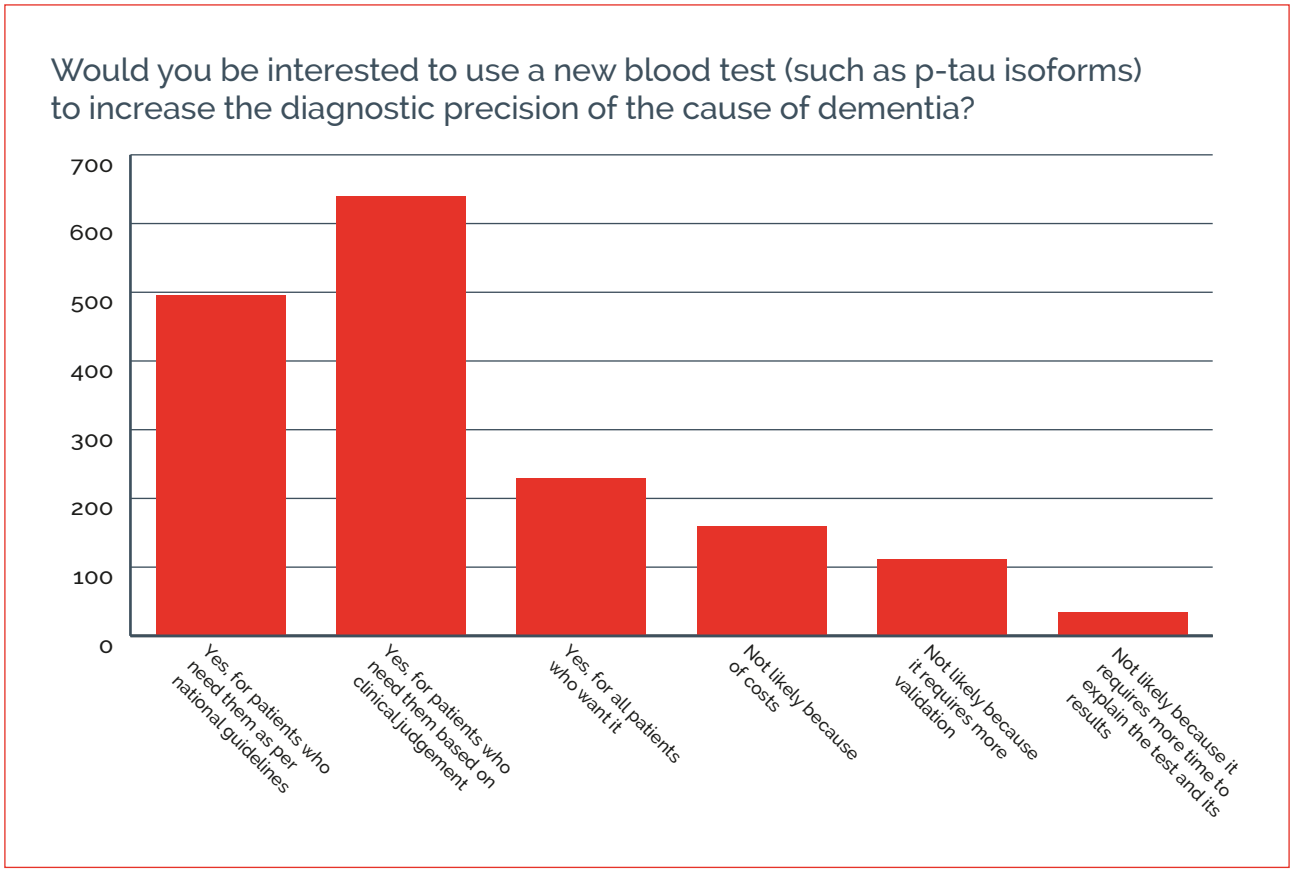


Chart 2. Clinician responses.

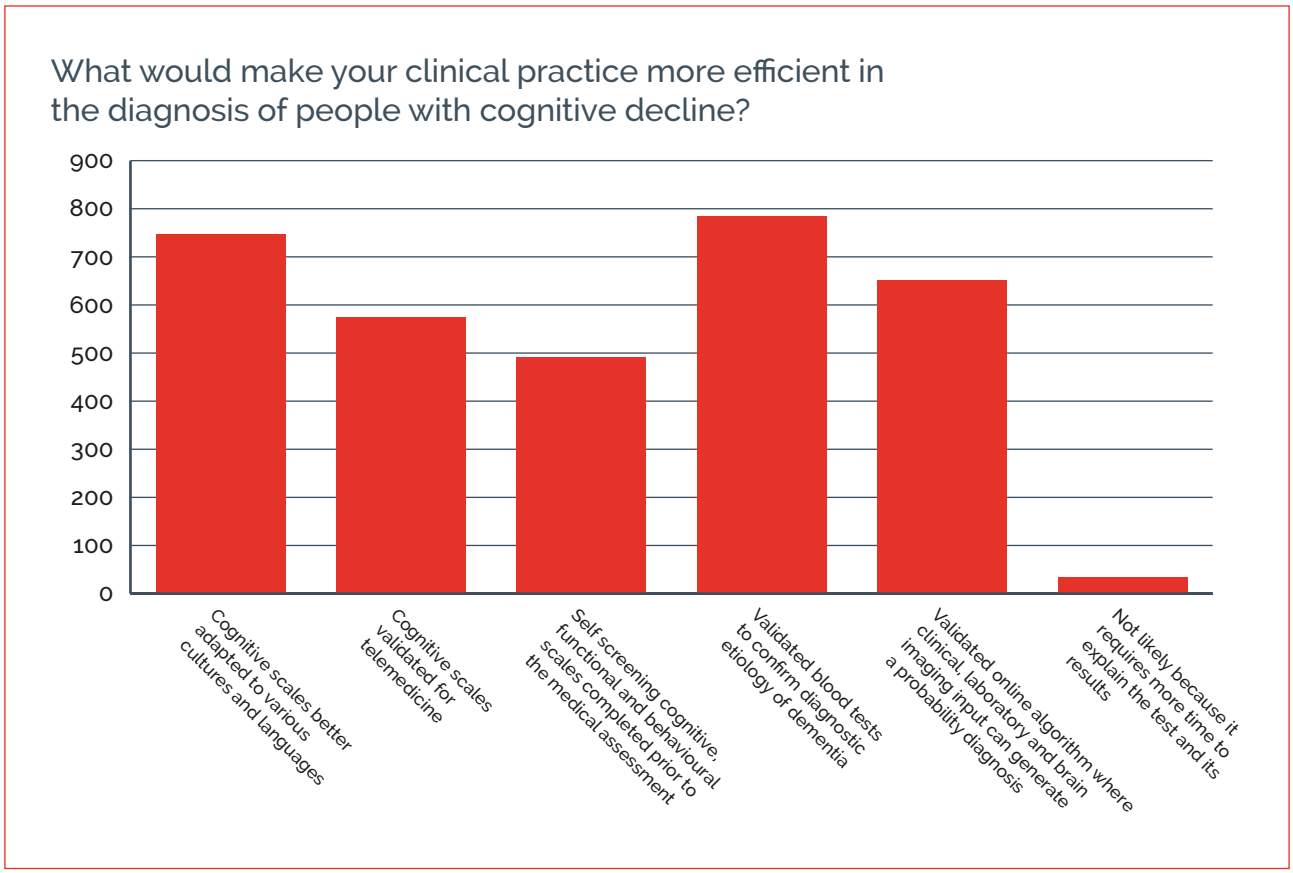


Chart 3. Clinician responses (multiple answers selected).

Expert essay

Will the use of blood-based biomarkers become standard practice in Alzheimer's disease?

Emily A. Largent

Department of Medical Ethics and Health Policy, University of Pennsylvania Perelman School of Medicine, USA

There is great enthusiasm within the fields of Alzheimer's disease care and research for blood-based biomarkers. Biomarkers (short for 'biological markers') are signs of disease pathology that can be measured using laboratory or imaging tests. Blood-based biomarkers have the potential to offer reliable, inexpensive, and widely available means of screening for Alzheimer's disease, tracking disease progression, and accelerating the development of disease-modifying therapies.

Historically, Alzheimer's disease has been diagnosed based on the detection of dementia with a characteristic onset and pattern of impairments as well as the exclusion of alternative causes of cognitive impairment. This diagnosis was confirmed post-mortem via autopsy. More recently, there has been a move away from this syndromal definition of Alzheimer's disease toward a biological definition. Biomarkers have been, and are currently being developed, to be used to identify the neuropathological changes characteristic of Alzheimer's disease in living individuals independent of clinical symptoms, if any.

Researchers have identified numerous promising blood-based biomarkers for Alzheimer's disease. These biomarkers are in various stages of validation, and it is necessary to ensure that any tests for blood-based biomarkers are reliable and their results are reproducible before widespread adoption. Blood-based biomarkers will offer many advantages over CSF and PET biomarkers. Blood tests are commonly used in clinical and research settings around the world, meaning that necessary clinical competencies and infrastructure are already well established. Blood draws are safer, less invasive, and less expensive than either lumbar puncture or PET imaging. Moreover, blood draws are easily repeated over time.

There have been notable advances in the use of cerebrospinal fluid (CSF) and positron emission tomography (PET) to measure biomarkers that are proxies for the neuropathologic changes of Alzheimer's disease, including accumulation of extracellular amyloid-ß plaques and tangles of tau protein. CSF is the clear fluid surrounding the brain and spinal cord and can be obtained through a lumbar puncture. PET imaging uses a radioactive substance called a tracer to visualise activity or proteins in the brain. Biomarker evidence of abnormalities in both amyloid-ß and pathological tau should be present to diagnose Alzheimer's disease (1). Magnetic resonance imaging (MRI) can be used to measure neurodegeneration, a loss of neurons that is part of the classification system for Alzheimer's disease. Neurodegeneration is not, however, specific to Alzheimer's disease and thus not considered equivalent to biomarker evidence of amyloid-ß deposition and pathologic tau accumulation.

> **"Blood tests are commonly used in clinical and research settings around the world, meaning that necessary clinical competencies and infrastructure are already well established.**

Various CSF and PET biomarkers are now widely used in Alzheimer's disease research (2). Unfortunately, the cost, burdensomeness, and infrastructure demands of CSF and PET biomarkers has greatly limited their use – and thus their utility – in clinical practice.

Assuming that one or more blood-based biomarkers is validated, we can speculate about the impact they may have on Alzheimer's disease research and, eventually, clinical practice. They may be used alone or in combination with other modalities to provide diagnostic information, assess the severity of disease, offer prognostic information, or provide insight into the efficacy of treatment (5,6).

In research

Blood-based biomarkers for Alzheimer's disease hold significant promise as an approach to population-based screening. They can be used as an initial screening tool to identify prospective research participants who then undergo

further assessment, for instance using CSF or PET biomarkers and neuropsychological testing to verify study eligibility. Adoption of a multi-step process that begins with a simple blood draw will enable the study of Alzheimer's disease in larger populations more quickly, with less cost and burden.

These advantages are likely to be particularly pronounced in prevention trials that enrol individuals with preclinical Alzheimer's disease, a stage of the disease characterised by the presence of neuropathological changes in the absence of cognitive or functional impairment. Preclinical Alzheimer's disease cannot be identified without testing for biomarkers, and screen failures are common in prevention trials due to the lower frequency of neuropathological changes in cognitively unimpaired adults (7). Difficulty recruiting enough suitable research participants is a barrier to completing prevention trials. Researchers should, therefore, actively be using blood-based biomarkers as a screening mechanism to advance the urgent goal of identifying disease-modifying therapies for Alzheimer's disease.

In clinical care

Regrettably, older adults are often inadequately assessed for cognitive decline during primary care visits due to limitations on clinician time as well as lack of clinician expertise. Availability of a blood-based biomarker test will aid in addressing persistent issues of missed and delayed diagnoses. People who do not have blood-based biomarkers indicative of Alzheimer's disease will also benefit from the availability of a blood test, as a negative result may aid in differential diagnosis and suggest other avenues for intervention. Blood-based biomarkers could potentially be used to reduce the number of unnecessary referrals for specialised care and needless diagnostic procedures, which could shorten waiting times and reduce healthcare costs (8).

Once a disease-modifying therapy for Alzheimer's disease is identified and approved for clinical use, it will be necessary to identify those individuals who might respond to therapy. In particular, if a drug is indicated for use in preclinical Alzheimer's disease, use of blood-based biomarkers to screen cognitively unimpaired adults is likely to become a standard of care. Blood-based biomarkers might also be used to monitor the efficacy of treatment and promote precision medicine, an approach to patient care that takes into account an individual's characteristics to identify the treatments that could work best for him or her (4).

Advances in the science of biomarkers should be paired with robust study of the ethical, legal, and social implications about learning one's biomarker results (9). This will include designing patient education and disclosure materials, tackling Alzheimer's disease stigma and discrimination, and evaluating whether the clinical use of biomarkers addresses or exacerbates health disparities. Further, efforts are needed on a global level to build the capacity to care for people living with Alzheimer's disease and Alzheimer's disease-related dementias.

References

1. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's Dement 2018;14:535–62. https://doi.org/10.1016/j.jalz.2018.02.018.
2. Bateman RJ, Barthélemy NR, Horie K. Another step forward in blood-based diagnostics for Alzheimer's disease. Nat Med 2020;26:314–6. https://doi.org/10.1038/s41591-020-0797-4.
3. Zetterberg H, Blennow K. Moving fluid biomarkers for Alzheimer's disease from research tools to routine clinical diagnostics. Mol Neurodegener 2021;16:10. https://doi.org/10.1186/s13024-021-00430-x.
4. Hampel H, O'Bryant SE, Molinuevo JL, Zetterberg H, Masters CL, Lista S, et al. Blood-based biomarkers for Alzheimer disease: mapping the road to the clinic. Nat Rev Neurol 2018;14:639–52. https://doi.org/10.1038/s41582-018-0079-7.
5. Henriksen K, O'Bryant SE, Hampel H, Trojanowski JQ, Montine TJ, Jeromin A, et al. The future of blood-based biomarkers for Alzheimer's disease. Alzheimer's Dement 2014;10:115–31. https://doi.org/10.1016/j.jalz.2013.01.013.
6. O'Bryant SE, Mielke MM, Rissman RA, Lista S, Vanderstichele H, Zetterberg H, et al. Blood-based biomarkers in Alzheimer disease: Current state of the science and a novel collaborative paradigm for advancing from discovery to clinic. Alzheimer's Dement 2017;13:45–58. https://doi.org/10.1016/j.jalz.2016.09.014.
7. Schindler SE, Bateman RJ. Combining blood-based biomarkers to predict risk for Alzheimer's disease dementia. Nat Aging 2021;1:26–8. https://doi.org/10.1038/s43587-020-00008-0.
8. Mattke S, Cho SK, Bittner T, Hlávka J, Hanson M. Blood-based biomarkers for Alzheimer's pathology and the diagnostic process for a disease-modifying treatment: Projecting the impact on the cost and wait times. Alzheimer's Dement Diagnosis, Assess Dis Monit 2020;12:1. https://doi.org/10.1002/dad2.12081.
9. Largent EA, Harkins K, Van Dyck CH, Hachey S, Sankar P, Karlawish J. Cognitively unimpaired adults' reactions to disclosure of amyloid PET scan results. PLoS One 2020;15:1. https://doi.org/10.1371/journal.pone.0229137.

Expert essay

Blood biomarkers for Alzheimer's disease: a fast-growing promise

Thomas K. Karikari, Andréa L. Benedet

Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, SWEDEN

There are well-established cerebrospinal fluid (CSF) and neuroimaging biomarkers that report on the underlying biology of Alzheimer's disease (1–2). Why then do we need blood biomarkers? CSF collection requires lumbar puncture, an invasive procedure with contra-indications and requiring specialised personnel to perform. Imaging biomarkers require position emissions tomography (PET) scanning, which is expensive, with accessibility limited to a few specialised hospitals (3). Therefore, while CSF and molecular neuroimaging techniques are excellent biomarkers, they lack the scalability, throughput, and simplicity for widespread routine clinical applications. This is where blood biomarkers come in: initially envisaged as first-line pre-screening tools, blood biomarkers now show immense diagnostic promise given their practical, scalable, and economic advantages.

> **Blood biomarkers now show immense diagnostic promise given their practical, scalable, and economic advantages.**

Following years of methodological advancements, we now have candidate blood-based methods to quantify amyloid (Aβ42/40) and tau pathologies (phosphorylated tau, p-tau), the two cardinal features of Alzheimer's disease, as well as neurodegeneration (with neurofilament light, NfL) (1,2). Similar to CSF biomarkers, characteristic blood changes include decreased Aβ42/40, and increased p-tau and NfL in Alzheimer's disease individuals as compared with controls. Blood Aβ42/Aβ40 modestly separates individuals with and without brain Aβ pathology (4,5). However, this biomarker is only marginally decreased in Alzheimer's disease (compared with more definite decreases in CSF Aβ42/Aβ40) regardless of the method used. Potential reasons for this observation include significant Aβ levels in peripheral tissues, large overlaps between diagnostic groups, and increases in normal ageing. Despite immunoprecipitation-mass spectrometry (IP-MS) methods showing modestly better performances, the low-throughput and extensive pre-analytical steps limit inter-laboratory transferability, and consequently, suitability of this method for routine use at this time (1). There are also substantial cohort differences in the optimal cut-points used to separate amyloid-positive from -negative individuals, also when a high-performance method is used (6), suggesting that the biomarker as such may lack in robustness. Glial fibrillary acid protein (GFAP), a marker of astrocytic activation, is another emerging blood marker related to amyloid pathology. GFAP is already increased in preclinical Alzheimer's disease (namely, cognitively normal adults with evident amyloid pathology), and predicts incident dementia (7). Blood GFAP increases proportionally with amyloid pathology – indexed by PET imaging and its combination with plasma Aβ42/Aβ40 detects cerebral amyloidosis. However, GFAP was also found to be elevated in other neurodegenerative diseases including frontotemporal dementia, traumatic brain injury and stroke. Given their analytical and disease-specificity limitations, blood Aβ42/Aβ40 and GFAP are candidate prognostic blood biomarkers that may best be used in combination with others to provide disease-specific information.

Blood p-tau continues to show promise as a marker of tau pathology in Alzheimer's disease. Concentrations of different p-tau analytes (for example, p-tau181, p-tau217 or p-tau231) gradually increase in the course of Alzheimer's disease; the levels are lowest in cognitively unimpaired adults, slightly increased in preclinical Alzheimer's disease, further elevated in mildly cognitively impaired elderly with amyloid pathology (Aβ+ MCI), and highest in Alzheimer's disease dementia (8–10). This time course is similar to those of CSF p-tau. Blood p-tau biomarkers predict current and future brain amyloid and tau accumulation, and correlate well with CSF biomarkers, and cognitive function. In longitudinal studies, blood p-tau increased according to disease severity: amyloid positive individuals had higher concentrations at baseline and at follow-up when compared with amyloid negative groups at identical clinical stages. Furthermore, those with increased p-tau baseline levels showed greater odds for worsening disease. In patients with autopsy-verified diagnosis and

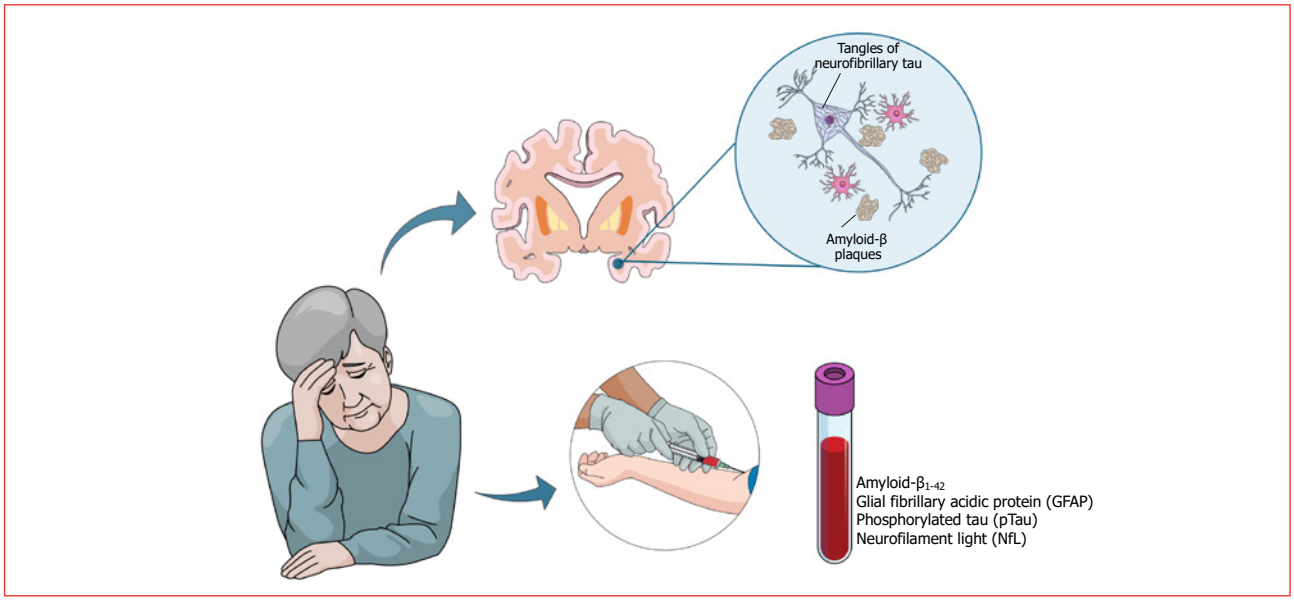


Figure 1. Schematic representation of blood-based plasma biomarkers. Novel biomarkers quantify in the peripheral blood, pathophysiological processes happening in the brain tissue.

ante mortem blood, p-tau elevations were most obvious 4–8 years prior to death, and distinguished pathology-confirmed Alzheimer's disease from non-ADs regardless of clinical diagnosis during life. Furthermore, p-tau concentrations agreed more strongly with diagnosis given at autopsy than during life. Notably, similar blood p-tau levels were found in people with pure Alzheimer's disease and those with concomitant disease, indicating that the biomarker is uniquely specific to the presence of Alzheimer's disease pathology.

Blood NfL is a candidate neurodegeneration biomarker that increases according to clinical diagnosis in Alzheimer's disease (11). However, compared with blood p-tau, these increases are not specific to Alzheimer's disease when associated with brain changes at the anatomical level (12). For instance, while longitudinal changes in blood p-tau associate specifically with amyloid-PET accumulation in Alzheimer's disease-characteristic brain regions, blood NfL increases are more wide-ranging. In agreement, blood NfL is increased in multiple neurodegenerative conditions (as a general marker of neuronal damage/injury) and may therefore be used together with other more-specific biomarkers (for example, p-tau) when evaluating for Alzheimer's disease. Commercial NfL methods are now measured as part of a routine clinical assessment in several European countries, including Sweden and the Netherlands; the first Alzheimer's disease-related blood biomarker to come this far. Other prospective blood-based neurodegeneration biomarkers, including total-tau and neutrophin 1 precursor (NT1), have shown prognostic potential but their performances do not appear suited for diagnostic use just yet.

Although blood-based Alzheimer's disease biomarkers have recently shown highly encouraging findings in research settings, efforts to standardise measurements to ensure transferability and reproducibility between laboratories are in their infancy. The different methodologies to quantify amyloid pathology in the blood are still poorly correlated, suggesting they do not measure the same analytes. Recently some methodological improvements have been introduced, still warranting updated comparisons between them. For p-tau, preliminary method comparisons have shown high correlations and similar performances between biomarker assays, especially in symptomatic Alzheimer's disease, but still a lot of work is required to validate assays for clinical use. NfL has been proven to be a very robust blood biomarker, with highly associated measures in samples processed using standard and unconventional methods. However, further method comparison is needed for harmonisation of techniques and readings to support interpretation in clinical practice.

Although blood-based Alzheimer's disease biomarkers have recently shown highly encouraging findings in research settings, efforts to standardise measurements to ensure transferability and reproducibility between laboratories are in their infancy.

In conclusion, blood biomarkers have shown very promising diagnostic performances, and were associated with key disease features in Alzheimer's disease, reinforcing their great potential for routine clinical evaluations, research studies, and therapeutic trials. With further development of reliable assays

on fully automated instruments, these blood tests are expected to transform Alzheimer's disease care by greatly simplifying access to timely and cost-effective diagnostic and prognostic screening, which will not only immediately benefits patients, families and clinicians, but will also enable the development and evaluation of new disease-modifying therapies.

References

1. Ashton NJ, Hye A, Rajkumar AP, Leuzy A, Snowden S, Suárez-Calvet M, et al. An update on blood-based biomarkers for non-Alzheimer neurodegenerative disorders. Nat Rev Neurol [Internet]. 2020;16(5):265–84. https://doi.org/10.1038/s41582-020-0348-0
2. Zetterberg H, Blennow K. Moving fluid biomarkers for Alzheimer's disease from research tools to routine clinical diagnostics. Mol Neurodegener. 2021;16(1):10.
3. Hampel H, O'Bryant SE, Molinuevo JL, Zetterberg H, Masters CL, Lista S, et al. Blood-based biomarkers for Alzheimer disease: mapping the road to the clinic. Nat Rev Neurol [Internet]. 2018;14(11):639–52. https://doi.org/10.1038/s41582-018-0079-7
4. Schindler SE, Bollinger JG, Ovod V, Mawuenyega KG, Li Y, Gordon BA, et al. High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis. Neurology. 2019;93(17):E1647–59.
5. Palmqvist S, Janelidze S, Stomrud E, Zetterberg H, Karl J, Zink K, et al. Performance of Fully Automated Plasma Assays as Screening Tests for Alzheimer Disease-Related β-Amyloid Status. JAMA Neurol [Internet]. 2019;76(9):1060–9. https://doi.org/10.1001/jamaneurol.2019.1632
6. West T, Kirmess KM, Meyer MR, Holubasch MS, Knapik SS, Hu Y, et al. A blood-based diagnostic test incorporating plasma Aβ42/40 ratio, ApoE proteotype, and age accurately identifies brain amyloid status: findings from a multi cohort validity analysis. Mol Neurodegener [Internet]. 2021;16(1):30. https://doi.org/10.1186/s13024-021-00451-6
7. Asken BM, Elahi FM, La Joie R, Strom A, Staffaroni AM, Lindbergh CA, et al. Plasma Glial Fibrillary Acidic Protein Levels Differ along the Spectra of Amyloid Burden and Clinical Disease Stage. J Alzheimer's Dis [Internet]. 2020;78(1):265–76. https://doi.org/10.3233/JAD-200755
8. Karikari TK, Benedet AL, Ashton NJ, Lantero Rodriguez J, Snellman A, Suárez-Calvet M, et al. Diagnostic performance and prediction of clinical progression of plasma phospho-tau181 in the Alzheimer's Disease Neuroimaging Initiative. Mol Psychiatry [Internet]. 2021 Feb 1;26(2):429–42. https://pubmed.ncbi.nlm.nih.gov/33106600
9. Ashton NJ, Pascoal TA, Karikari TK, Benedet AL, Lantero-Rodriguez J, Brinkmalm G, et al. Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology. Acta Neuropathol [Internet]. 2021;141(5):709–24. https://doi.org/10.1007/s00401-021-02275-6
10. Palmqvist S, Janelidze S, Quiroz YT, Zetterberg H, Lopera F, Stomrud E, et al. Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. JAMA – J Am Med Assoc [Internet]. 2020;324(8):772–81. https://doi.org/10.1001/jama.2020.12134
11. Ashton NJ, Janelidze S, Al Khleifat A, Leuzy A, van der Ende EL, Karikari TK, et al. A multicentre validation study of the diagnostic value of plasma neurofilament light. Nat Commun [Internet]. 2021 Dec 1;12(1). https://pubmed.ncbi.nlm.nih.gov/34099648
12. Benedet AL, Leuzy A, Pascoal TA, Ashton NJ, Mathotaarachchi S, Savard M, et al. Stage-specific links between plasma neurofilament light and imaging biomarkers of Alzheimer's disease. Brain [Internet]. 2020;143(12):3793–804. https://doi.org/10.1093/brain/awaa342

Expert essay

CSF and blood biomarkers for non-Alzheimer's dementias

Nicholas J. Ashton, Henrik Zetterberg, Kaj Blennow

Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, SWEDEN

Primary neurodegenerative disorders (NDDs) are characterised by aggregates of abnormal proteins in the central nervous system. Six hallmark proteins enable the classification of most NDDs: two of them form extracellular aggregates, amyloid-β (Aβ) and the prion protein (PrPsc), while four aggregate intracellularly: tau, alpha-synuclein (α-synuclein), TAR DNA-binding protein 43 (TDP-43) and fused in sarcoma (FUS), leading to amyloidopathies, prionopathies, tauopathies, α-synucleinopathies, TDP43-proteinopathies and FUS inclusions, respectively (1). The neurodegenerative pathologies often coexist, and additional vascular changes are also prevalent causing clinical and neuropathological heterogeneity. The presenting clinical manifestations and syndromes vary between NDDs but are related to the severity, type, and regional distribution of the proteinopathies. Alzheimer's disease is typically characterised by memory impairment, aphasia, apraxia, and agnosia, related to the involvement of medial temporal lobe and parietal cortex. In contrast, the frontotemporal dementias are characterised by behavioural and language changes, and Lewy body dementias (Parkinson disease dementia and dementia with Lewy bodies) by executive, attentional, and visuospatial impairment, and non-cognitive symptoms such as parkinsonism, REM-sleep behaviour disorder, autonomic symptoms and visual hallucinations. The neuroanatomical distribution of proteinopathy pathology help to establish consensus protocols for neuropathological assessment and diagnosis. The clinico-pathological correlation is however difficult to establish. In addition, most neurodegenerative disorders are heterogeneous diseases, namely combinations of proteinopathies, thus biomarkers, such as imaging and biofluid analysis, are crucial for accurate diagnosis which may allow detection in early prodromal or even pre-clinical stages for early interventions when available. With the exception of Alzheimer's disease, where the most recent diagnostic criteria (2) include biomarkers to establish the typical proteinopathy, non-Alzheimer's disease neurodegenerative disorders are mainly diagnosed by clinical features. In Alzheimer's disease, there is already excellent imaging (3), cerebrospinal fluid (CSF) (4) and promising blood biomarkers (5) being developed. In contrast, fluid biomarkers in non-Alzheimer's dementia remain in their infancy but will greatly benefit from the developments in the Alzheimer's disease field.

The core CSF biomarkers for Alzheimer's disease (Aβ42/40, T-tau and P-tau), reflecting the defining Aβ and tau pathologies as well as neurodegeneration, consistently demonstrate diagnostically significant changes across studies (6). However, the concentrations of these core Alzheimer's disease biomarkers are largely normal in the majority of dementias outside of the Alzheimer's disease continuum (7). This can be of great utility in the differential diagnosis of individuals with cognitive symptoms. There are isolated exceptions to this rule; Aβ42 is abnormally decreased in approximately half of dementia with Lewy body cases and many patients with Parkinson's disease dementia (8), which highlights the overlapping pathologies with Alzheimer's disease found at post-mortem. Furthermore, marked increases of T-tau in Creutzfeldt-Jakob disease (CJD) is a common observation, whereas the concentration of P-tau remains normal or only marginally changed in CJD (9) – this makes a ratio of P-tau/T-tau an excellent biomarker in the diagnosis of CJD (10). An unpredicted finding is that levels of CSF t-tau and p-tau are largely normal in frontotemporal dementia. The same holds true for other primary tauopathies (for example, primary progressive supranuclear palsy [PSP]). Neurofilament light chain (NFL) is the smallest of the neurofilament triplet proteins that are the structural components of the axons. NFL is released from the axons throughout life and increasingly in normal ageing; however, in response to axonal injury, NFL release into the extracellular space, CSF and blood is accelerated. Several studies have shown that CSF NFL levels are highest in brain disorders with subcortical pathology, such as vascular dementia (VaD) and normal pressure hydrocephalus (11). Notably, CSF NFL concentrations are clearly higher in frontotemporal dementia than in pure Alzheimer's disease without concomitant cerebrovascular disease (12), which supports that NFL aids in this differential diagnostic specific situation. In addition, CSF NFL also shows a very marked increase in CJD (correlating with CSF T-tau), due to the very extreme level of neurodegeneration (13). Importantly, while CSF NFL is relatively normal in Parkinson's

disease, several studies have shown a very marked increase in CSF NFL in atypical parkinsonian disorders, specifically in corticobasal syndrome (CBD), multiple systemic atrophy (MSA), and PSP (14). Measurements of total α-synuclein in CSF has been proposed as a biomarker for Parkinson's dementia and dementia with Lewy bodies, but most studies only show minor reductions in Parkinson's dementia, with considerable overlap between controls and other patient groups. Recent developments in real-time quaking-induced conversion (RT-QuIC) technology, which explores the self-replicating property of proteinopathic proteins, show great promise in accurate diagnosis of α-synucleinopathies (15), and potentially also TDP-43 (16). As mentioned in the previous essay, biomarkers reflecting post- and presynaptic pathology (for example, neurogranin, GAP-43, SNAP25 and synaptotagmin-1) are specifically increased in individuals with amyloid pathology.

The development of blood biomarkers for non-Alzheimer's disease dementias has not had the same recent success as for Alzheimer's disease (17). α-Synuclein and TDP-43 can be detected and quantified in blood, but their concentrations do not associate well with CSF or neuropathological findings and are likely confounded by high peripheral expression. However, Alzheimer's disease blood biomarkers, specifically p-tau, are extremely useful in differentiating Alzheimer's disease from non- Alzheimer's disease dementias with very high accuracy (18–20). In addition, they can also detect co-pathology in disorders such as dementia with Lewy bodies (21,22). As a close correlation exists between CSF and plasma NfL, CSF findings have been largely replicated in blood (23). While plasma NfL has limited specificity for an accurate diagnosis, it is a robust marker for ongoing neurodegeneration. Nonetheless, plasma NfL is clinically useful in identifying atypical parkinsonian disorders (for example, CBD, MSA and PSP) in individuals with parkinsonism, dementia in individuals with Down syndrome, dementia among psychiatric disorders, and frontotemporal dementia in people with cognitive impairment (23). GFAP is a marker of astrogliosis and is increased in the brains of non- Alzheimer's disease dementia individuals and it is also increased in the CSF of several dementias. However, GFAP changes in blood in non-Alzheimer's disease neurodegenerative disorders appear relatively minor; when measured in blood, the marker appears particularly sensitive to Alzheimer's disease-related Aβ pathology.

In summary, CSF and blood biomarkers for non-Alzheimer's disease dementias still rely on negative Alzheimer's disease biomarkers (which have a very high diagnostic utility for amyloid and tau pathologies) and the non-specific increase of NfL, as supportive evidence alongside clinical assessments. While much work is needed to develop robust biological markers for TDP43 pathology and primary tauopathies, there is now great promise in characterizing α-synucleinopathies by RT-QuiC. This will greatly aid a broad spectrum of dementias but, in particular, in the early diagnosis of Parkinson's disease, Parkinsons' dementia and dementia with Lewy bodies.

References

1. Kovacs GG. Molecular pathological classification of neurodegenerative diseases: Turning towards precision medicine. Int J Mol Sci. 2016;17(2).
2. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's Dement. 2018;14(4):535–62.
3. Leuzy A, Heurling K, Ashton NJ, Scholl M, Zimmer ER. In vivo Detection of Alzheimer's Disease. Yale J Biol Med. 2018;91:291–300.
4. Molinuevo JL, Ayton S, Batrla R, Bednar MM, Bittner T, Cummings J, et al. Current state of Alzheimer's fluid biomarkers. Acta Neuropathol. 2018;136:821–53.
5. Ashton NJ, Leuzy A, Karikari TK, Mattsson-Carlgren N, Dodich A, Boccardi M, et al. The validation status of blood biomarkers of amyloid and phospho-tau assessed with the 5-phase development framework for AD biomarkers. Eur J Nucl Med Mol Imaging [Internet]. 2021;48(7):2140–56. https://doi.org/10.1007/s00259-021-05253-y
6. Olsson B, Lautner R, Andreasson U, Öhrfelt A, Portelius E, Bjerke M, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol. 2016;15(7):673–84.
7. Oeckl P, Steinacker P, Feneberg E, Otto M. Neurochemical biomarkers in the diagnosis of frontotemporal lobar degeneration: an update. J Neurochem. 2016;138:184–92.
8. Andersson M, Zetterberg H, Minthon L, Blennow K, Londos E. The cognitive profile and CSF biomarkers in dementia with Lewy bodies and Parkinson's disease dementia. Int J Geriatr Psychiatry. 2011;26(1):100–5.
9. Otto M, Wiltfang J, Tumani H, Zerr I, Lantsch M, Kornhuber J, et al. Elevated levels of tau-protein in cerebrospinal fluid of patients with Creutzfeldt-Jakob disease. Neurosci Lett. 1997;225(3):210–2.
10. Riemenschneider M, Wagenpfeil S, Vanderstichele H, Otto M, Wiltfang J, Kretzschmar H, et al. Phospho-tau/total tau ratio in cerebrospinal fluid discriminates Creutzfeldt-Jakob disease from other dementias. Mol Psychiatry. 2003;8(3):343–7.
11. Bridel C, Van Wieringen WN, Zetterberg H, Tijms BM, Teunissen CE, Alvarez-Cermeño JC, et al. Diagnostic Value of Cerebrospinal Fluid Neurofilament Light Protein in Neurology: A Systematic Review and Meta-analysis. JAMA Neurol [Internet]. 2019 Sep 1 [cited 2021 Jul 14];76(9):1035–48. https://jamanetwork.com/journals/jamaneurology/fullarticle/2735955
12. Sjögren M, Rosengren L, Minthon L, Davidsson P, Blennow K, Wallin A. Cytoskeleton proteins in CSF distinguish frontotemporal dementia from AD. Neurology. 2000;54(10):1960–4.
13. Steinacker P, Blennow K, Halbgebauer S, Shi S, Ruf V, Oeckl P, et al. Neurofilaments in blood and CSF for diagnosis and prediction of onset in Creutzfeldt-Jakob disease. Sci Rep. 2016;6:38737.
14. Hansson O, Janelidze S, Hall S, Magdalinou N, Lees AJ, Andreasson U, et al. Blood-based NfL: A biomarker for differential diagnosis of parkinsonian disorder. Neurology. 2017;88(10):930–7.
15. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Avanzini G, Bestmann S, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol [Internet]. 2009;120(12):2008–39. /Users/sservaes/Library/Application Support/Papers2/Articles/2009/Rossi/Clinical Neurophysiology 2009 Rossi.pdf

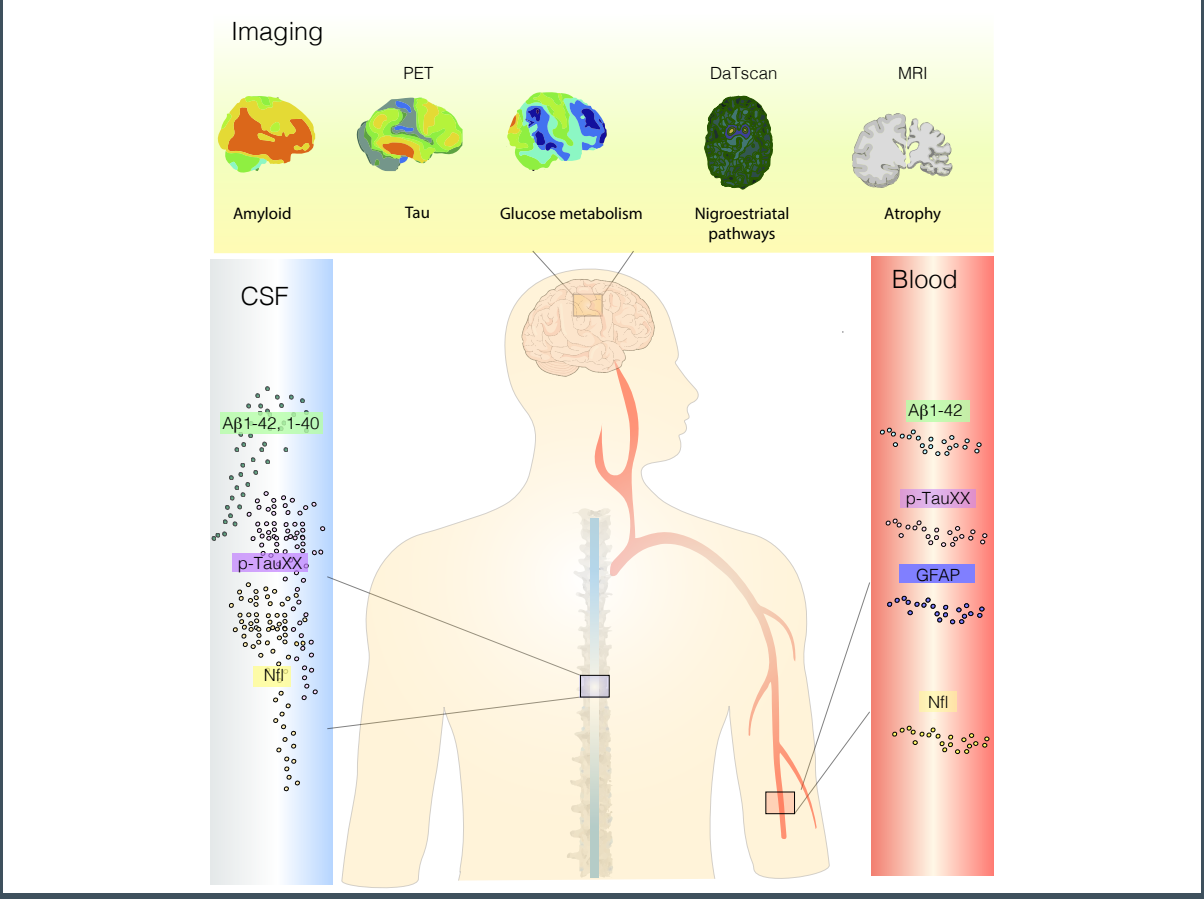
16. Scialò C, Tran TH, Salzano G, Novi G, Caponnetto C, Chiò A, et al. TDP-43 real-time quaking induced conversion reaction optimization and detection of seeding activity in CSF of amyotrophic lateral sclerosis and frontotemporal dementia patients. Brain Commun. 2020;2(2).
17. Ashton NJ, Hye A, Rajkumar AP, Leuzy A, Snowden S, Suárez-Calvet M, et al. An update on blood-based biomarkers for non-Alzheimer neurodegenerative disorders. Nat Rev Neurol [Internet]. 2020;16(5):265–84. https://doi.org/10.1038/s41582-020-0348-0
18. Karikari TK, Pascoal TA, Ashton NJ, Janelidze S, Benedet AL, Rodriguez JL, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. Lancet Neurol [Internet]. 2020;19(5):422–33. https://doi.org/10.1016/S1474-4422(20)30071-5
19. Ashton NJ, Pascoal TA, Karikari TK, Benedet AL, Lantero-Rodriguez J, Brinkmalm G, et al. Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology. Acta Neuropathol [Internet]. 2021;141(5):709–24. https://doi.org/10.1007/s00401-021-02275-6
20. Palmqvist S, Janelidze S, Quiroz YT, Zetterberg H, Lopera F, Stomrud E, et al. Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. JAMA – J Am Med Assoc [Internet]. 2020;324(8):772–81. https://doi.org/10.1001/jama.2020.12134
21. Hall S, Janelidze S, Londos E, Leuzy A, Stomrud E, Dage JL, et al. Plasma Phospho-Tau Identifies Alzheimer's Co-Pathology in Patients with Lewy Body Disease. Mov Disord. 2021;36(3):767–71.
22. Lantero Rodriguez J, Karikari TK, Suárez-Calvet M, Troakes C, King A, Emersic A, et al. Plasma p-tau181 accurately predicts Alzheimer's disease pathology at least 8 years prior to post-mortem and improves the clinical characterisation of cognitive decline. Acta Neuropathol [Internet]. 2020;140(3):267–78. https://doi.org/10.1007/s00401-020-02195-x
23. Ashton NJ, Janelidze S, Al Khleifat A, Leuzy A, van der Ende EL, Karikari TK, et al. A multicentre validation study of the diagnostic value of plasma neurofilament light. Nat Commun [Internet]. 2021 Dec 1;12(1). https://pubmed.ncbi.nlm.nih.gov/34099648/.

Conclusions

The emergence of biomarkers into the diagnosis of dementia is being hailed by physicians around the world as an inexpensive and effective method to identify and monitor the accumulation of abnormal proteins in the brain. Physicians are anticipating the widespread adoption of these blood tests into their everyday practice as high sensitivity techniques to quantify disease pathophysiology in peripheral blood samples will advance clinical care.

The image below image combines the laboratory evaluations for dementia articulated throughout Section II including imaging, cerebrospinal fluid and blood biomarkers. Not only do they help confirm the diagnosis, but also offer insight into the underlying cause of the syndrome. Specialised tests such as PET and SPECT allow for the visualisation of a host of biochemical processes. thus providing for increased diagnostic accuracy. A lumbar puncture is a safe and effective procedure that detects the presence of pathological processes in the brain and the novel biomarkers will allow for precise identification of accumulated abnormal proteins in the brain in a widespread and affordable way.

This is especially relevant as the population ages and more people will seek out a dementia assessment in the coming years. Though still in its infancy when it comes to standardisation, transferability and reproducibility, plasma biomarkers promise to accelerate diagnosis and permit a level of yet unseen personalised care on a global scale given their ease of use, affordability and adaptability.



Visual overview of biomarker testing reviewed throughout Part II.

Additional references

1. Nakamura A, Kaneko N, Villemagne VL, Kato T, Doecke J, Doré V, et al. High performance plasma amyloid-β biomarkers for Alzheimer's disease. Nature 2018;554:249–54. https://doi.org/10.1038/nature25456.
2. West T, Kirmess KM, Meyer MR, Holubasch MS, Knapik SS, Hu Y, et al. A blood-based diagnostic test incorporating plasma Aβ42/40 ratio, ApoE proteotype, and age accurately identifies brain amyloid status: findings from a multi cohort validity analysis. Mol Neurodegener 2021;16:30. https://doi.org/10.1186/s13024-021-00451-6.
3. Karikari TK, Pascoal TA, Ashton NJ, Janelidze S, Benedet AL, Rodriguez JL, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. Lancet Neurol 2020;19:422–33. https://doi.org/10.1016/S1474-4422(20)30071-5.
4. Hansson O, Seibyl J, Stomrud E, Zetterberg H, Trojanowski JQ, Bittner T, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimer's Dement 2018;14:1470–81. https://doi.org/10.1016/j.jalz.2018.01.010.
5. Ashton NJ, Pascoal TA, Karikari TK, Benedet AL, Lantero-Rodriguez J, Brinkmalm G, et al. Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology. Acta Neuropathol 2021;141:709–24. https://doi.org/10.1007/s00401-021-02275-6.
6. Palmqvist S, Janelidze S, Quiroz YT, Zetterberg H, Lopera F, Stomrud E, et al. Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. JAMA – J Am Med Assoc 2020;324:772–81. https://doi.org/10.1001/jama.2020.12134.
7. Thijssen EH, La Joie R, Wolf A, Strom A, Wang P, Iaccarino L, et al. Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration. Nat Med 2020;26:387–97. https://doi.org/10.1038/s41591-020-0762-2.
8. Swift IJ, Sogorb-Esteve A, Heller C, Synofzik M, Otto M, Graff C, et al. Fluid biomarkers in frontotemporal dementia: Past, present and future. J Neurol Neurosurg Psychiatry 2021;92:204–15. https://doi.org/10.1136/jnnp-2020-323520.
9. Ashton NJ, Janelidze S, Al Khleifat A, Leuzy A, van der Ende EL, Karikari TK, et al. A multicentre validation study of the diagnostic value of plasma neurofilament light. Nat Commun 2021;12. https://doi.org/10.1038/s41467-021-23620-z.
10. Zerr I. RT-QuIC for detection of prodromal α-synucleinopathies. Lancet Neurol 2021;20:165–6. https://doi.org/10.1016/S1474-4422(21)00036-3.
11. Rossi M, Baiardi S, Teunissen CE, Quadalti C, Beek M van de, Mammana A, et al. Diagnostic Value of the CSF α-Synuclein Real-Time Quaking-Induced Conversion Assay at the Prodromal MCI Stage of Dementia With Lewy Bodies. Neurology 2021:10.1212/WNL.0000000000012438. https://doi.org/10.1212/WNL.0000000000012438.
12. Iranzo A, Fairfoul G, Ayudhaya ACN, Serradell M, Gelpi E, Vilaseca I, et al. Detection of α-synuclein in CSF by RT-QuIC in patients with isolated rapid-eye-movement sleep behaviour disorder: a longitudinal observational study. Lancet Neurol 2021;20:203–12. https://doi.org/10.1016/S1474-4422(20)30449-X.
13. Tagai K, Ono M, Kubota M, Kitamura S, Takahata K, Seki C, et al. High-Contrast In Vivo Imaging of Tau Pathologies in Alzheimer's and Non-Alzheimer's Disease Tauopathies. Neuron 2021;109:42-58.e8. https://doi.org/10.1016/j.neuron.2020.09.042.
14. Palleis C, Brendel M, Finze A, Weidinger E, Botzel K, Danek A, et al. Cortical [(18) F]PI-2620 Binding Differentiates Corticobasal Syndrome Subtypes. Mov Disord; 2021.
15. Brendel M, Barthel H, Van Eimeren T, Marek K, Beyer L, Song M, et al. Assessment of 18F-PI-2620 as a Biomarker in Progressive Supranuclear Palsy. JAMA Neurol 2020;77:1408–19. https://doi.org/10.1001/jamaneurol.2020.2526.
16. Craig-Schapiro R, Perrin RJ, Roe CM, Xiong C, Carter D, Cairns NJ, et al. YKL-40: A novel prognostic fluid biomarker for preclinical Alzheimer's disease. Biol Psychiatry 2010;68:903–12. https://doi.org/10.1016/j.biopsych.2010.08.025.
17. Abu-Rumeileh S, Steinacker P, Polischi B, Mammana A, Bartoletti-Stella A, Oeckl P, et al. CSF biomarkers of neuroinflammation in distinct forms and subtypes of neurodegenerative dementia. Alzheimer's Res Ther 2019;12:1. https://doi.org/10.1186/s13195-019-0562-4.
18. Suárez-Calvet M, Morenas-Rodríguez E, Kleinberger G, Schlepckow K, Caballero MÁA, Franzmeier N, et al. Early increase of CSF sTREM2 in Alzheimer's disease is associated with tau related-neurodegeneration but not with amyloid-β pathology. Mol Neurodegener 2019;14:1. https://doi.org/10.1186/s13024-018-0301-5.
19. Pereira JB, Janelidze S, Smith R, Mattsson-Carlgren N, Palmqvist S, Teunissen CE, et al. Plasma GFAP is an early marker of amyloid-beta but not tau pathology in Alzheimer's disease. Brain; 2021.
20. Bellaver B, Ferrari-Souza JP, Uglione da Ros L, Carter SF, Rodriguez-Vieitez E, Nordberg A, et al. Astrocyte Biomarkers in Alzheimer Disease: A Systematic Review and Meta-analysis. Astrocyte Biomarkers in Alzheimer Disease: A Systematic Review and Meta-analysis. Neurology; 2021.
21. Verberk IMW, Laarhuis MB, van den Bosch KA, Ebenau JL, van Leeuwenstijn M, Prins ND, et al. Serum markers glial fibrillary acidic protein and neurofilament light for prognosis and monitoring in cognitively normal older people: a prospective memory clinic-based cohort study. Lancet Heal Longev 2021;2:e87–95. https://doi.org/10.1016/S2666-7568(20)30061-1.
22. Salvadó G, Milà-Alomà M, Shekari M, Minguillon C, Fauria K, Niñerola-Baizán A, et al. Cerebral amyloid-β load is associated with neurodegeneration and gliosis: Mediation by p-tau and interactions with risk factors early in the Alzheimer's continuum. Alzheimer's Dement 2021;17:788–800. https://doi.org/10.1002/alz.12245.
23. Nilsson J, Gobom J, Sjödin S, Brinkmalm G, Ashton NJ, Svensson J, et al. Cerebrospinal fluid biomarker panel for synaptic dysfunction in alzheimer's disease. Alzheimer's Dement Diagnosis, Assess Dis Monit 2021;13:1. https://doi.org/10.1002/dad2.12179.
24. Kester MI, Teunissen CE, Crimmins DL, Herries EM, Ladenson JKH, Scheltens P, et al. Neurogranin as a cerebrospinal fluid biomarker for synaptic loss in symptomatic Alzheimer disease. JAMA Neurol 2015;72:1275–80. https://doi.org/10.1001/jamaneurol.2015.1867.
25. Butt OH, Long JM, Henson RL, Herries E, Sutphen CL, Fagan AM, et al. Cognitively normal APOE ε4 carriers have specific elevation of CSF SNAP-25. Neurobiol Aging 2021;102:64–72. https://doi.org/10.1016/j.neurobiolaging.2021.02.008.

Part III

Personal testimonies

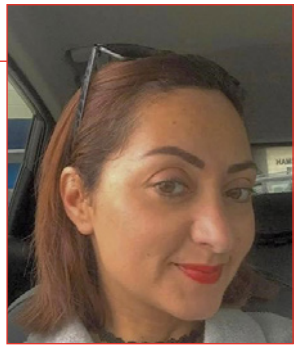
América Velasco Amador, Mexico

My mom has dementia. When we began to notice some behavioural changes in her mood and memory loss, we started to look for specialists. Some told us that she had depression, others microinfarcts, and some doctors told us that it was normal for her age. We were not satisfied and kept looking until we found her a geriatrician who is still, to this day, her doctor. She explained to us what cognitive impairment is and how to treat it.

We looked for different treatment options and thanks to the Alzheimer's Family Foundation, we found support and guidance that has helped us to take my mom on the best path. And we, as caregivers, can walk it in the best way. We organise ourselves so that the burden does not fall on one person and we ensure that my mother in addition to being well cared for, has been able to slow the disease. Seven years after her first diagnosis, my mother is still 'functioning' reasonably well.

Translated from Spanish

Anoud Hariri, Jordan



I'm a caregiver for my mother. She was diagnosed with Alzheimer's disease at the age of 53, but later on, we were informed that it wasn't Alzheimer's, it was frontotemporal dementia. Anyways, my mum went through all of the phases.

It was very difficult for us. When we found out, it was a shock for us because we never had any Alzheimer's disease or dementia in our family on both sides. And you know, some of the sickness is taboo, so when we just first heard about it, it was really a shock, and we were then in denial.

We went to see several doctors because we couldn't believe it. My mum was very young to have this disease and we didn't have any knowledge about it. We were very confused. We didn't know how to act with her, because she went through all the phases really quickly.

Carmel Geoghegan, Ireland

In 2014, my mum received a very late diagnosis for vascular and frontotemporal dementia. We left the neurologist's office with no information. I had no real understanding of what it all meant. Over the following three years until end of life, we had a rollercoaster of a time trying desperately to access support and to make sense of what was happening.

Looking back, I think this was all avoidable if, on receipt of the diagnosis, we had been directed to a central point where we could have been guided towards the right services and given the supports that we needed for our mum to remain at home, which she did.

Emily Ong, Member of Dementia Alliance International, Singapore

I was diagnosed with young-onset dementia in 2017 but was only referred to a support group two years later. The initial period was very difficult. I was provided with nothing except that standard prescription: 'Based on your symptoms, you are likely to have young-onset dementia. I will see you in six months.'

Without support, my family and I had to figure out what young-onset dementia was and how it would impact me, as a person living with dementia and us, as a family. I was robbed of hope twice, once during the diagnosis and the second time through the absence of support after the diagnosis.

Are we merely symptoms of a disease to be treated? Is cognitive impairment an undeserving condition whose patients are not entitled to palliative care, even though dementia is also a life-limiting condition, like cancer?

If you would have asked me if there is anything I am struggling with on a daily basis, I would have shared my inability to follow a recipe, as I cannot hold information long enough in my head. I need to line up the ingredients in separate bowls, and in the order that I cook them.

Healthcare professionals, please avoid the tendency to pigeonhole patients with dementia. Get to know your patients and take the time to understand their history. Meet them on their terms and see the reality of how the changes in cognitive functioning interfere with their daily lives. We are individuals and not checklist items.

José Antonio García, Spain

Translated from Spanish

I am 65 years old and was diagnosed with Alzheimer's disease in 2015, when I was 59 years old. I was made to feel useless and had to quit my job. One good thing that I received from my healthcare professional was advice that the best thing for me to do is to stay physically and mentally active, which I do to this day and I am doing very well.

During the three years that the diagnostic process and neurology tests lasted for, the healthcare professionals limited themselves to giving me medication and did not give me enough information about the pharmacological effect. I was passed back to my family doctor, but since my diagnosis, I only saw the neurologist twice, in 2018 and 2021.

On my own, I looked for the Confederación Española de Alzheimer (CEAFA) for non-pharmacological help. This year, I decreased the medication and increased my activities and relationships in general and am now leading a practically normal life. I am in a clinical trial for a drug against Alzheimer's disease and I belong to PEPA (Panel de Expertos de Personas con Alzheimer) in order to help bring greater visibility to dementia as well as the needs of this group and the means to maintain our self-esteem.

In terms of things that could have been done differently, maybe the follow-up by the neurologist should be at least annually, with the necessary tests to find out the progression of the disease. There is a lack of information about the processes and the resources available.

Early diagnosis is very important because at this age, we still have responsibilities to our children and our elders. Our capabilities must be kept intact so that we can maintain our independence for as long as possible. Both our healthcare professionals and society in general need to provide us with maximum knowledge of the disease and with the means to improve it.

Mary Beth Wighton, Co-chair, Dementia Advocacy Canada and Member of Dementia Alliance International (DAI), Canada

'You cannot have dementia – you are too young.'

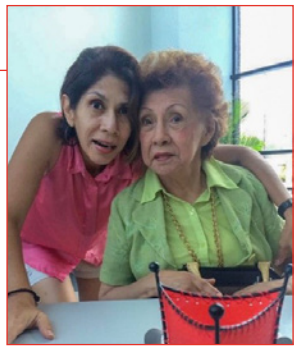
And so, the journey began for me, a 46-year-old, to rule out all other possibilities of why I was experiencing poor judgement, memory loss, muscle spasms, swallowing problems and impulsivity. The following comments are taken directly from my medical file or have been said to me:

- 'I honestly believe this is all psychiatric.'
- 'I think Mary Beth has adopted a sick role to not deal with her humiliations and to punish herself.'
- 'There is no genuine memory problem, and the issue is entirely emotional.'
- And the real kicker: 'If you do have dementia, it is game over!'

Coupled with these unprofessional and insensitive remarks, I was subjected to a myriad of tests, all the while trying different medications to see if they would help with the symptoms. During an incredibly stressful four years for me and my family, I was given 12 different diagnoses, including PTSD, OCD, Conversion Disorder, Major Depression and REM Sleep Behaviour Disorder.

Finally, a geriatrician stated, 'You have probable frontotemporal dementia, and you can no longer drive – effective immediately.' The transition between symptom recognition and my diagnosis was protracted and had unacceptable and unhelpful delays. The stigma of being too young to have dementia clouded the opinions of the experts. This experience is not uncommon. It continues to happen to people around the world. It is time to standardise and implement proven pathways to a diagnosis. We have a human right to a more ethical pathway to care.

Perla Echeverria Cuidador, Venezuela



Translated from Spanish

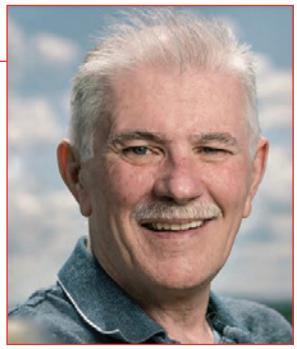
I am the daughter of a patient diagnosed with Alzheimer's disease since November 2012. For nine years, my family has been learning every day to live with this condition. At first, it was very hard because we refused to accept it. We did not know what to do or how to deal with it.

It is very, very important to seek help. Here in Puerto Ordaz, there is an Alzheimer's Foundation and they helped me a lot. I attended the talks and the doctors provided all the information. Also, people caring for relatives with dementia shared their experiences – this is very important so that you don't feel alone in the world. With help, we acquire a certain boldness to deal with such a situation. Otherwise, without alternatives and help, we wear ourselves out: we fight, we cry, we feel frustrated, and we blame the patient.

Now, we have a new lifestyle at home, and we know how to cope and experience the Alzheimer's stages little by little. In my mother's case, the progression of the disease has been very slow. She is on medication, she is being cared for, and we are aware of any changes or situations that are out of the ordinary. We let the doctor know so that she can make the necessary adjustments. My mother is doing very well, and her condition is stable. Her doctor is taking good care of her.

It is very important to take the medicine. I don't think it will cure, but at least it slows down the progression of the disease and gives the person a great quality of life.

Roger Marple, Canada



I was diagnosed with young-onset dementia in 2015.

My diagnosis was transparent, open, and professionally given. It was not a total surprise to me, as it was one of the possibilities my neurologist had pointed out. He explained that my form of dementia was a terminal condition, described how this condition progresses through all its stages, and prescribed vitamins and medication. He also made recommendations for ensuring my affairs were in order. He said, 'Come back in three months and I'll see how you are tolerating the medication', and off I went. Everything with this diagnosis process worked the way it was supposed to, and I appreciated the openness of his comments.

It is human nature to be depressed with news of a diagnosis like this. Often people experience this 'hamster wheel' of despair thinking how things will look down the road with dementia. I know I did for a while. There are two things I would recommend when doctors are diagnosing this. One is to give the person hope and encourage us to be all that we can be, despite the coming challenges, through a simple comment like, 'It is possible to live a meaningful life for some time to come.' The other is to offer a referral to a community support organisation, like the Alzheimer's Society, as they can proactively answer many questions and concerns.

These two recommendations would only take a moment, but would help the receiver of the news immensely, and would change the trajectory on how people would approach a diagnosis such as this.

Véronica Frias Salinas, Mexico

Translated from Spanish

I am going to tell you about the first time I took my mom to the doctor. I took her because she had already forgotten a lot of things, like leaving her keys in the door of her house when she came to visit me.

When I took her to the doctor, he did some examinations and some written tests there in his office and told me she probably had dementia. He gave her medication and told me nothing else, then said that he would check on her again in six or seven months. However, when she went home, she probably didn't take the medication because she forgot.

I decided to take her to another doctor. This doctor sent her for tests with a psychologist – some cognitive tests and other analyses. He then sent her for different types of tests and gave me a more complete diagnosis. He told me that she had Alzheimer's disease and explained the level of progression that she had. From that moment on, I decided to bring her to my house and start taking care of her so that she could continue her treatment.

Ranaivosoa Nancy Prisca, Madagascar

Translated from Malagasy

My mother had previously suffered a stroke. During the 4 or 5 years that we took care of her, we didn't think too much about Alzheimer's disease. At one point, when we talked to a doctor, we asked him if we should go to a neurologist for further diagnosis because of my mother's changing personality, or if we should take other measures. After examining the scan, the doctor told us to leave it at that, but if something 'abnormal' happened later, we could then ask for a neurologist's opinion and that it was not yet necessary.

Then, while attending one of the carer discussion groups organised by the Madagascar Alzheimer's Association, we heard about the warning signs of Alzheimer's disease and we realised she had those symptoms. We always thought it was just the aftermath of her stroke. We are now very curious to know if it is the after-effects of the stroke or if it is Alzheimer's disease.

There is really not enough information about this disease, and the doctors do not explain it enough. If a person has a stroke, it doesn't go any further in terms of searching for other possibilities, and the diagnosis will just stop at the aftermath of the stroke. And all the management will be done around this diagnosis by the carers as well as by the doctor. I think doctors should have a big role in educating the public about Alzheimer's disease. I am sure that many people had Alzheimer's disease before and didn't know it.

Sarmistha Dutta Gupta, India

My mother has been suffering from vascular dementia for the last six years. However, it was nearly two or three years prior to the official diagnosis that I figured out something was going wrong. So finally when I took her to the doctor, she was tested and medically diagnosed. That was the first time I heard of something called vascular dementia and nobody in my circle had heard of it either.

When I shared the news with my extended family, people had a sense of disbelief because my mother never showed any physical signs or symptoms. She continued to look nice and pretty and so people thought it was perfectly normal for a 74-year-old woman to forget things at times and I was merely making a mountain out of a molehill and they would actually not want to believe and not want to take it seriously at all, and that made an already difficult situation rather traumatic for me.

Part IV
Formulation of diagnosis

Chapter 14
Differential diagnosis

Pedro Rosa-Neto

Key points

- The diagnosis is generally finalised at the second visit, usually within six months after the initial assessment.
- Over 80% of people over the age of 65 with a typical amnestic presentation of dementia will receive a diagnosis of Alzheimer's disease.
- If the structural MRI indicates the presence of significant vascular pathology, the diagnosis might be mixed Alzheimer and vascular dementia.
- Atypical dementias (non-amnestic presentations) usually require specialised assessments that may include neuropsychology, biomarkers and genetics testing since they may be caused by several possible conditions.
- As disease-specific blood biomarkers become available and machine learning is being developed to support clinical diagnosis, early identification of Alzheimer's disease will facilitate access to secondary prevention and disease-modifying therapies.

General background

Usually, within six months of the initial clinical assessment, a second visit is scheduled, and some clarification may be required regarding an individual's medical history. This process is greatly helped by having a family member or friend present at the appointment. Some of the cognitive/memory tests may be repeated, and the first laboratory test results are reviewed with the individual. The clinician should have enough information to formulate a diagnosis. If some uncertainty exists because of unusual symptoms (such as looking for words or having visual complaints), changes in the physical examination (such as one-sided muscle stiffness/rigidity), or unexpected results on brain imaging (such as large ventricles), a referral to a specialist may be required. Additional information about how clinicians differentiate the various causes of dementia is below.

Amnestic dementia is the most common clinical presentation in people over the age of 65, with a clinical history of difficulty retaining new information and subsequent decline of other cognitive domains, which ultimately compromise a person's independence and autonomy. People who present with amnestic symptoms, apart from abnormal cognition, have a normal neurological examination at the very early stage. The routine laboratory test results are normal. Their neuroimaging tests show some degree of ventricular enlargement and brain volume reduction (atrophy), particularly in the hippocampus. These individuals can be treated and followed in the primary care setting; at later stages, they will require significant functional support. Over 80% of these individuals will have a pathological diagnosis of Alzheimer's disease characterised by amyloid plaques and tau aggregates in the brain. If assessed with biomarkers, they will present high retention of amyloid and tau PET imaging agents and hypometabolism. In the CSF, Aβ42 will be reduced, and tau and p-tau will have increased (1).

In an alternative scenario called atypical dementias, rather than obvious memory decline, the first and dominant clinical manifestation might include loss of language function, behavioural abnormalities, executive dysfunction, hallucinations, attention deficit, loss of perceptual-motor functions and social cognition abnormalities. The dementia symptoms frequently emerge before 65 years of age. The neurological examination is often abnormal. The structural MRI frequently reveals focal abnormalities. Yet, the atypical presentation of Alzheimer's disease may be the source of these cases. In addition, dementia with Lewy bodies, frontotemporal dementia and Parkinson's disease dementia also cause atypical dementias phenotypes.

Cognitive decline may also be the principal manifestation in rare neurodegenerative disorders such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multisystem atrophy and other uncommon diseases.

Background for clinicians

The diagnosis of dementia is predominantly clinical, so the physician's preliminary assessment is likely bolstered during this second visit by viewing the progression of symptoms as well as a slight decline indicated on the cognitive test results. The main cause of the dementia is also mostly based on the profile of symptoms (amnestic versus non-amnestic), the person's age and co-morbidities (predominantly vascular). Table 1 lists the causes of dementia in adulthood. The common types are examined in detail in the next section.

Table 1. Non-exhaustive list of causes of dementia

Neurodegenerative dementias

- Alzheimer's disease
- PART
- LATE-NC
- Argyrophilic grain disease
- Autosomal Dominant Alzheimer's disease
- Corticobasal degeneration
- Down syndrome related dementia
- Frontotemporal dementias
- Dementia with Lewy bodies
- Parkinson's disease dementia
- Progressive supranuclear palsy

Vascular diseases

- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
- Cerebral amyloid angiopathy
- Primary angiitis of the central nervous system
- Secondary central nervous system vasculitis
- Vascular dementia

Toxic environmental

- Chronic traumatic encephalopathy
- Alcohol-related dementia

Infectious diseases

- HIV-associated neurocognitive disorder
- Herpes encephalitis
- Neurosyphilis
- Prion disease
- Progressive multifocal leukoencephalopathy
- Whipple disease
- Subacute sclerosing panencephalitis

Inflammatory and autoimmune diseases

- Encephalopathy due to systemic autoimmune disease
- Multiple sclerosis
- Neurosarcoidosis
- Non-paraneoplastic auto-immune encephalopathy
- Paraneoplastic encephalopathy

Neurometabolic disorders

- Adult-onset leukodystrophies
- Adult polyglucosan body disease
- Adult neuronal ceroid lipofuscinosis
- Diffuse hereditary leukoencephalopathy with axonal spheroids
- Late-onset lysosomal storage diseases
- Mitochondrial disease

Others

- Dentatorubral pallidoluysian atrophy
- Familial idiopathic basal ganglia calcification (Fahr disease)
- Familial encephalopathy with neuroserpin inclusion bodies
- Huntington's disease
- Normal pressure hydrocephalus
- Pantothenate kinase associated neurodegeneration
- Spinocerebellar atrophy
- Superficial siderosis
- Wilson disease

Dementia syndromes

Dementia is a syndrome characterised by a decline in at least two cognitive functions such as learning and memory, language, executive function, complex attention, perceptual-motor or social cognition. These symptoms must represent a decline from a previous level of function and be severe enough to interfere with daily function and independence.

Abnormalities in the blood supply flow to the brain as well as cerebrovascular diseases cause dementia. It is widely accepted that dementia symptoms reflect neuronal depletion resultant from the progressive accumulation of dysfunctional brain proteins, a process called proteinopathies. Specifically, the accumulation of beta amyloid and hyperphosphorylated tau (3/4 R tau) are the signature markers of Alzheimer's disease. Frontotemporal lobar degeneration and amyotrophic lateral sclerosis result from the brain accumulation of either tau protein isoforms (3R-tau; Pick's disease), the transactive response DNA binding protein (TDP43), or the Fused-in-Sarcoma (FUS) protein. Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy result from the abnormal accumulation of dysfunctional alpha synuclein protein. This framework allows us to appreciate some features from the clinical syndromes described below. Firstly, distinct proteinopathies can cause similar symptoms if they affect similar brain circuits. Secondly, as the accumulation of these dysfunctional proteins started many years before the onset of their symptoms, dementia reflects an advanced stage of various brain proteinopathies. Progress in biomarkers allow an in vivo diagnosis of these conditions. Biomarkers for non-Alzheimer's disease neurodegenerative conditions constitute an unmet need as most of these disorders require an autopsy to confirm the final diagnosis (2).

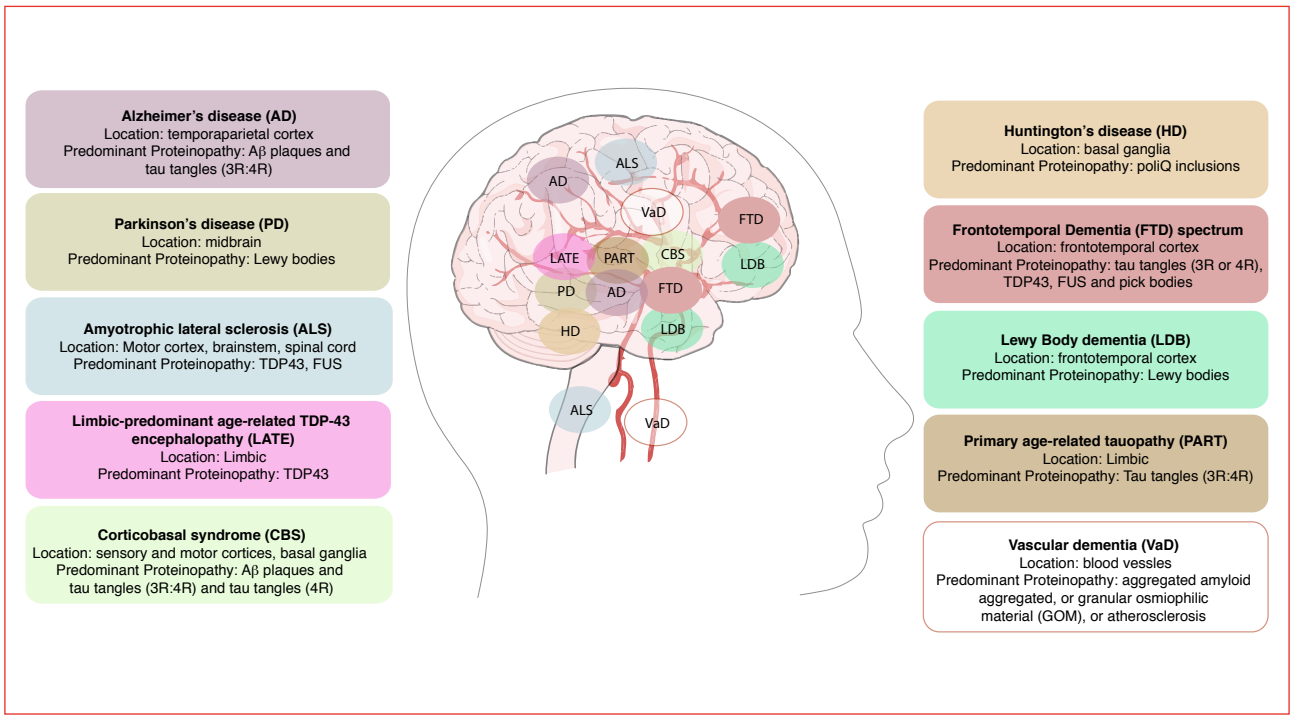


Figure 1. Schematic diagram summarising vascular abnormalities and proteinopathies involved in cognitive decline and dementia.

Diagnostic approach

The diagnostic approach is summarised in Figure 2. Based on clinical history, cognitive screening, neurological examination, neuropsychiatric and functional assessments, dementia is classified as typical, atypical, or non-degenerative. People with a typical amnestic syndrome present with normal laboratory test results, as well as the presence of degenerative features on the structural neuroimaging, receive a probable Alzheimer's disease diagnosis. If the structural MRI indicates the presence of vascular pathology, the diagnosis may shift to mixed dementia. As biomarkers for amyloid and tau are unavailable for large-scale use, their role is limited in this population.

Cases of atypical dementias should be further assessed with specialised tests that include a customised investigation with neuropsychology, biomarkers and genetics testing. A comprehensive diagnostic assessment takes into consideration a wide range of diagnoses (Figure 1). A summary description of relevant syndromes follows.

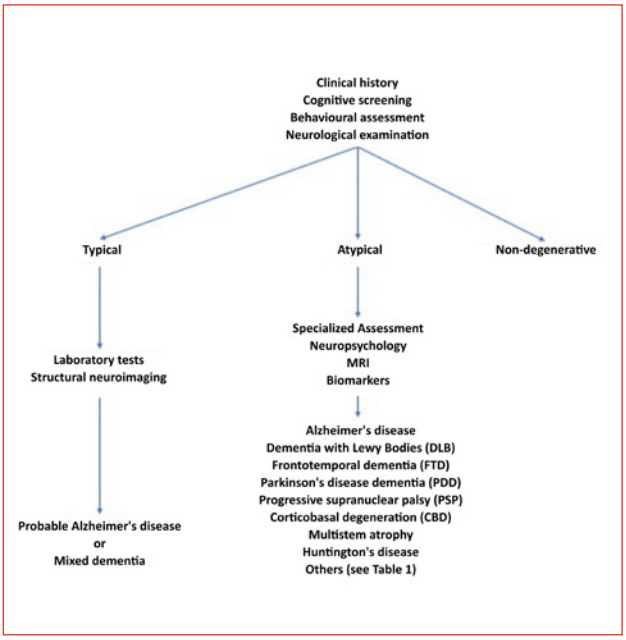


Figure 2. Diagnostic approach for people with dementia with typical and atypical presentations.

Dementias with dominance of amnestic symptoms

Amnestic Alzheimer disease is the most common form of dementia where forgetfulness is the central cognitive symptom. Amnestic individuals may also search for words during a conversation (language) and have difficulty handling complex tasks (executive functions). As the disease progresses, they may also struggle to adapt to new circumstances (reasoning), get lost in familiar places (orientation) and develop problems dressing themselves and/or handling objects (praxis). As expected, individuals who present with these amnestic symptoms, apart from abnormal cognition, receive normal range results on the neurological examination, and this, when in its initial stages. Biomarkers display positivity for Alzheimer's disease pathophysiology in the predicted 80% range of all cases (3, 4). Their structural neuroimaging shows some degree of brain volume reduction (atrophy), particularly in the hippocampus. They may show signs of small vessel or more extensive cerebrovascular disease. PET typically shows hypometabolism in the hippocampus, posterior cingulate, precuneus and inferior parietal cortices. Amnestic dementia cases without biomarker evidence of amyloid are designated as suspected non-Alzheimer's disease pathophysiology (SNAP). These individuals can be followed and treated in primary care (Figure 2). Autopsy series show amyloid plaques, neurofibrillary tangles as well as neuronal depletion in 70–80 % of the cases. Possible non-Alzheimer's pathological entities observed in amnestic cases are hippocampal sclerosis, argyrophilic grain disease, and primary age-related tauopathy and limbic-predominant age-related TDP-43 encephalopathy (5).

Argyrophilic grain disease is a finding frequently described in pathological series. Clinicopathological studies reveal a heterogenous clinical presentation characterised by slowly progressive amnestic Alzheimer's type dementia. Neuropsychiatric symptoms such as anxiety, mood and personality changes are frequently described. Few studies describe asymmetric amygdala and hippocampus atrophy, sometimes extending to the lateral temporal neocortex as the major MRI findings. PET reveals important mesial temporal lobe hypometabolism. The pathology is characterised by grain like deposits in neuronal dendrites labelled with antibodies specific for 4R, accompanied by oligodendroglial inclusions, ramified astrocytes and ballooned neurons in the amygdala, hippocampus and medial temporal lobe (6).

Limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) affects the mesial temporal and limbic frontal cortex. In these memory circuits, TDP-43 proteinopathy has been associated with cognitive and functional impairment nearly indistinguishable from amnestic Alzheimer's dementia. LATE-NC explains typical amnestic dementia negative for amyloid and tau biomarkers. MRI reveals atrophy predominantly

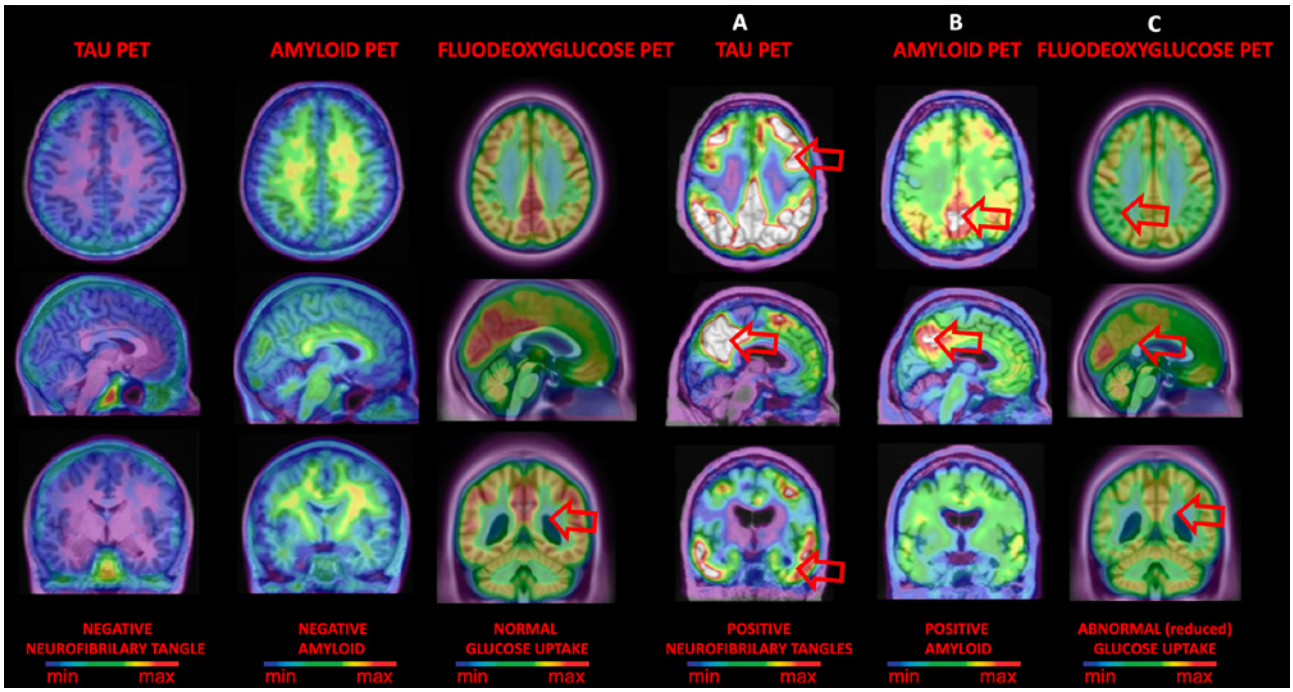


Figure 3. Typical dementia case with PET scans showing abnormal load of neurofibrilary tangles (a), amyloid (b) and presence of neuronal injury (c).

in medial temporal regions. In LATE-NC, PET reveals important mesial temporal lobe hypometabolism with increased ratio of inferior to medial temporal metabolism as compared to Alzheimer's dementia cases. TDP-43 accumulation is commonly observed after the seventh decade and frequently is associated with hippocampal sclerosis and Alzheimer's disease pathophysiology. The absence of biomarkers for TDP-43 aggregates requires an autopsy to diagnose LATE-NC (7).

Primary age-related tauopathy (PART) is a neurodegenerative condition characterised by neurofibrillary tangles (NFT) in the presence of infrequent or no amyloid plaques. In PART, the neurofibrillary pathology is mostly restricted to structures in the medial temporal lobe, basal forebrain, brainstem, and olfactory areas (8). In the autopsy studies, PART is frequently described in cognitively unimpaired individuals, occasionally found in people with mild cognitive impairment, and infrequently observed in dementia cases. Biomarkers can diagnose PART in living individuals (negative biomarker evidence for amyloid and positive for neurofibrillary tangles; Figure 3). PART biomarker profile also meets criteria for non-Alzheimer's disease pathologic change. PART hypometabolism observed in PET is indistinguishable from amnestic Alzheimer's dementia (9).

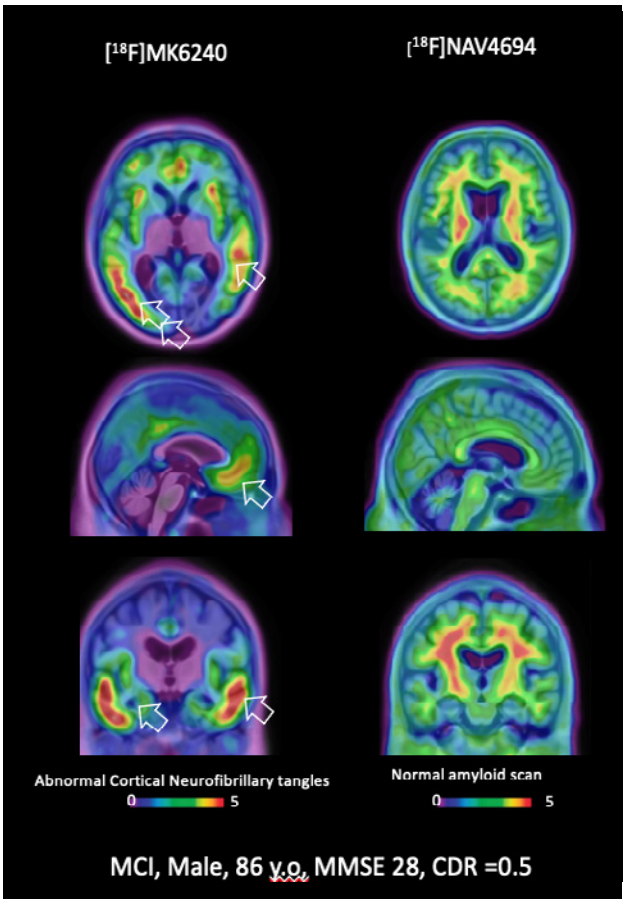


Figure 4. Typical presentations of imaging in patients with PART. Typical dementia case with PET scans showing normal load of amyloid and abnormal load of tau and presence of neuronal injury.

Dementias with dominance of non-amnestic cognitive symptoms

Posterior cortical atrophy (PCA) is an atypical dementia variant characterised by neurodegeneration in the interface between temporal partial and occipital cortices. As visual abnormalities constitute the first and dominant symptom (difficulty reading or driving), affected individuals are often initially evaluated by optometrists for visual complaints. The neuropsychology assessment reveals minimal memory impairment. The neurological examination shows a wide range of visual spatial deficits. Neuroimaging shows predominant occipitoparietal or occipitotemporal atrophy. The same regions appear hypometabolic in PET. Biomarkers reveal the presence of Alzheimer's disease pathophysiology (positive for amyloid and tau) in most cases. In PCA autopsied cases, apart from Alzheimer's disease, the neuropathology might also reveal 4R tau, dementia with Lewy bodies, gliosis and prion disease (10).

Primary progressive aphasia (PPA) designates a clinically and pathologically heterogeneous group of dementias in which language difficulties are the first and dominant symptoms, with relative sparing of memory deficits (11). Based on the language deficits patterns, these cases are subcategorised as non-fluent, semantic, or logopenic (12). The logopenic variant is characterised by effortful speech due to word-finding pauses and paraphasic speech errors. They show difficulties in repeating sentences. Grammar or comprehension remain intact in mild stages of the disease. Biomarkers for Alzheimer's disease are typically positive logopenic PPA. MRI normally indicates atrophy while PET indicates hypometabolism in posterior temporal language areas. On the sematic PPA, individuals are fluent, but comprehension is impaired mainly for single words. People with PPA also lose their ability to read words with irregular spelling (surface dyslexia). While biomarkers for Alzheimer's disease are typically negative in these cases, MRI reveals atrophy and PET exposes hypometabolism predominantly in the left anterior temporal lobes. Semantic PPA is frequently due to TDP43 pathology. For people with nonfluent PPA speech is effortful as a consequence of agrammatism, and articulatory difficulties. Comprehension and memory are relatively spared in mild disease stages. Non-fluent PPA symptoms might remain restricted to expressive language function for years before dementia emerges. While biomarkers for Alzheimer's disease are typically negative in these cases, MRI reveals atrophy and PET shows hypometabolism predominantly in the left anterior insula, premotor and inferior frontal cortices (Broca region). Regarding the pathology, the vast non-fluent cases are associated with non-Alzheimer's disease pathology including TDP43 or 4R tau aggregates (11).

Individuals with dominance of behavioural and dysexecutive symptoms display difficulties with planning and organising daily activities or completing routine tasks. They also struggle with listening to others, paying attention or following instructions. Family members and friends report a change in previous personality traits. Behavioural changes may include irritability and difficulties controlling their emotions or impulses. They may also have no interest in previously enjoyed hobbies or social events. Family and friends also describe an uncharacteristic indifference and lack of empathy towards them. In social interactions, they frequently make inappropriate comments and may engage in inappropriate activity, sometimes touching or kissing strangers or even urinating in public spaces without any sense of embarrassment. Repetitive or ritualistic behaviours such as hoarding, compulsive inspections (such as the need to continuously check the dials on the stove to ensure it is turned off), or obsessive cleaning are commonly reported in these cases. Changes in food preferences, such as developing a sweet tooth and increased consumption of alcohol or tobacco, may also occur. Biomarker evidence of amyloid and tau help identify people with frontal/dysexecutive variant of Alzheimer's disease from frontotemporal dementia. MRI reveals atrophy and PET reveals hypometabolism in frontal and temporal areas. In the subset of people with amyloid and tau, behavioural symptoms overshadow memory deficits. A small percentage of individuals with behavioural or dysexecutive symptoms without evidence of Alzheimer's disease pathophysiology may also develop amyotrophic lateral sclerosis symptoms in the course of the disease (13). The pathology of behavioural variant of frontotemporal dementia includes 3R tau inclusions, also known as Pick's bodies of Picks disease. TDP, 4R tau and FUS inclusions.

Dementia with motor or extrapyramidal manifestations

Dementia with Lewy bodies is an atypical dementia characterised by early impairments in attention as well as executive and visuospatial functions, with memory impairments emerging later in the course of the disease. Cognition and levels of alertness fluctuates in patients. From the motor perspective, individuals characteristically show parkinsonian symptoms, such as bradykinesia, limb rigidity and gait disorder, which increases the risk of falls. Anxiety and depression are frequently present. Systematised paranoid delusions and visual hallucinations occur in approximately two-thirds of people. Vocalisation during sleep, somniloquy or complex motor behaviours (acting out) are common in dementia with Lewy bodies as REM sleep disorder manifestations. Nearly half of people with dementia with Lewy bodies show severe sensitivity to antipsychotic drugs. As the comorbidity between Alzheimer's disease and dementia with Lewy bodies is high, biomarkers provide evidence of amyloid and tau. While MRI reveals global or hippocampal atrophy, PET shoes hypometabolism, particularly in visual associative areas. The sparing of the posterior cingulate metabolism (cingulate islands sign) has been proposed as a biomarker of dementia with Lewy bodies. Imaging dopamine transporters with SPECT shows dopaminergic depletion in the striatum in dementia with Lewy bodies. However, this finding is also observed in Parkinson's dementia, multiple system atrophy, and progressive supranuclear palsy. Autopsy studies shows frequent comorbidity between Alzheimer's disease and vascular pathology with limbic, cortical and striatal Lewy body inclusions.

Parkinson's dementia Cognitive decline and dementia are common in Parkinson's disease. As with dementia with Lewy bodies, the cognitive impairment in Parkinson's disease has an early and heterogeneous profile featuring fatigue, difficulties planning, accomplishing tasks or multitasking (executive dysfunction) as well as difficulties reading, drawing and copying (impaired visuospatial function), though with less prominent language and memory deficits. As in dementia with Lewy bodies, neuropsychiatric symptoms include apathy, mood changes, paranoid delusions, complex visual hallucinations (such as seeing animals or people who are not there). Autonomic deficits, excessive daytime sleepiness and REM sleep behaviour disorder are frequently present. The diagnosis of Parkinson's dementia is made when parkinsonism symptoms start approximately one year before the onset of dementia, and cognitive deficits impair daily life, independent of Parkinson's disease's motor or autonomic symptoms.

Progressive supranuclear palsy is characterised by vertical supranuclear gaze palsy, axial rigidity, and prominent postural instability with falls. Frequently motor manifestations can be preceded by fatigue and apathy. The cognitive changes are characterised by executive dysfunction, including impaired abstract thought, decreased verbal fluency and motor perseveration. Behavioural changes, including indifference, disinhibition, or non-fluent aphasia, can be early manifestations of progressive supranuclear palsy. Biomarkers for Alzheimer's disease are typically negative. Neuroimaging with MRI reveal midbrain brainstem atrophy (hummingbird sign or penguin silhouette), and superior cerebellar peduncle atrophy. Positron emission tomography (PET) scanning reveals decreased glucose metabolism in the midbrain, striatum and prefrontal cortex. Definite PSP diagnosis is obtained post-mortem by the presence of 4R tau aggregates in the neuropathological examination (14).

Corticobasal syndrome is a movement disorder characterised by progressive asymmetric akinesia, rigidity and dystonia, apraxia, alien-limb phenomena and focal myoclonus. However, cognitive symptoms such as apathy and difficulties multitasking may constitute an early syndrome manifestation. In addition, motor language abnormalities ranging from mild phonologic impairments to nonfluent aphasia may also constitute another early manifestation. Neuropsychiatric manifestations include indifference, social withdrawal, compulsive behaviour, unmotivated laughter and irritability. Unilateral ideomotor apraxia is an important corticobasal syndrome feature. Biomarkers for Alzheimer's disease pathophysiology are positive for amyloid and tau in nearly 50% of the cases. MRI shows asymmetric cortical atrophy encompassing the frontal and parietal regions with ventricle enlargement and corpus callosum atrophy. The atrophic cortex and its underlying white matter might show hyperintensity in T2 weighted images. PET reveals asymmetric hypometabolism in the posterior frontal, inferior parietal, and superior temporal regions and the ipsilateral thalamus and striatum. Definite diagnosis is obtained post-mortem typically by the presence of amyloid and tau or 4R tau aggregates in the neuropathological examination (15, 16).

Prion diseases are a group of neurodegenerative conditions associated with the misfolding and aggregation of a membrane protein called prion protein. In abnormal conditions, the prion protein forms fibrils inside the neurons, causing neuronal death. Sporadic Creutzfeldt-Jakob disease (sCJD), sporadic fatal insomnia and protease-sensitive prionopathy, Gerstmann-Sträussler-Scheinker syndrome are non-transmissible prion diseases. Kuru, iatrogenic Creutzfeldt-Jakob disease, and variant Creutzfeldt-Jakob disease are transmissible forms of prion diseases.

Rapidly progressive dementia and myoclonus are hallmarks of Creutzfeldt-Jakob disease. Cognitive impairment in affected individuals initially impairs memory and concentration. Subsequently, they rapidly develop aphasia, apraxia, visuospatial, and frontal lobe syndromes.

Behavioural abnormalities include apathy, alterations in the sleep-wake cycle and visual hallucinations. Myoclonus is present in nearly all individuals (17). Apart from its typical presentation, Creutzfeldt-Jakob disease has visual (Heidenhain), cerebellar (Oppenheimer-Brownell), thalamic, and striatal variants (18). PET and CSF Aβ42 fail to suggest amyloid deposits in Creutzfeldt-Jakob disease. Diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) MRI show hyperintensity in the striatum and cortex. On the electroencephalogram, these individuals show periodic sharp wave complexes. Non-specific cerebrospinal fluid biomarkers for neuronal injury such as 14–3–3 protein and total tau protein are elevated. Real-time quaking-induced conversion assay supports the presence of disease-associated prion protein in the cerebrospinal fluid. The investigation of Creutzfeldt-Jakob disease should exclude treatable aetiologies as treatable diseases such as paraneoplastic syndromes, and autoimmune encephalitis might mimic Creutzfeldt-Jakob disease. Neuropathology provides the definitive diagnosis (19). Although neuropathology provides a definitive diagnosis of CJD, a brain biopsy is seldom required (20).

Presence of cerebrovascular disease

Vascular dementia along with the risk factors for cerebrovascular disease, is extensively examined in Chapter 22. Vascular dementia refers to dementia caused by or associated with either cerebrovascular disease or abnormal cerebral blood flow. Poststroke dementia has a stepwise cognitive decline after a clinically diagnosed stroke. Vascular dementia follows the same progressive cognitive decline without a concurrent history of symptomatic stroke. The extension and severity of cerebrovascular disease, brain reserve, comorbidities with neurodegeneration, age, education, race, and diabetes are risk factors for these conditions. The cognitive profile of poststroke dementia is clinically heterogeneous, often marked by prominent impairment of executive functions, sometimes with variable involvements of episodic memory and other cortical signs of including aphasia or apraxia. Strategic anterior thalamic stroke could mimic Alzheimer's dementia in some cases (21, 22). The diagnosis of poststroke or vascular dementia is based on imaging evidence of cerebrovascular disease sufficient to justify cognitive symptoms. MRI-T2, FLAIR and susceptibility sequences better detect cerebral vascular disease than a head CT. Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) criteria provide radiologic definitions of cerebrovascular disease (22).

Coexistence of pathophysiological processes

Multiple-aetiology dementia is diagnosed when a person with vascular dementia also meets the diagnostic criteria for another neurodegenerative disorder. It is common for Alzheimer pathology to coexist with other processes, including vascular lesions, cortical Lewy bodies, TAR DNA binding protein 43 (TDP-43) deposits, argyrophilic grain disease, and Parkinson's disease. The combination of two pathologies can potentially influence the clinical presentation and course of the disease and present diagnostic challenges (23). In general, these additional pathologies result in a greater likelihood of dementia and rate of decline (24, 25)

Survey results

The replies obtained from the 2,327 people with dementia and carers indicated that basic assessments such as a history, neurological examination, basic laboratory screening tests and cognitive assessment are widely used as dementia tests. Currently, biomarkers are not available worldwide and therefore not part of the clinical practice in many countries. However, 70% of the 1,111 multidisciplinary clinicians who replied are willing to use blood biomarkers, if available; this is an unmet need in dementia that could make clinical practice more efficient worldwide.

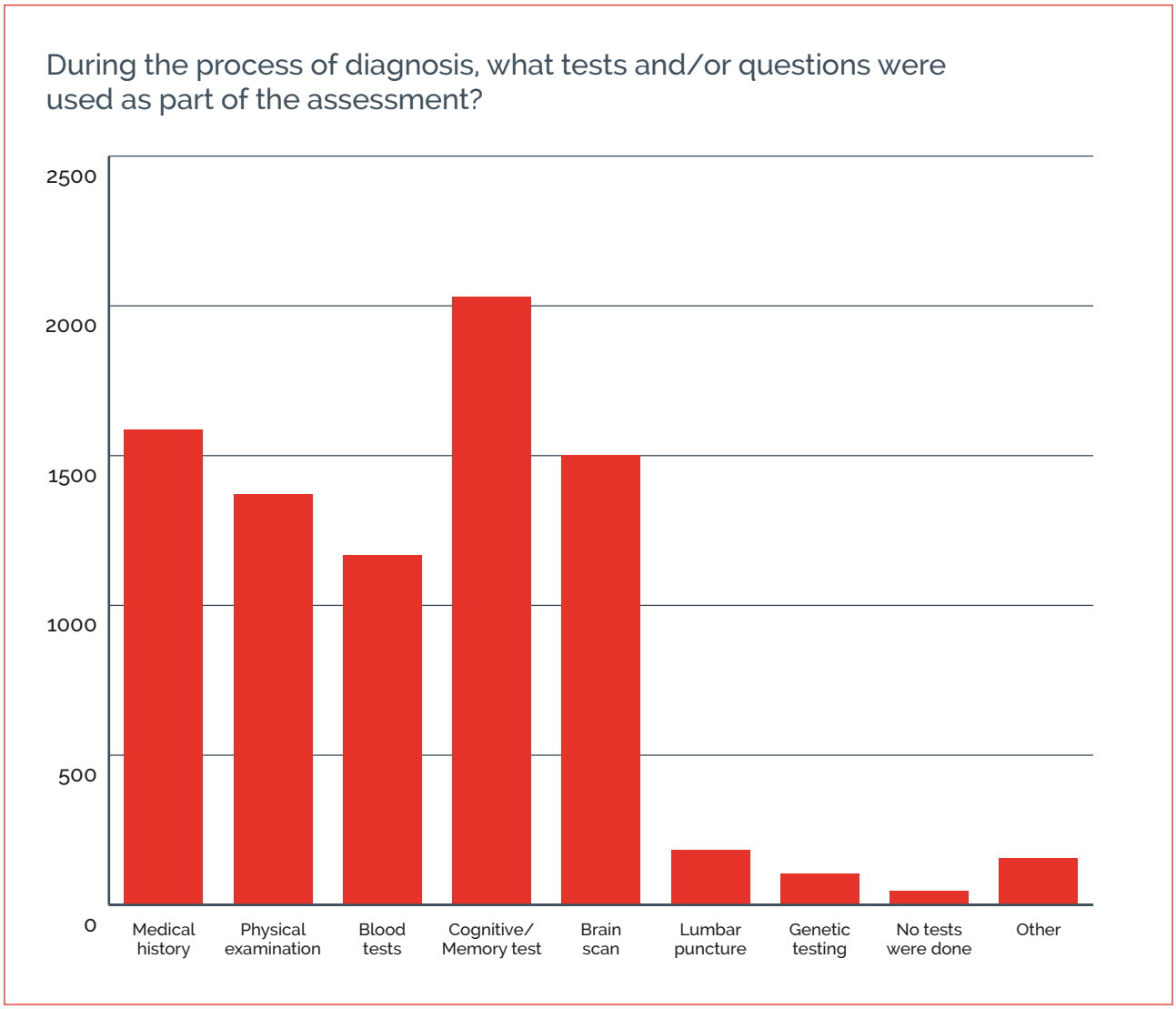


Chart 1. People with dementia and carer responses (multiple answers selected).

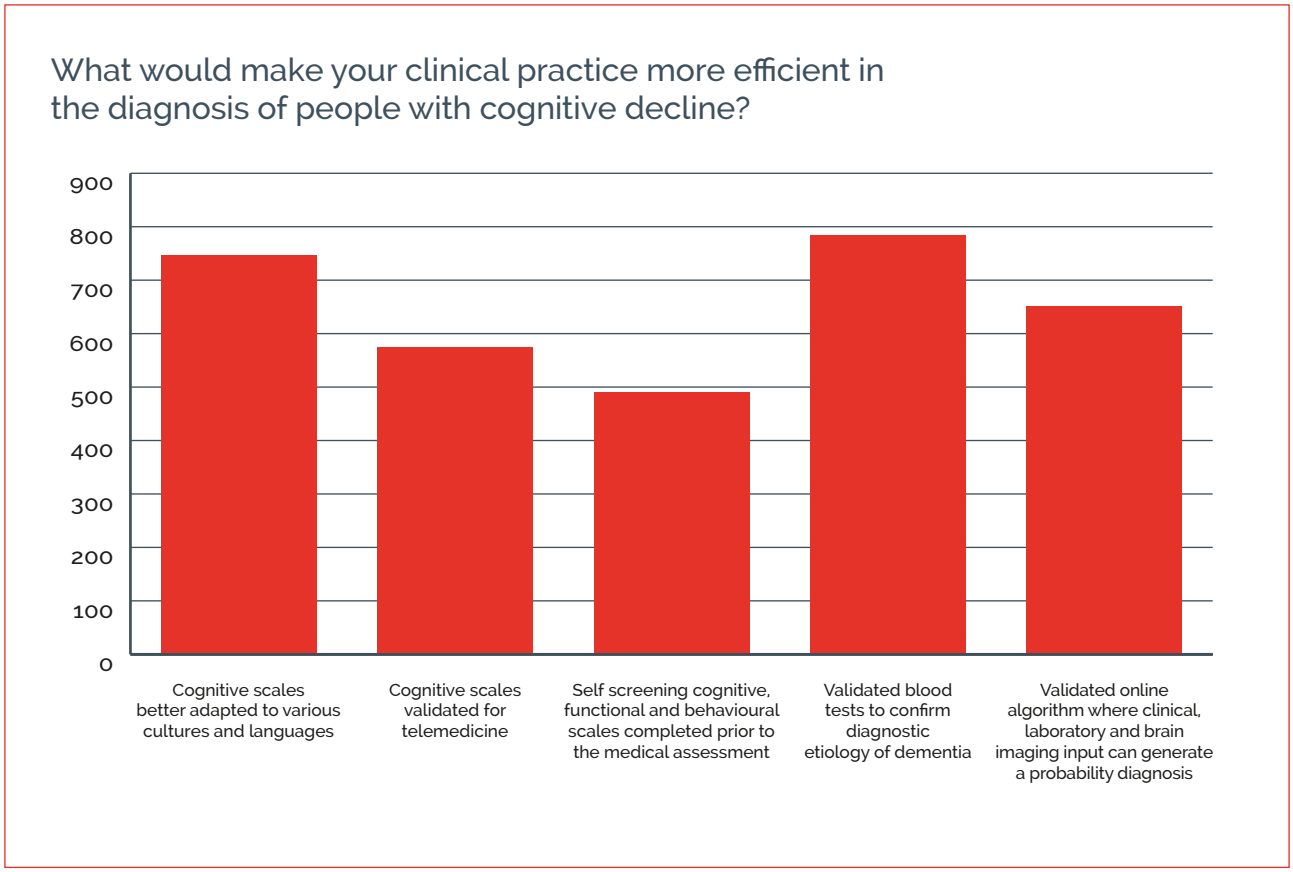


Chart 2. Clinician responses (multiple answers selected).

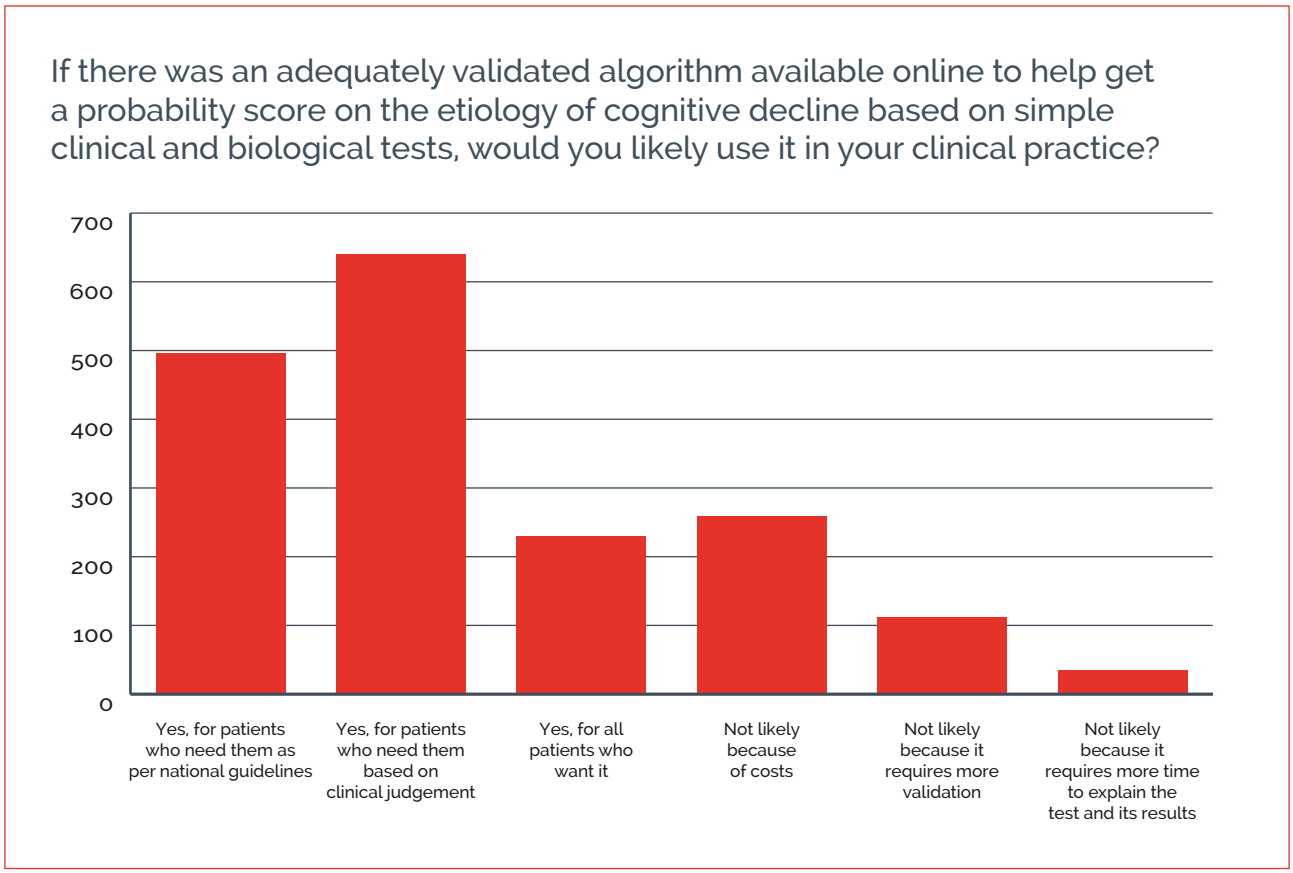


Chart 3. Clinician responses.

Expert essay

Machine learning and artificial intelligence for Alzheimer's disease

Bharat R Rao,[1] Sulantha Mathotaarachchi,[2] Michael Reitermann[1]

[1] Enigma Biomedical Group, UNITED STATES
[2] Enigma Biomedical Group, CANADA

Machine learning and artificial intelligence (AI) have revolutionised many industries and can transform the care of Alzheimer's disease and other chronic conditions. Modern machine learning techniques, when given access to large amounts of patient data, are capable of learning robust, high-performing models for Alzheimer's disease that can identify novel markers of risk, predict disease to help clinicians intervene earlier, model disease progression and even suggest precision-medicine interventions for individual patients. Although the adoption of machine learning to support clinical decisions for Alzheimer's disease is in its infancy, this area has great promise, especially considering the US FDA's recent approval of Aduhelm (aducanumab), the first drug approved to treat people with Alzheimer's disease.

Today there are several research studies involving the use of machine learning, image processing and statistical learning with amyloid PET scans, FDG PET scans and 3D MRI scans from large cohorts such as the Alzheimer's Disease Neuroimaging Initiative (ADNI). Potential applications include early detection (1), classification of diagnosis and staging (2), prognostic prediction of disease (3–5), and differential diagnosis (6,7). Deep learning-based brain segmentation techniques and white matter hyper intensity quantification techniques show promise for early diagnosis and disease staging of Alzheimer's disease (8,9). Although much of this research takes the form of retrospective analyses, an increasing number of clinical trials are using machine learning in conjunction with imaging reads to reduce the burden on radiologists, both to identify candidates for clinical trials and to detect and quantify surrogate markers for trial end points.

In addition to plaque, abnormal accumulation of tau protein (detected via tracers, such as MK6240) has been associated with neurodegeneration and cognitive impairment. Using machine learning to detect brain tau burden via in vivo tau imaging, combined with amyloid and MRI imaging, can provide clinical and research biomarkers in a holistic approach to support differential diagnosis (10). Furthermore, the closer association of tau with cognitive impairment as well as neuronal dysfunction makes it suitable for AI-based methods to automatically monitor disease progression and to identify candidates for clinical trials.

The FDA's recent approval of Aduhelm to treat people with Alzheimer's disease should accelerate the clinical adoption of machine learning for Alzheimer's disease. Aduhelm is the first approved treatment directed at the underlying pathophysiology of Alzheimer's disease, the presence of amyloid beta plaques in the brain. Clinical trials have shown a reduction in these plaques, and the FDA's expectation is that Aduhelm will lead to a reduction in the clinical decline of people with Alzheimer's disease. The current protocol mandates an amyloid scan (or lumbar puncture) to detect the presence of amyloid plaque prior to starting treatment. Further, treatment must be preceded by a baseline MRI scan within one year before treatment and two additional scans prior to successive infusions. As this therapy is rolled out across the Alzheimer's disease population, there will be a tremendous opportunity for machine learning/artificial intelligence to support radiologists via computer-aided diagnosis software to detect the presence of amyloid. Machine learning/artificial intelligence can also help to track the progression of the intermediate clinical endpoint (plaque burden) in post-market studies, gather data to determine the impact of therapy on other surrogate endpoints (for example, the accumulation of tau) and eventually support the potential linkage of treatment with diminishing cognitive decline (in turn, measured by AI-based digital diagnostics).

A recent study identified four different trajectories of tau deposition in people with Alzheimer's disease (11). This is particularly relevant for the development of new therapies. Considering that 'diseases of the blood' were deemed incurable only a century ago; today, these are subdivided into dozens of leukaemias and lymphomas, many of which can be completely cured if detected early. Similarly, one can imagine a future in which Alzheimer's disease, instead of being managed as a single monolithic condition with inevitable progression, is subdivided into different subtypes each with different prognoses and treatment pathways. Machine

learning-based clustering and unsupervised learning methods that analyse imaging and clinical data can play a role in helping automatically identify increasingly fine-grained Alzheimer's disease subtypes with variations in therapy response.

> **One can imagine a future in which Alzheimer's disease, instead of being managed as a single monolithic condition with inevitable progression, is subdivided into different subtypes each with different prognoses and treatment pathways.**

As Aduhelm and future Alzheimer's disease treatments increasingly move into clinical practice, machine learning can play an amplified role in the proactive and early identification of Alzheimer's disease, potentially even before the presentation of clinical symptoms or imaging evidence. As with all chronic diseases, the earlier the intervention, the greater the potential benefit. It will probably not be feasible to rely on neuroimaging as the primary screen for Alzheimer's disease, namely the ability to perform amyloid scans on the general population at age 50 to detect signs of early Alzheimer's disease. Machine intelligence/artificial intelligence can serve as an initial blunt screening tool, potentially leveraging non-imaging data and even genetic data to identify those at high risk for future Alzheimer's disease, and as candidates for diagnostic neuroimaging scans. However, it is in the use of AI-based blood biomarker panels (possibly augmented with cerebrospinal fluid data) where machine intelligence/artificial intelligence can have an immeasurable impact.

Recent research studies have identified several emerging blood-based biomarkers as potential surrogate markers for amyloid and tau in the brain (12,13). These biomarkers are significantly cheaper and more convenient compared to imaging alternatives. These blood biomarkers, perhaps combined with patient demographics and potentially clinical information, have the potential to identify individuals at high-risk for progression to Alzheimer's disease before symptoms present and possibly even before imaging evidence (14). An AI-based blood biomarker panel could be used to identify patients for trials for new drugs, to track progression of clinical endpoints, predict future cognitive decline, or possibly as a screening test.

There are several ongoing Alzheimer's disease research projects which go beyond the analysis of neuroimaging and fluid data. Research studies are investigating artificial intelligence/machine learning applications for analysing recorded speech and word usage, predict progression from MCI to Alzheimer's disease, as well as predict future disease prior to clinical symptoms. Other data being investigated includes sociodemographic characteristics, clinical and neuropsychological test scores, cardiovascular risk indices, gene expression data, retinal vasculature, and large-scale administrative health data.

Finally, artificial intelligence can be used within interactive tools and mobile/web apps. As treatment guidelines are being developed, there is great interest among physicians to avail themselves of clinical decision-support tools, possibly via cloud-based implementations of these guidelines, that can orient clinicians (and patients) in the early identification and management of Alzheimer's disease. Several start-ups have developed applications (apps) for consumers (and physicians) to conduct cognitive tests. We expect that in the coming decade, an increasing number of digital diagnostics and therapeutics will be prescribed/used by patients, carers and even consumers to help in the management of this disease.

References

1. Liu X, Chen K, Wu T, Weidman D, Lure F, Li J. Use of multimodality imaging and artificial intelligence for diagnosis and prognosis of early stages of Alzheimer's disease. Vol. 194, Translational Research. Mosby Inc.; 2018. p. 56–67.
2. Basaia S, Agosta F, Wagner L, Canu E, Magnani G, Santangelo R, et al. Automated classification of Alzheimer's disease and mild cognitive impairment using a single MRI and deep neural networks. NeuroImage Clin. 2019 Jan;21.
3. Mathotaarachchi S, Pascoal TA, Shin M, Benedet AL, Kang MS, Beaudry T, et al. Identifying incipient dementia individuals using machine learning and amyloid imaging. Neurobiol Aging. 2017.
4. Franzmeier N, Koutsouleris N, Benzinger T, Goate A, Karch CM, Fagan AM, et al. Predicting sporadic Alzheimer's disease progression via inherited Alzheimer's disease-informed machine-learning.
5. Moradi E, Pepe A, Gaser C, Huttunen H, Tohka J. Machine learning framework for early MRI-based Alzheimer's conversion prediction in MCI subjects. Neuroimage. 2015;104:398–412.
6. Kim JP, Kim J, Park YH, Park B, Lee JS, Kim E-J, et al. Machine learning based hierarchical classification of frontotemporal dementia and Alzheimer's disease. 2019
7. Castellazzi G, Cuzzoni MG, Cotta Ramusino M, Martinelli D, Denaro F, Ricciardi A, et al. A Machine Learning Approach for the Differential Diagnosis of Alzheimer and Vascular Dementia Fed by MRI Selected Features. Front Neuroinform. 2020 Jun;14:25.
8. Atlason HE, Love A, Sigurdsson S, Gudnason V, Ellingsen LM. SegAE: Unsupervised white matter lesion segmentation from brain MRIs using a CNN autoencoder. NeuroImage Clin. 2019 Jan;24:102085.
9. Akkus Z, Galimzianova A, Hoogi A, Rubin DL, Erickson BJ. Deep Learning for Brain MRI Segmentation: State of the Art and Future Directions. Vol. 30, Journal of Digital Imaging. Springer New York LLC; 2017. p. 449–59.
10. Knopman DS, Lundt ES, Therneau TM, Vemuri P, Lowe VJ, Kantarci K, et al. Entorhinal cortex tau, amyloid-β, cortical thickness and memory performance in non-demented subjects. Brain. 2019 Apr;142(4):1148–60.

11. Vogel JW, Young AL, Oxtoby NP, Smith R, Ossenkoppele R, Strandberg OT, et al. Four distinct trajectories of tau deposition identified in Alzheimer's disease. Nat Med. 2021 May;27(5):871–81.
12. Karikari TK, Pascoal TA, Ashton NJ, Janelidze S, Benedet AL, Rodriguez JL, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. Lancet Neurol [Internet]. 2020;19(5):422–33. https://doi.org/10.1016/S1474-4422(20)30071-5
13. Ashton NJ, Hye A, Rajkumar AP, Leuzy A, Snowden S, Suárez-Calvet M, et al. An update on blood-based biomarkers for non-Alzheimer neurodegenerative disorders. Nat Rev Neurol [Internet]. 2020;16(5):265–84. https://doi.org/10.1038/s41582-020-0348-0
14. Karaglani M, Gourlia K, Tsamardinos I, Chatzaki E. Accurate Blood-Based Diagnostic Biosignatures for Alzheimer's Disease via Automated Machine Learning. J Clin Med. 2020 Sep;9(9):3016.

Conclusions

As a matter of course in today's primary care environment, most clinicians follow the prescribed protocols to formulate and render a diagnosis of dementia and its most likely aetiology. This is necessary to determine what kind of dementia an individual may have, be it a typical form like Alzheimer's disease to rarer, atypical types such as dementia with Lewy bodies that would require specialised and collaborating assessment. This includes taking a family history and laboratory testing data.

However, there are new developments that will impact this routine in due course. Firstly, accelerated changes in the field of biomarkers coupled with people seeking answers to their cognitive complaints much sooner than before will engender changes both in data collection and analysis. The majority of clinicians welcome these changes as they foresee quicker and more detailed analysis results as well as being able to render a diagnosis in the earliest stages of the syndrome.

The advent, but more importantly, the advancements of machine learning and artificial intelligence are inching the world of clinical decision-support tools towards more of a reality in dementia care. This even extends to mobile applications that can administer cognitive tests and provide individuals and their carers with digital diagnostic and therapeutic support. In the future, the prospect of identifying risk markers, forecasting disease to support differential diagnosis and modelling disease progression will likely revolutionise the management of dementia.

Additional references

1. Ismail Z, Black SE, Camicioli R, Chertkow H, Herrmann N, Laforce R, et al. Recommendations of the 5th Canadian Consensus Conference on the diagnosis and treatment of dementia. Alzheimer's Dement [Internet]. 2020 Aug 1 [cited 2021 Jul 8];16(8):1182–95. https://pubmed.ncbi.nlm.nih.gov/32725777.
2. Elahi FM, Miller BL. A clinicopathological approach to the diagnosis of dementia. Nat Rev Neurol [Internet]. 2017;13(8):457–76. https://www.ncbi.nlm.nih.gov/pubmed/28708131.
3. Beach TG, Monsell SE, Phillips LE, Kukull W. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005-2010. J Neuropathol Exp Neurol [Internet]. 2012;71(4):266–73. https://dx.doi.org/10.1097/nen.0b013e31824b211b.
4. Landau SM, Horng A, Fero A, Jagust WJ. Amyloid negativity in patients with clinically diagnosed Alzheimer disease and MCI. Neurology [Internet]. 2016;86(15):1377–85. https://dx.doi.org/10.1212/wnl.0000000000002576.
5. Scheltens P, Blennow K, Mmb B, De Strooper B, Frisoni GB, Salloway S, et al. Alzheimer's disease. Lancet [Internet]. 2016;388(10043):505–17. https://dx.doi.org/10.1016/s0140-6736(15)01124-1.
6. Ferrer I, Santpere G, Van Leeuwen FW. Argyrophilic grain disease [Internet]. Vol. 131, Brain. Brain; 2008 [cited 2021 Jul 20]. p. 1416–32. https://pubmed.ncbi.nlm.nih.gov/18234698
7. Nelson PT, Dickson DW, Trojanowski JQ, Jack CR, Boyle PA, Arfanakis K, et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): Consensus working group report. Brain. 2019 Jun;142(6):1503–27.
8. Duyckaerts C, Braak H, Brion JP, Buée L, Del Tredici K, Goedert M, et al. PART is part of Alzheimer disease. Acta Neuropathol [Internet]. 2015;129(5):749–56. https://www.ncbi.nlm.nih.gov/pubmed/25628035.
9. Bell WR, An Y, Kageyama Y, English C, Rudow GL, Pletnikova O, et al. Neuropathologic, genetic, and longitudinal cognitive profiles in primary age-related tauopathy (PART) and Alzheimer's disease. Alzheimer's Dement [Internet]. 2019;15(1):8–16. https://dx.doi.org/10.1016/j.jalz.2018.07.215.
10. Crutch SJ, Lehmann M, Schott JM, Rossor MN, Crutch SJ, Lehmann M, et al. Posterior cortical atrophy. Lancet Neurol [Internet]. 2012 [cited 2021 Jul 20];11:170–8. www.thelancet.com/neurology.
11. Mesulam MM, Rogalski EJ, Wieneke C, Hurley RS, Geula C, Bigio EH, et al. Primary progressive aphasia and the evolving neurology of the language network. Nat Rev Neurol [Internet]. 2014;10(10):554–69. https://dx.doi.org/10.1038/nrneurol.2014.159.
12. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology [Internet]. 2011;76(11):1006–14. https://dx.doi.org/10.1212/wnl.0b013e31821103e6.

13. Burrell JR, Halliday GM, Kril JJ, Ittner LM, Götz J, Kiernan MC, et al. The frontotemporal dementia-motor neuron disease continuum. Lancet [Internet]. 2016;388(10047):919–31. https://dx.doi.org/10.1016/s0140-6736(16)00737-6.
14. Jabbari E, Holland N, Chelban V, Jones PS, Lamb R, Rawlinson C, et al. Diagnosis Across the Spectrum of Progressive Supranuclear Palsy and Corticobasal Syndrome. JAMA Neurol [Internet]. 2020;77(3):377–87. https://dx.doi.org/10.1001/jamaneurol.2019.4347.
15. Kouri N, Whitwell JL, Josephs KA, Rademakers R, Dickson DW. Corticobasal degeneration: A pathologically distinct 4R tauopathy. Nat Rev Neurol [Internet]. 2011;7(5):263–72. https://dx.doi.org/10.1038/nrneurol.2011.43.
16. Di Stasio F, Suppa A, Marsili L, Upadhyay N, Asci F, Bologna M, et al. Corticobasal syndrome: neuroimaging and neurophysiological advances. Eur J Neurol [Internet]. 2019;26(5):701-e52. https://dx.doi.org/10.1111/ene.13928.
17. Safar JG, Geschwind MD, Deering C, Didorenko S, Sattavat M, Sanchez H, et al. Diagnosis of human prion disease. Proc Natl Acad Sci U S A [Internet]. 2005;102(9):3501–6. https://dx.doi.org/10.1073/pnas.0409651102.
18. Appleby BS, Appleby KK, Crain BJ, Onyike CU, Wallin MT, Rabins P V. Characteristics of established and proposed sporadic creutzfeldt-jakob disease variants. Arch Neurol [Internet]. 2009;66(2):208–15. https://dx.doi.org/10.1001/archneurol.2008.533
19. Zanusso G, Monaco S, Pocchiari M, Caughey B. Advanced tests for early and accurate diagnosis of Creutzfeldt-Jakob disease. Nat Rev Neurol [Internet]. 2016;12(7):427. https://www.ncbi.nlm.nih.gov/pubmed/27174240.
20. Hermann P, Appleby B, Brandel JP, Caughey B, Collins S, Geschwind MD, et al. Biomarkers and diagnostic guidelines for sporadic Creutzfeldt-Jakob disease. Lancet Neurol [Internet]. 2021;20(3):235–46. https://dx.doi.org/10.1016/s1474-4422(20)30477-4
21. Kalaria RN. The pathology and pathophysiology of vascular dementia. Neuropharmacology [Internet]. 2018;134:226–39. https://dx.doi.org/10.1016/j.neuropharm.2017.12.030.
22. Van Der Flier WM, Skoog I, Schneider JA, Pantoni L, Mok V, Chen CLH, et al. Vascular cognitive impairment. Nat Rev Dis Prim [Internet]. 2018 Feb 15 [cited 2021 Jul 20];4. https://pubmed.ncbi.nlm.nih.gov/29446769/.
23. Schneider JA, Bennett DA. Where vascular meets neurodegenerative disease. Stroke [Internet]. 2010;41(10 SUPPL. 1):S144–6. https://dx.doi.org/10.1161/strokeaha.110.598326
24. Fierini F. Mixed dementia: Neglected clinical entity or nosographic artifice? J Neurol Sci [Internet]. 2020;410(11666):2. https://dx.doi.org/10.1016/j.jns.2019.116662.
25. Skoog I, Nilsson L, Palmertz B, Andreasson L-A, Svanborg A. A Population-Based Study of Dementia in 85-Year-Olds. N Engl J Med [Internet]. 1993;328(3):153–8. https://dx.doi.org/10.1056/nejm199301213280301.

Chapter 15
Disclosure of results

Serge Gauthier

Key points

- A timely diagnosis of dementia has many benefits such as post diagnosis support and planning for the future.
- Disclosure of results is the moment most feared by people seeking a diagnosis as well as their family members or friends.
- Although most clinicians are at ease with disclosing a dementia diagnosis, they need to be aware that a risk of catastrophic reaction may exist.
- Clinicians should promote informed decision-making, employ proven health communication techniques and provide guidance on appropriate next steps.
- The COVID-19 pandemic has increased the need for remote clinical assessment and disclosure of the diagnosis of dementia.

General background

No doubt, the moment most feared by people seeking a diagnosis, as well as their friends or family members who accompanied them through the diagnostic journey, is the disclosure of the results. Based on a human rights-based approach, the person with dementia should be informed of their diagnosis. However, many people with dementia due to Alzheimer's disease, have a lack of awareness regarding their cognitive and functional decline (this phenomenon is called 'anosognosia') that makes them uninterested in the diagnosis and its likely causes. On the other end of the spectrum are those people who are so anxious about their diagnosis that a catastrophic reaction such as severe depression, and even suicidal thoughts are possible. At this point, the clinician is usually aware enough about the person's state of mind to use a stepwise disclosure approach; they may say, for example, 'You do have a memory problem and I am glad that you came to see me, let's check your test results and see how I can help you.' Most clinicians will answer a direct question truthfully when there is a low risk of a catastrophic reaction. This outlook is reflected in the survey results. All clinicians will inform the designated legal representative to initiate post diagnosis management (refer to Chapter 16), but often the person accompanying them is a first-degree relative who also has a vested interest in the genetic risk for themselves. This is addressed at length in the upcoming expert essay. The disclosure is usually conducted in person with the clinician; however, COVID-19 pandemic restrictions has increased the need to disclose a dementia diagnosis remotely.

Survey results

The majority of the 1,111 multidisciplinary clinicians who replied to the survey stated that they were comfortable disclosing a dementia diagnosis in their practice.

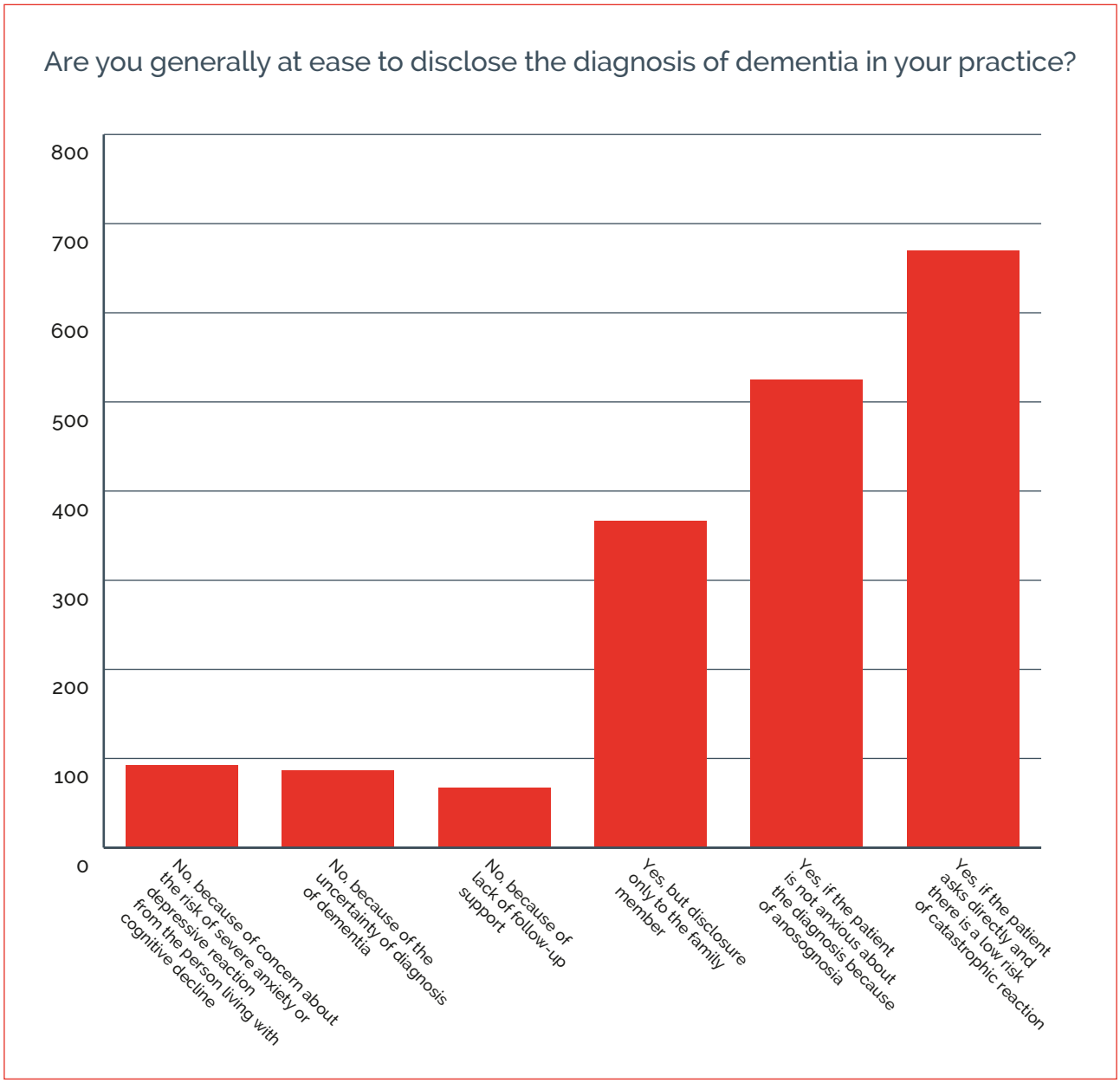


Chart 1. Clinician responses.

The 2,327 people with cognitive complaints dementia and their carers who participated in the survey, indicated that they saw various clinicians during their diagnostic workup. The majority were given the diagnosis by a neurologist.

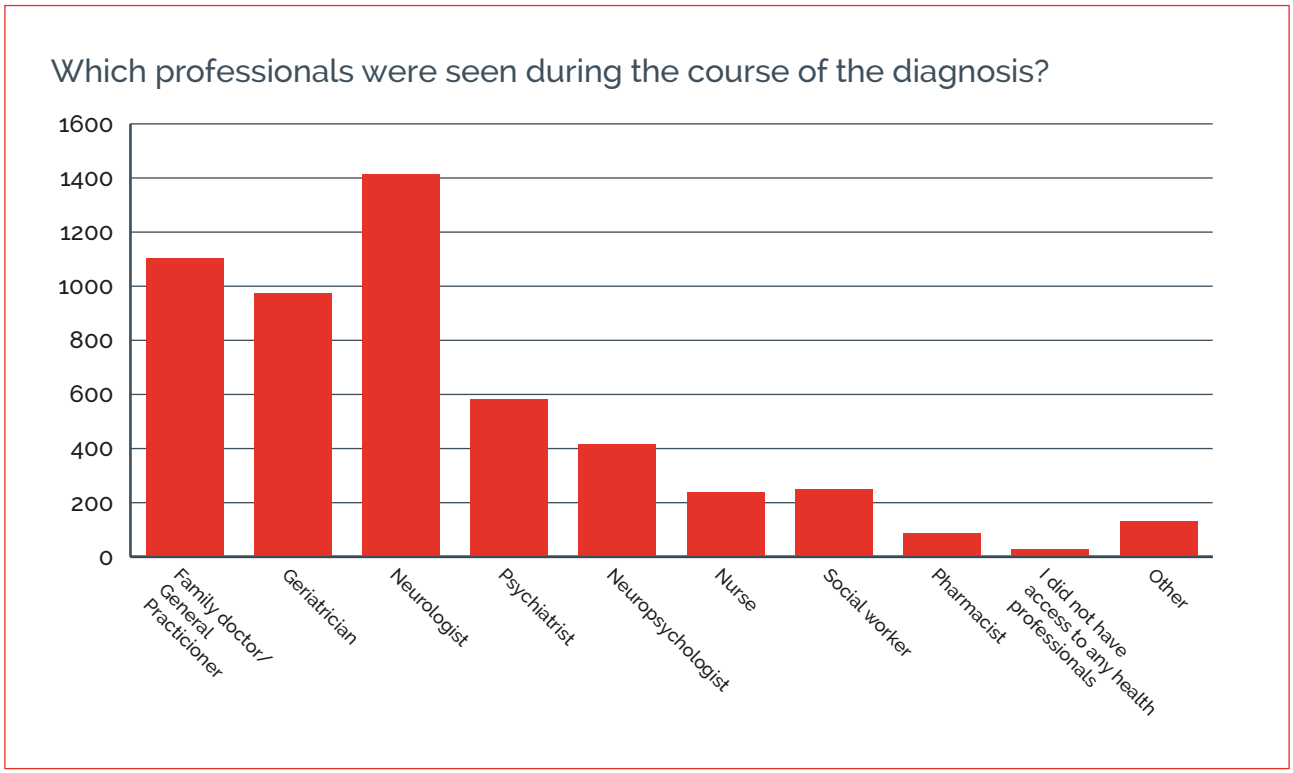


Chart 2. People with dementia and carer responses (multiple answers selected).

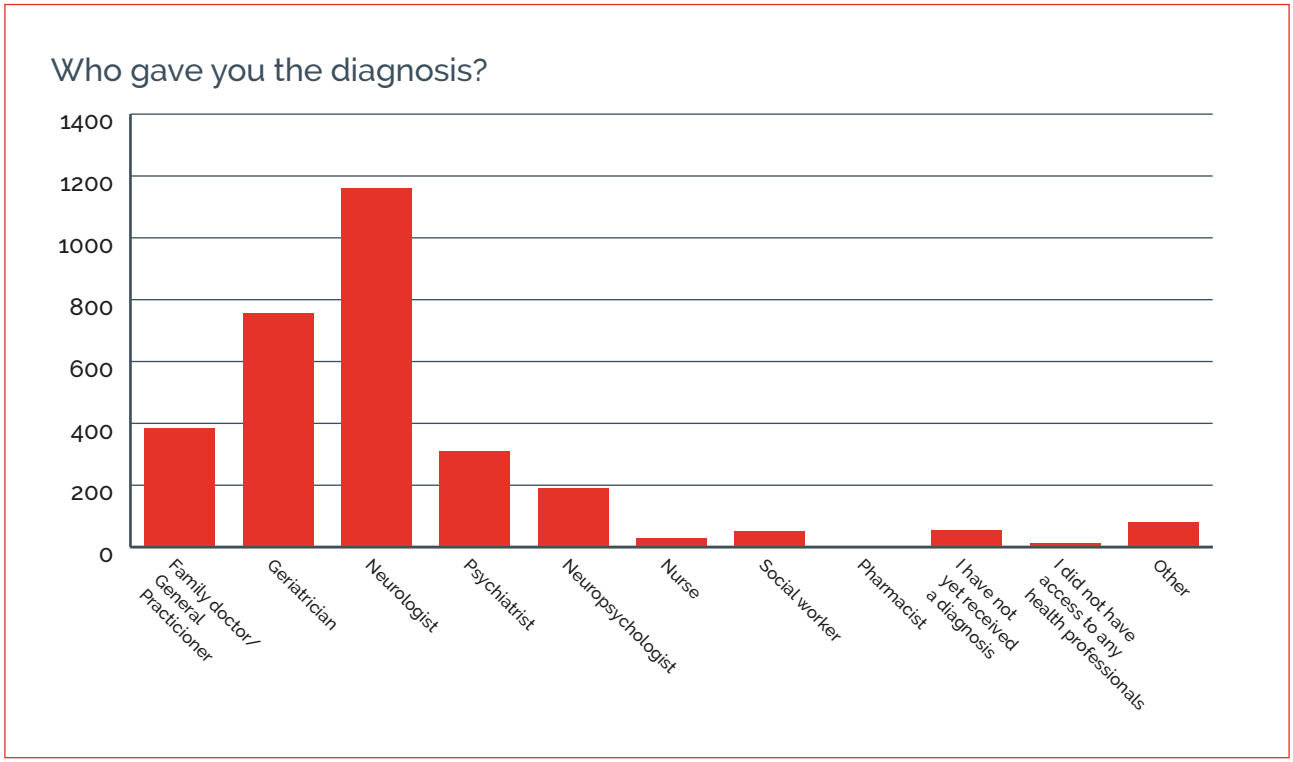


Chart 3. People with dementia and carer responses.

Expert essay

Disclosing APOE genotype to individuals at risk for Alzheimer's disease

J. Scott Roberts,[1] Robert C. Green[2]

[1] Department of Health Behavior & Health Education, University of Michigan School of Public Health, Ann Arbor, Michigan, UNITED STATES
[2] Mass General Brigham and Harvard Medical School, UNITED STATES

Background

The link between the apolipoprotein E (APOE) gene on chromosome 19 and the risk of Alzheimer's disease dementia has been well-established for decades. Carriers of the e4 allele, who represent approximately a quarter of the general population, are at increased disease risk compared to the general population (where lifetime risk is approximately 10–15%), with e4 homozygotes presenting a particularly high risk (1). However, the e4 allele is neither necessary nor sufficient to cause Alzheimer's disease, and a recent pooled analysis of four large population-based cohort studies of older adults found that lifetime Alzheimer's disease risk in e4 homozygotes is less than 50%, a lower estimate than previous research had suggested (2).

Given its limitations in the predictive value and lack of proven Alzheimer's disease prevention options, APOE genotyping for susceptibility testing in asymptomatic individuals has generally been discouraged by medical experts. For example, a 2011 consensus statement from the American College of Medical Genetics and the National Society of Genetic Counselors recommended against APOE testing for predictive purposes in both clinical and direct-to-consumer (DTC) genetic testing contexts (3). Nevertheless, there is significant public interest in genetic susceptibility testing for Alzheimer's disease, particularly among those with a family history of the disease. Such individuals perceive numerous potential benefits from testing, including learning results that can inform advance planning (for example, purchasing insurance), decisions regarding medical care and clinical research, and engagement in health behaviours to reduce disease risk (4). In 2017, the DTC genetic testing company 23andMe obtained approval from the US Food & Drug Administration (FDA) to offer APOE testing for Alzheimer's disease risk assessment, which has provided millions of its customers the opportunity to learn their genotype.

APOE disclosure has also taken place as part of research studies of the psychological and behavioural impact of genetic susceptibility testing for Alzheimer's disease. Our REVEAL Study, a series of randomised trials examining APOE disclosure in populations at risk for Alzheimer's disease (for example, first-degree relatives), has demonstrated methods for successfully communicating genetic risk for Alzheimer's disease using processes that a) minimise risks such as a misunderstanding of results and clinically significant distress reactions, and b) require less time and human resources than traditional predictive genetic testing and counselling protocols for neurodegenerative diseases (such as Huntington's disease) (5).

> **Prior to undergoing APOE genotyping, individuals should be afforded the opportunity to learn about its potential benefits, risks, and limitations. They should know that testing will not provide them with a simple 'yes/no' answer about whether they will ultimately develop Alzheimer's disease dementia, and they should be mindful that results may have implications for other family members.**

Best practices in APOE disclosure

Our experience in disclosing APOE genotype status to over 1,000 individuals has yielded some key recommendations for healthcare professionals considering this practice.

1) Promote informed decision-making

Prior to undergoing APOE genotyping, individuals should be afforded the opportunity to learn about its potential benefits, risks, and limitations. They should know that testing will not provide them with a simple 'yes/no' answer about

whether they will ultimately develop Alzheimer's disease dementia, and they should be mindful that results may have implications for other family members; for example, all children of e4-homozygotes would necessarily be e4 carriers themselves. Concerns about genetic discrimination may be pertinent for some, with legal protections such as the US Genetic Information Non-discrimination Act (which covers health insurers and employers but not life, disability, or long-term care insurers) worthy of consideration. Such issues can be addressed in a variety of formats, including online decision aids (for example, www.genetestornot.org) that do not require involvement of genetic specialists (6).

2) Employ proven health communication techniques in disclosure

Ideally, knowledgeable healthcare professionals experienced in communicating sensitive health risk information should divulge results, with telephone and videoconferencing as acceptable alternatives to in-person disclosure. Given widely varying levels of health literacy and numeracy among laypersons, communication may need to be tailored to individuals receiving risk information (under the auspice that sometimes 'less is more'). Visual aids can enhance understanding of quantitative risk information, especially when comparing risk across different groups. In the REVEAL Study, we have used pictographs (Figure 1) to simultaneously demonstrate both absolute and relative risk associated with being an APOE4 carrier (7). Limitations of risk estimates should be conveyed. Individuals may possess risk or protective factors for Alzheimer's disease not accounted for in models generating risk estimates. In addition, the studies on which risk estimates are based often lack notable diversity in terms of race/ethnicity.

3) Provide guidance on appropriate next steps

APOE disclosure should be accompanied by recommendations for reducing disease risk. Although there are no proven means of preventing Alzheimer's disease, several health behaviours and interventions show promise in lowering the risk of Alzheimer's disease and related dementias, including regular physical activity and management of hypertension. The World Health Organization (WHO) summarised such approaches in its recently issued guidelines for risk reduction of cognitive decline and dementia (8). Individuals should also be made aware of substantive dementia education resources such as the Alzheimer's Association and the US National Institute on Aging. In addition, encouragement to participate in clinical Alzheimer's disease research may be appropriate

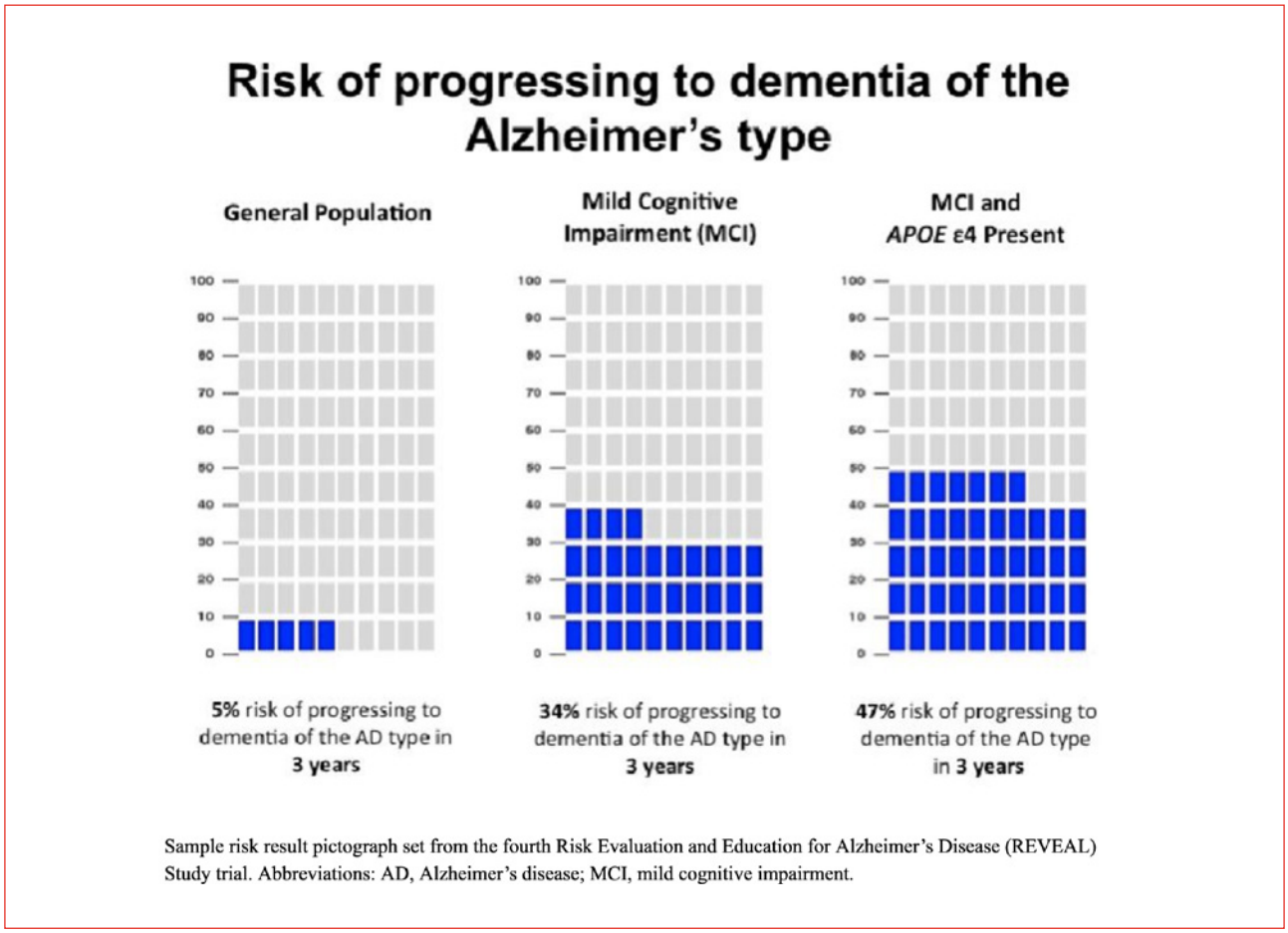


Figure 1. Reprinted from Lautenbach et al, 2013.

in some cases. All key information disclosed to individuals should be concisely summarised in a take-home document for future reference.

Emerging trends

APOE disclosure is increasingly being used or considered for purposes beyond merely informing interested individuals about their chances of developing Alzheimer's disease dementia. For example, APOE genotyping has been employed to help identify asymptomatic, elevated risk participants for Alzheimer's disease prevention drug trials (9). As noted elsewhere in this report (Chapter 24), APOE testing could assist in reducing costs of the Alzheimer's disease diagnostic process by helping determine which cognitively impaired individuals need (or don't need) expensive follow-up biomarker testing such as amyloid neuroimaging. The recent US FDA approval of aducanumab to treat Alzheimer's disease suggests a potential adjunctive role for APOE testing in informing medical decision-making, given that e4 carriers are at significantly elevated risk for the side effect of amyloid imaging related abnormalities (ARIA); APOE genotyping has already been used to inform clinical management of a e4-homozygote patient experiencing vasogenic oedema (ARIA-E) and intracerebral haemorrhage (ARIA-H) side effects from aducanumab use (10). These developments demonstrate the rapidly evolving uses and implications of APOE testing even three decades after its introduction.

References

1. Van Cauwenberghe C, Van Broeckhoven C, Sleegers K. The genetic landscape of Alzheimer disease: clinical implications and perspectives. Genet Med. 2015/08/27. 2016 May;18(5):421–30.
2. Qian J, Wolters FJ, Beiser A, Haan M, Ikram MA, Karlawish J, et al. APOE-related risk of mild cognitive impairment and dementia for prevention trials: An analysis of four cohorts. PLoS Med. 2017 Mar;14(3):e1002254.
3. Goldman JS, Hahn SE, Catania JW, LaRusse-Eckert S, Butson MB, Rumbaugh M, et al. Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genet Med. 2011 Jun;13(6):597–605.
4. Roberts JS, Cupples LA, Relkin NR, Whitehouse PJ, Green RC. Genetic Risk Assessment for Adult Children of People With Alzheimer's Disease: The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study. J Geriatr Psychiatry Neurol. 2005 Dec;18(4):250–5.
5. Roberts JS, Christensen KD, Green RC. Using Alzheimer's disease as a model for genetic risk disclosure: implications for personal genomics. Clin Genet. 2011/07/18. 2011 Nov;80(5):407–14.
6. Ekstract M, Holtzman GI, Kim KY, Willis SM, Zallen DT. Evaluation of a Web-based decision aid for people considering the APOE genetic test for Alzheimer risk. Genet Med. 2017;19(6):676–82.
7. Lautenbach DM, Christensen KD, Sparks JA, Green RC. Communicating genetic risk information for common disorders in the era of genomic medicine. Annu Rev Genomics Hum Genet. 2013;14:491–513.
8. Geneva: World Health Organization. Risk Reduction of Cognitive Decline and Dementia: WHO Guidelines. 2019.
9. Langlois CM, Bradbury A, Wood EM, Roberts JS, Kim SYH, Riviere M-E, et al. Alzheimer's Prevention Initiative Generation Program: Development of an APOE genetic counseling and disclosure process in the context of clinical trials. Alzheimer's Dement Transl Res Clin Interv. 2019;5:705–16.
10. VandeVrede L, Gibbs DM, Koestler M, La Joie R, Ljubenkov PA, Provost K, et al. Symptomatic amyloid-related imaging abnormalities in an APOE ε4/ε4 patient treated with aducanumab. Alzheimer's Dement Diagnosis, Assess Dis Monit. 2020 Jan;12(1):e12101.
11. Yates J, Stanyon M, Samra R, Clare L. Challenges in disclosing and receiving a diagnosis of dementia: A systematic review of practice from the perspectives of people with dementia, carers, and healthcare professionals [Internet]. International Psychogeriatrics. Cambridge University Press; 2021 [cited 2021 Jul 12]. p. 1–32. https://www.cambridge.org/core/journals/international-psychogeriatrics/article/challenges-in-disclosing-and-receiving-a-diagnosis-of-dementia-a-systematic-review-of-practice-from-the-perspectives-of-people-with-dementia-carers-and-healthcare-professionals
12. Bailey C, Dooley J, McCabe R. 'How do they want to know?' Doctors' perspectives on making and communicating a diagnosis of dementia. Dementia [Internet]. 2019 Nov 1 [cited 2021 Jul 12];18(7–8):3004–22. https://pubmed.ncbi.nlm.nih.gov/29658306
13. Society A. Comment on how coronavirus is affecting dementia assessment and diagnosis | Alzheimer's Society [Internet]. 2020 [cited 2021 Jul 12]. https://www.alzheimers.org.uk/news/2020-08-10/coronavirus-affecting-dementia-assessment-diagnosis
14. Recorded Dementia Diagnoses – NHS Digital [Internet]. [cited 2021 Jul 12]. https://digital.nhs.uk/data-and-information/publications/statistical/recorded-dementia-diagnoses
15. Martin-Khan M, Flicker L, Wootton R, Loh PK, Edwards H, Varghese P, et al. The Diagnostic Accuracy of Telegeriatrics for the Diagnosis of Dementia via Video Conferencing. J Am Med Dir Assoc [Internet]. 2012 [cited 2021 Jul 12];13(5):487.e19-487.e24. https://pubmed.ncbi.nlm.nih.gov/22572552
16. Neuroprogressive and Dementia | NHS Research Scotland | NHS Research Scotland [Internet]. [cited 2021 Jul 12]. https://www.nhsresearchscotland.org.uk/research-areas/dementia-and-neurodegenerative-disease
17. Underwood BR, Thompsell A, Sidhom E, Burns A. Providing memory assessment services during COVID-19 [Internet]. Aging and Mental Health. Routledge; 2020 [cited 2021 Jul 12]. https://www.tandfonline.com/doi/abs/10.1080/13607863.2020.1830946
18. Clarke CL, Wilkinson H, Watson J, Wilcockson J, Kinnaird L, Williamson T. A Seat Around the Table: Participatory Data Analysis With People Living With Dementia. Qual Health Res [Internet]. 2018 May 16 [cited 2021 Jul 12];28(9):1421–33. https://journals.sagepub.com/doi/abs/10.1177/1049732318774768

Expert essay

Sharing the diagnosis of dementia in the post-COVID-19 clinic: patient and practitioner perspectives: dementia assessment and diagnosis during lockdown

Denise Munro,[1] Lindsay Kinnaird,[1] Tom Russ,[1] Katie Gambier-Ross,[2] Heather Wilkinson,[2] Rose Vincent[2]

[1] Alzheimer Scotland Dementia Research Centre, University of Edinburgh, SCOTLAND
[2] Edinburgh Centre for Research on the Experience of Dementia, University of Edinburgh, SCOTLAND

The timely diagnosis of dementia has many benefits for an individual such as accessing medication and post diagnosis support, and planning for the future. Most people with suspected dementia are seen at a memory clinic, but the COVID-19 pandemic resulted in many memory clinics moving to remote consultations using telephone and video-calling.

Receiving a diagnosis of dementia is often a negative experience for the person and their close family (1). There is also a recognition that making a diagnosis is 'nuanced and challenging' (2) for the clinician; the shift to remote diagnosis has made this even more complex. It has also raised concerns about how remote diagnosis is being experienced by the person with dementia and if it is possible for it to be delivered sensitively with appropriate support.

There are arguably disadvantages to a remote diagnosis including difficulty picking up on the person's non-verbal cues and distress, technical issues such as time lags with connection, and having an uncontrolled environment for the assessment and diagnosis of dementia. Indeed, anecdotal

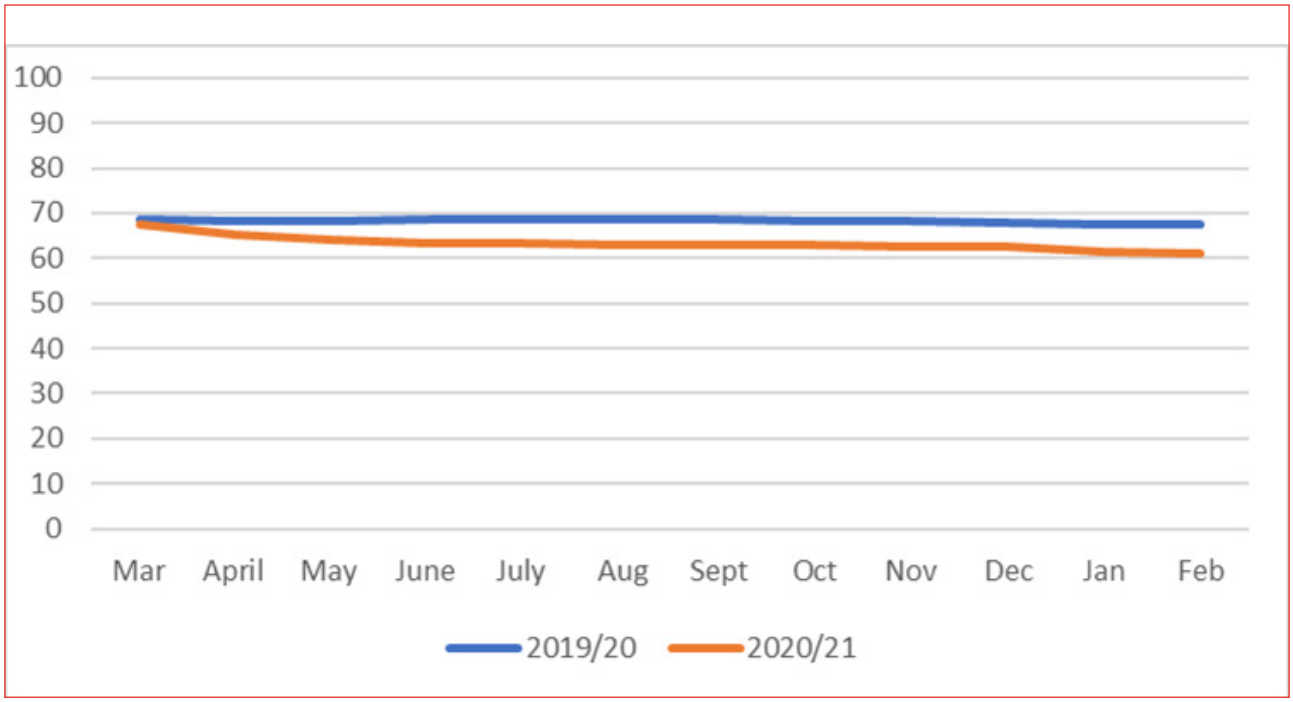


Figure 1. Proportion of the total estimated number of people with dementia who have been diagnosed. Percentage of the total estimated number of people with dementia who received a diagnosis pre-lockdown (2019/20) and during lockdown (2020/21). Source: NHS Digital (4).

experience highlights that not being able to see how someone responds during this discussion makes the process much more challenging for the clinician.

The number of people being diagnosed with dementia has decreased since the beginning of the first UK lockdown in March 2020 compared to the previous year, and this has resulted in a 7.6% drop in the number of people with a diagnosis of dementia for the period (Figure 1). This substantial reduction has been attributed to a range of factors including clinical guidance on reducing the priority of non-urgent primary care, people being fearful of contracting COVID-19 and also not wishing to burden health services during a pandemic (3).

Purpose of study

While standardised assessment tools have been suggested as reliable for the diagnosis of dementia via video-calling (5), the impact this has on the individual remains a key consideration. Being informed that you have dementia is a significant event in a person's life, and how the assessment and diagnosis is experienced will remain with that person for a long time. The rationale for this research is to impact positively on the practice of remote diagnosis and crucially, the experience of the person with dementia and their close family members.

The study arose from discussions with two key groups: 1) debates within clinical services around what is considered ethical and best practice and 2) consultation with the Patient Public Interest Group of the NHS Scotland Neuroprogressive and Dementia Clinical Research Network (6). Delivering a remote diagnosis may become the new normal post-pandemic, but there is a lack of understanding on how this is experienced by the person with dementia (7). It is also disputed whether the practice of remote diagnosis should continue at all.

We want to explore the experience of people given a diagnosis over the phone or video-calling as well as the staff working in memory clinics. This research project will consider the emotional impact, practical implications and ethical considerations of delivering and receiving a remote diagnosis of dementia. The focus will be on the impact on the individual, drawing conclusions from the findings of the interviews and the consensus reached through an Online National Forum to make a recommendation on whether remote diagnosis should continue, and if so, how it should be conducted.

Study approach

A Research Advisory Group has been established comprising people with personal experience of dementia. This Group will inform and advise the research team throughout the research process, meeting regularly to work collaboratively on planning, analysis and reporting.

The research team will interview approximately thirty people who received a remote diagnosis of dementia from the beginning of the first UK lockdown in March 2020. Staff from memory clinics and equivalent services who have been carrying out remote dementia assessment and diagnosis will also be interviewed. Recruitment to the study will be UK-wide, making the findings applicable to all four nations of England, Scotland, Wales and Northern Ireland, and arguably further afield. The findings from these interviews will be analysed in collaboration with the Research Advisory Group, drawing on methods used by research team members in previous co-produced research projects with people living with dementia (8).

Led by the values of co-production, our approach brings together people with personal experience and researchers to work in partnership. To include these perspectives, we are ensuring involvement is accessible and equally valuing the knowledge of everyone involved.

The second phase of the project will bring together a wider range of stakeholders including people with personal experience of dementia, professionals and people working in dementia fields in an online consultation. The findings from the interviews will be presented at this event and discussions held to allow the participants to contribute to the outputs of the research project.

Outputs from the study

Learning from people who have received a diagnosis during a global pandemic will allow us to enhance practice for the future, including a more nuanced understanding of the ethical implications. It is also important that we learn how practitioners have adapted their approaches to meet the challenges of working remotely with their patients.

There will be several outputs from this project to share the learning as extensively as possible. These will include clinical guidelines for practitioners, a briefing paper for policymakers, academic papers to develop the evidence base and a short, animated film and podcasts targeted at a wider audience. These outputs will also be shared with people who have contributed to the research as members of the Research Advisory Group, taking part in the online consultation or being interviewed for the study, as well as being distributed more widely.

References

1. Yates J, Stanyon M, Samra R, Clare L. Challenges in disclosing and receiving a diagnosis of dementia: A systematic review of practice from the perspectives of people with dementia, carers, and healthcare professionals [Internet]. International Psychogeriatrics. Cambridge University Press; 2021 [cited 2021 Jul 12]. p. 1–32. https://www.cambridge.org/core/journals/international-psychogeriatrics/article/challenges-in-disclosing-and-receiving-a-diagnosis-of-dementia-a-systematic-review-of-practice-from-the-perspectives-of-people-with-dementia-carers-and-healthcare-professionals
2. Bailey C, Dooley J, McCabe R. 'How do they want to know?' Doctors' perspectives on making and communicating a diagnosis of dementia. Dementia [Internet]. 2019 Nov 1 [cited 2021 Jul 12];18(7–8):3004–22. https://pubmed.ncbi.nlm.nih.gov/29658306
3. Society A. Comment on how coronavirus is affecting dementia assessment and diagnosis | Alzheimer's Society [Internet]. 2020 [cited 2021 Jul 12]. https://www.alzheimers.org.uk/news/2020-08-10/coronavirus-affecting-dementia-assessment-diagnosis
4. Recorded Dementia Diagnoses – NHS Digital [Internet]. [cited 2021 Jul 12]. https://digital.nhs.uk/data-and-information/publications/statistical/recorded-dementia-diagnoses
5. Martin-Khan M, Flicker L, Wootton R, Loh PK, Edwards H, Varghese P, et al. The Diagnostic Accuracy of Telegeriatrics for the Diagnosis of Dementia via Video Conferencing. J Am Med Dir Assoc [Internet]. 2012 [cited 2021 Jul 12];13(5):487.e19-487.e24. https://pubmed.ncbi.nlm.nih.gov/22572552
6. Neuroprogressive and Dementia | NHS Research Scotland | NHS Research Scotland [Internet]. [cited 2021 Jul 12]. https://www.nhsresearchscotland.org.uk/research-areas/dementia-and-neurodegenerative-disease
7. Underwood BR, Thompsell A, Sidhom E, Burns A. Providing memory assessment services during COVID-19 [Internet]. Aging and Mental Health. Routledge; 2020 [cited 2021 Jul 12]. https://www.tandfonline.com/doi/abs/10.1080/13607863.2020.1830946
8. Clarke CL, Wilkinson H, Watson J, Wilcockson J, Kinnaird L, Williamson T. A Seat Around the Table: Participatory Data Analysis With People Living With Dementia. Qual Health Res [Internet]. 2018 May 16 [cited 2021 Jul 12];28(9):1421–33. https://journals.sagepub.com/doi/abs/10.1177/1049732318774768.

Conclusions

A visit to a healthcare professional to receive diagnostic results can be a nerve-wracking experience. It can elicit fear – fear of the unknown and perhaps also that suspicions may be confirmed. Some people with anosognosia, a lack of awareness about their condition, may appear indifferent or unconcerned while others may feel high levels of anxiety and may have depression or suicidal thoughts. A skilled clinician, while remaining truthful, should be able to discern which way an individual is leaning in their reaction and adapt their responses accordingly during the disclosure process.

When it comes to taking matters into your own hands, the proliferation of genotyping kits has given people the opportunity to explore their probability of developing dementia. Some individuals prefer to know their risk level so they can be prepared and plan for the future. There are, however, predictive limitations to these types of available kits, and most medical professionals discourage their use for this purpose.

The COVID-19 pandemic, and its restrictions, led to changes in the diagnostic process, and how disclosure is conducted. Telephones, and now video-calling, has made remote disclosure a reality. However, constraints are evident, especially as the uncontrolled environment may inhibit the ability of the clinician to pick up on an individual's non-verbal cues, not to mention any technical issues that may interfere. Learning from both the clinicians' experience and people who have received a remote diagnosis should provide direction for an effective reciprocal exchange and development of best practice.

Chapter 16
Initial management following a diagnosis of dementia

Claire Webster

Key points

- Increased education about dementia will have a significant positive impact on the quality of life of people who have been diagnosed with dementia as well as their carers.
- The World Alzheimer Report survey suggests that the greatest difficulties encountered upon receiving the diagnosis of dementia were lack of adequate information (54%), access to specialised tests (28%), financial constraints (25%) and access to healthcare services (21%).
- People with dementia and carers should be provided with information about the type of dementia they face and potential changes in decision-making capacity.

General background

The previous chapter highlighted how the diagnosis of dementia presents challenges for clinicians as well as the person living with dementia and their family members, whether it was the evolution of the condition through its various stages or the initiation of a care management plan. This chapter takes on a different perspective. It is a testimonial written by one of this World Alzheimer Report authors, a former carer who accompanied her mother through the diagnosis process, and in doing so, discovered a lack in essential support mechanisms of information and guidance. This not only impacted her mother but also how she as a carer navigated the healthcare system to deal with these obstacles. The ensuing consequences and lessons learned led her onto a path of carer advocate.

Survey results

The 1,111 multidisciplinary clinicians who responded to this survey indicated the frequency with which they provide information or make suggestions about specific issues. Most contact a family member of the person with dementia when one was not present at the diagnostic assessment (66%). Relatively few will contact their employer if needed (11%), and many refer to specialised services for mood and/or behavioural support (40%).

Among the 2,327 persons with dementia and carers who completed the survey, only 45% indicated that they were given adequate information about dementia and its initial management, 26% were given a booklet, and 32% were provided advice on nutrition and exercise. Among those who replied that they had difficulties with some aspects of the diagnosis, the lack of adequate information was the main issue (54%), ahead of access to specialised tests (28%), financial constraints (25%) and access to healthcare services (21%). The average satisfaction level for the diagnostic process overall was 3.17 where 0 is not favourable and 5 is excellent.

Some questions were common in both the clinicians and people with dementia and carers surveys with differences in some areas reported in Table 1.

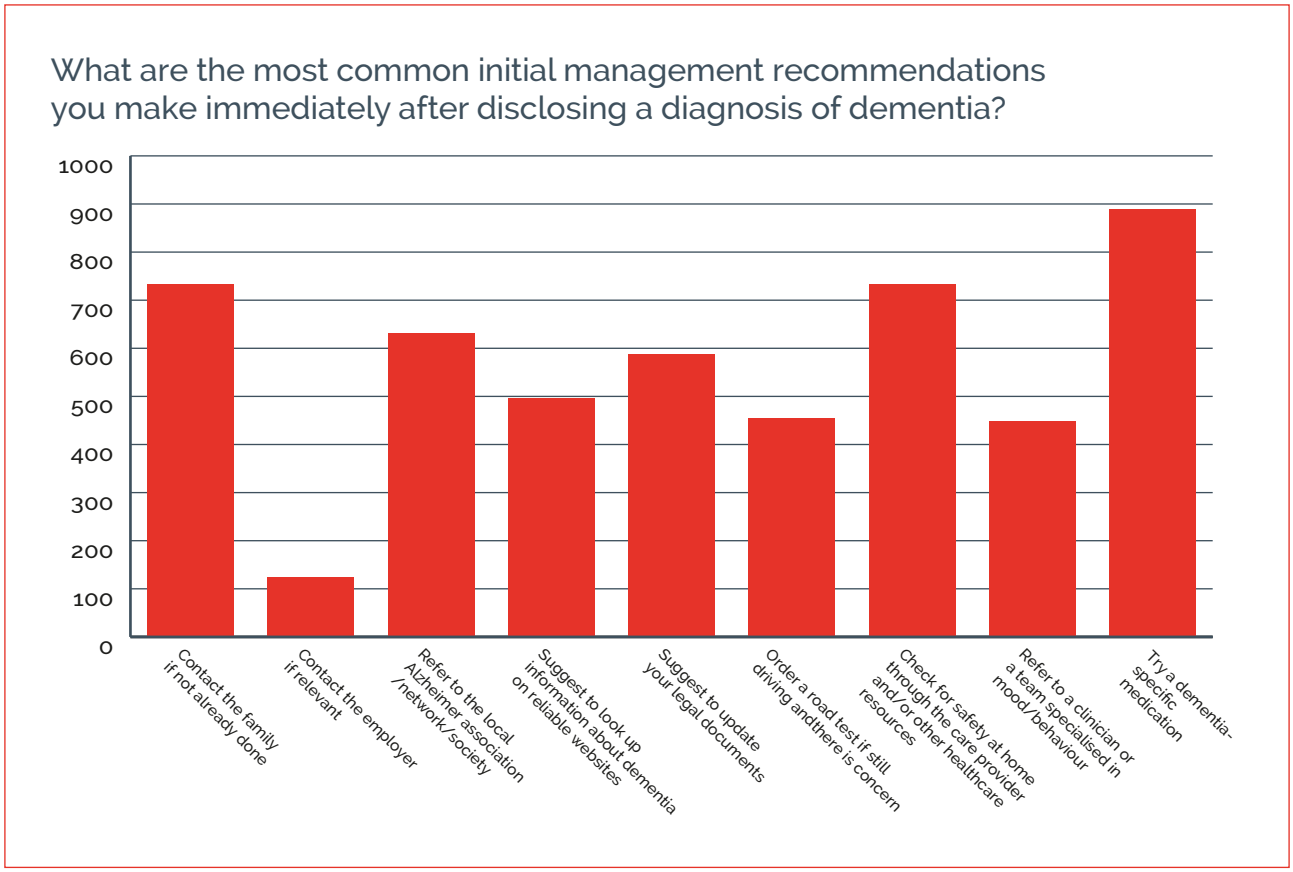


Chart 1. Clinician responses (multiple answers selected).

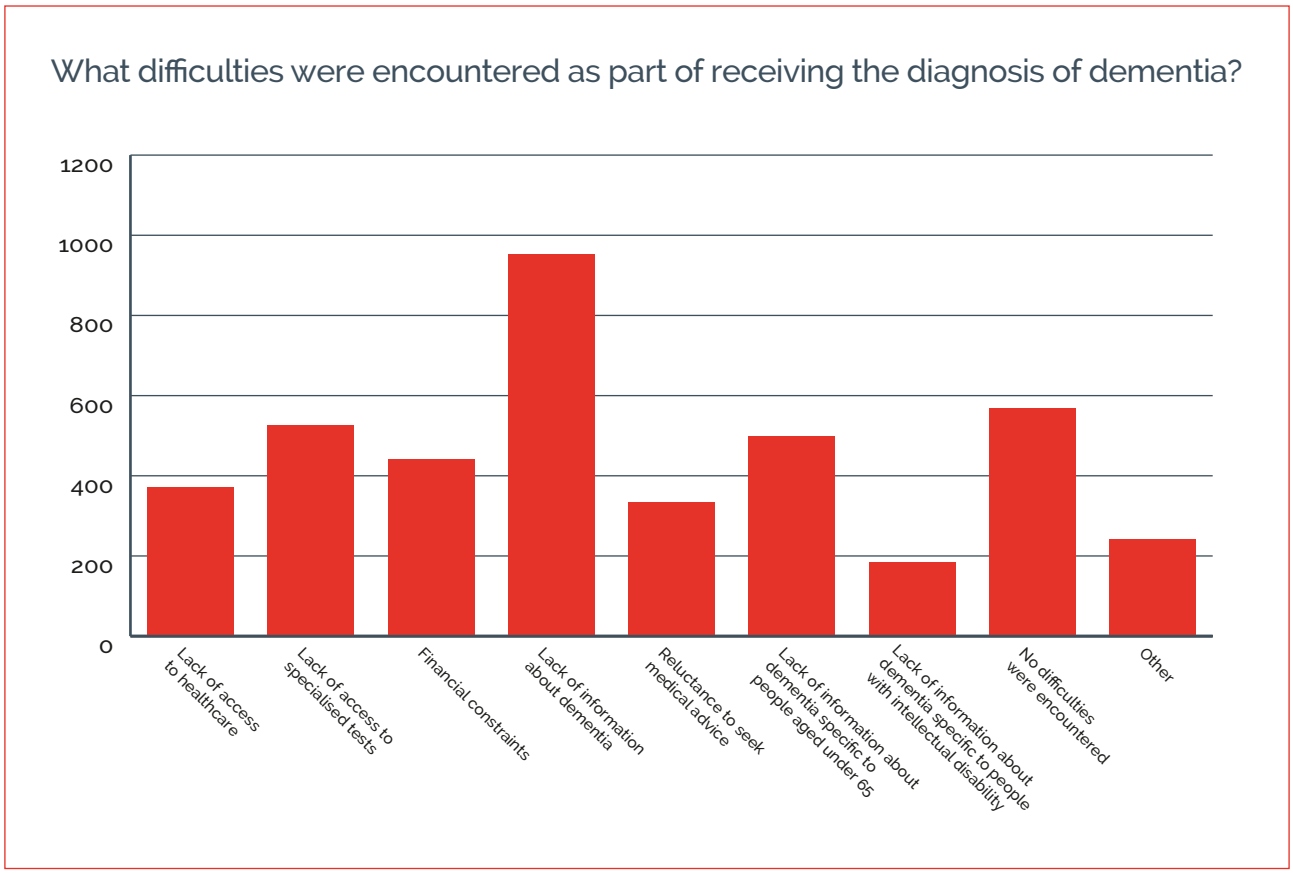


Chart 2. People with dementia and carer responses (multiple answers selected).

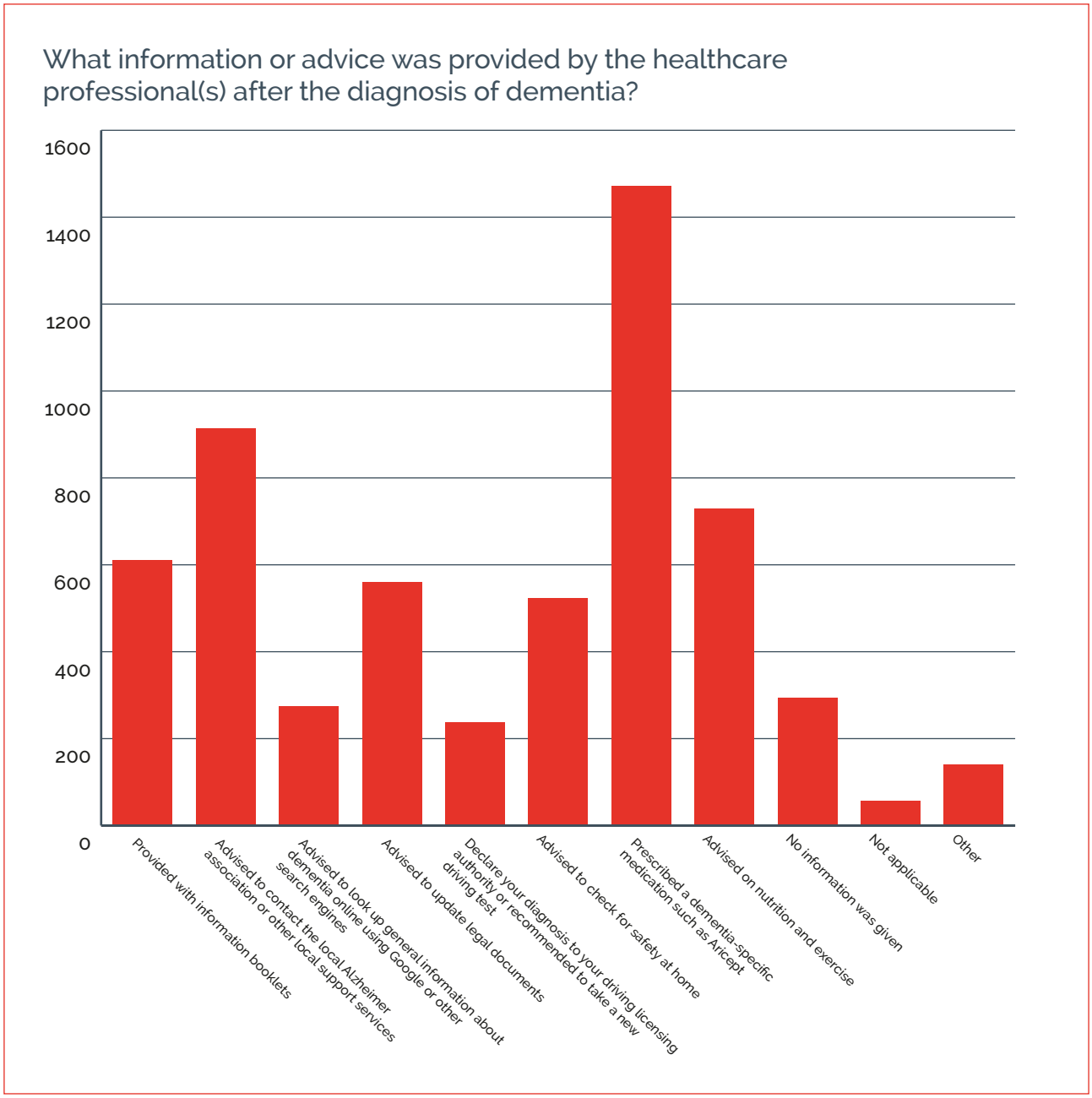


Chart 3. People with dementia and carer responses (multiple answers selected).

Table 1. Selection of survey responses

	Clinicians	People with dementia & carers
Refer to local Alzheimer association or support network	57%	39%
Look up information about dementia on websites	44%	12%
Advice to update legal documents	53%	24%
Advice to assess driving abilities	41%	10%
Advice to assess safety at home by a health professional	65%	22%
Initiate anti-dementia drug treatment	80%	65%

Expert essay

Navigating the journey of dementia after a diagnosis – a prescription of education and support

Claire Webster

Certified Dementia Care Consultant, Founder Caregiver Crosswalk Inc and Founder, McGill University Dementia Education Program, CANADA

Accept, educate, plan ahead navigate, advocate

There are guiding principles that I wish I had known during my mother's Alzheimer's disease diagnosis in September, 2006. She was 74 years old when I took her to the neurologist after consulting with our family physician about her unusual behaviour and significant personality changes following the death of my father in 2005. My mother had been a physically active, independent, and outgoing woman, but over an 18-month period, had become socially withdrawn and impatient, suffering severe mood swings ranging from bouts of anger to depression. She had increasing difficulty managing her finances and preparing meals for herself. She developed a fear of stairs and had zero tolerance for loud noise, often putting her hands over her ears while rocking back and forth in distress. My mother became obsessed with the next-door neighbour, convinced she was operating a cocaine lab (which was definitely not the case). I also noticed that her car had numerous dents and marks that indicated a series of accidents, and that her summer tyres had not been rotated for the winter months.

A few symptoms had begun to appear a year prior to my father's passing. He would often point these out, but I refused to acknowledge them as anything more than her experiencing carer stress. When the symptoms began to worsen after my father's death, I thought my mother was suffering from depression and grief. She'd been his primary carer for over 30 years. My concerns intensified when I realised that she was no longer able to manage her finances and pay for household expenses. She began donating money to the same charity multiple times a year and having unjustified, random expenses. She was often confused, had difficulty finding her words and started to use odd and inappropriate language in the presence of my young children, often screaming at them for no reason. She had also been hoarding hundreds of empty plastic fruit containers that I found in her kitchen cabinets as well as keeping expired food in the refrigerator.

Me and my mother, Vieno Leskinen, Montreal, Quebec, Canada, April 2015.

I decided it was time for her see a doctor. I didn't know who to consult as her symptoms were more behavioural than physical. Against her will, and in full denial of anything being wrong, I made an appointment with her family doctor, who then referred us to a neurologist. He asked us a series of questions about my mother's cognitive and physical well-being while she sat beside me, in great frustration, refusing to accept or admit to any of the information that was being shared. Her medical history included high cholesterol and a minor stroke at the age of 68. There was a history of cardiac issues in her family and she herself would suffer a heart attack three years post diagnosis a few hours following hip replacement surgery.

The neurologist performed the MoCA (Montreal Cognitive Assessment Test). She scored 17/30. The neurologist then informed us that she had Alzheimer's disease, and upon learning that she was still driving, immediately called the driver's licencing bureau, and without any warning, had her driver's licence cancelled while we were still sitting in his office.

In shock, and completely unaware about anything related to dementia, I asked the doctor if he could explain what Alzheimer's disease was, how to manage it, what to expect and if my mother could still live on her own. The doctor answered, 'No, she cannot live on her own; there is information about the disease on the internet. Good luck Mrs. Webster.' That was it. Nothing else. We left the doctor's office without any information or guidance about the symptoms of the disease, how to plan for the future, the importance of accessing support services from the community or any other information about what the next steps should be. I was totally unfamiliar with the symptoms, expectations and challenges that she, and inevitably I, would face in caring for her. I was instantly compelled to educate myself on the disease.

I was her only child, and at the time of her diagnosis I was 38 years old and raising a family of three young children while holding down a full-time job managing a company with my husband. Over the next few years, with multiple responsibilities caring for both my family and my mother, not to mention facing other personal challenges, I would get caught up in a cyclone of caregiving. When the air settled, I had severe burnout and post-traumatic stress disorder. The lack of a 'prescription of care' (namely being provided information and guidance), from the neurologist or any other healthcare professional with whom I met, would have a significant impact on my mother's quality of care and safety over the coming years, as well as having a ripple effect on my own mental and physical health. My young children would witness not only the decline of their grandmother, but also the unravelling of their mother.

A lack of education about a dementia diagnosis will have a significant impact on the quality of care as well as safety of the individual and their carer(s).

I spent the majority of my carer years in a state of anger and denial. I was angry at the disease for robbing my mother of what should have been her golden years. I was angry at the disease for the carer burden placed on me during a time when my three young children needed me the most. I was in denial of how much I truly needed support and refused to ask for it. I developed coping mechanisms to deal with my stress, namely alcohol. It became both a dependence and a demon which I fortunately conquered and recovered from four years after my mother's death in 2016.

My mother's Alzheimer's disease diagnosis was the beginning of one of the most challenging periods of my life, but would also become the driving force behind my passion for educating and advocating for others. I would devote the rest of my life to improving the way carers are treated in our healthcare system and become a 'Carer Crusader'. Alzheimer's disease taught me about the power of human resilience. I witnessed it in my mother, as well as have come to recognise it in myself. I would not have been able to navigate this journey without the tremendous support and patience of my husband and three children. For that, I am forever grateful.

A lack of education about a dementia diagnosis will have a significant impact on the quality of care as well as safety of the individual and their carer(s).

The importance of education and support

Over the past 15 years, I've met with hundreds of carers with their own stories to tell. Across all these different lives, I realised that the threads that bind us are also the threads that can derail us. Dementia is complex and the medical community doesn't always provide enough of the necessary information, nor stress the importance of seeking out community support services, two essential components needed to help us take the best possible care of the person living with dementia. It is what I, and all the families I work with, strive for.

How can we accomplish this?

Accept the diagnosis

This is the first step to ensure that the person with dementia receives the best care possible. Many people with dementia experience anosognosia, or the inability to recognise that something is medically wrong. Given that, it falls to the carer to accept the situation and push through the shockwaves this diagnosis represents. Only by learning to adapt to all the cognitive and physical changes brought on by this condition will a carer be able to manage effectively. Likewise, learning to adjust your approach and behaviour when something doesn't work is just as important. In my experience, acceptance of all things dementia is the gateway to best care practices.

'Many thanks, but I'm not there yet'. I cannot tell you how many times I have used these very words or heard them from other carers over the years. We dismiss any attempt to enter our world though we desperately want help yet also feel overwhelmed with all the tasks at hand. Add in an unjustified sense of guilt and you have one solid barrier of resistance. Why is it that family carers sometimes feel that they do not have the right to ask for support when caring for their loved one, and more importantly, why do they feel

that they do not have the right to a life of their own? That is, until a crisis occurs that profoundly impacts on their own health and causes a ripple effect on everyone around them, including the person with dementia.

Accept support

Caring for someone with dementia is very demanding and you cannot to do it alone. In order to prevent carer burnout, it is extremely important to identify other family members, friends, community and/or public and private resources to help with household chores, caregiving tasks, transportation as well as mental health support and respite care. Seek out the necessary support services following the diagnosis in order to know what are your available options and prepare accordingly.

Educate yourself

Knowledge is your most powerful resource. Understanding as much as possible about dementia, how it progresses, recognising and managing challenging behaviour and how to plan for the future, prepares both the person with dementia and their carer for the journey. Again, this deliberate exploration equips you with the necessary tools to provide the best care possible. Learn all you can about the support services in your community that can assist both the carer and the person living with dementia. Whether it's your first, second or fifth medical appointment, arrive with a list of prepared questions or concerns you want to address. Your healthcare professional can also point you in the right direction regarding services and facilities that can assist you.

Plan

It is important to understand the evolution of dementia and the care that will be required across the stages. Planning for the future is an important part of the process in order to make decisions concerning health and personal care, living arrangements, finances as well as legal and estate planning. The progressive nature of the condition may make it difficult for the person living with dementia to express their needs and make independent choices. Given that, while still feasible to do with the person living with dementia, you may wish to meet with family members, financial and legal experts to arrange for a notarised mandate and power of attorney. These documents would authorise carers to lawfully make decisions on their behalf if they no longer can.

The COVID-19 pandemic has been a huge lesson for us all in the matter of 'expect the unexpected'. Life can get interrupted in ways we could never see coming. Therefore, prepare yourself by having both a Plan A and a Plan B in place.

Navigate

In addition to becoming as well informed as possible about dementia, it is equally important to know about all the support services available to you, be it community organisations, public healthcare/government agencies, private home care agencies, or public and private long-term care residences. Experience has taught me that learning how to navigate and access these programmes can be a lengthy process, especially if high demand results in waiting lists. Being better informed and starting the process early in the diagnosis will lead to better results.

Strategies I found helpful:

- Educate yourself on the disease – why is the person with dementia doing what they are doing?
- Pick your battles – If what they are doing is not hurting them or others, let them be. What we may find to be unusual behaviour, may be very comforting to an individual with dementia.
- Be a detective and not a judge – take the time necessary to investigate what is happening in the surroundings that could be causing anger, anxiety or discomfort. As people living with dementia lose their ability to communicate with words, they may have a difficult time expressing their emotional and physical needs.
- Join their journey – carers often become frustrated with the person living with dementia as they feel that the stories that they are telling may be over exaggerated and/or repeated multiple times. To avoid conflict, it is best to join their journey and engage in recollections of events provided that the stories are not distressing. Should the need arise to validate their version of events, be mindful of how you communicate. Avoid using sentences such as 'That's not true! Why can't you remember? I told you many times before!' Instead, use words such as 'I'm sorry that you feel that way. Help me understand why you feel like that happened. It sounds like…It seems as if…'
- Carers should ask themselves how their own mood, patience and energy levels are in order not to transfer their own frustrations onto the person that they are caring for, which can result in confrontation. Caring for a person with dementia requires a tremendous amount of patience and energy and it is therefore very important that carers make their own health and wellbeing a priority.

Advocate

As a former carer, the role of advocate was one of my most important. This safeguarded my mother's wellbeing and dignity throughout the remainder of her life. As the condition progresses, and if the person with dementia begins to lose their ability to communicate effectively and speak up for themselves, it is imperative that their carers assume this responsibility. Essentially, you become their voice. This role necessitates a tremendous amount of dedication and commitment as you will be making difficult life decisions on their behalf. These include the type of care they need, living arrangements, as well as legal, financial, and medical decisions. I often use the term 'tough love' with the families that I counsel to describe those hard decisions.

Safety

As dementia advances, a person's vision, mobility and cognitive decline may have a direct impact on their activities of daily living such as driving, managing personal finances, cooking, eating, bathing, grooming, dressing, sleeping as well as other aspects of their day-to-day life. Keeping the person safe thus becomes a priority to prevent falls, injuries, and significant financial mistakes. Certain rooms in the home have higher risks than others, such as the kitchen, bathroom, and stairs. Meet with an occupational therapist or a specialist who can properly assess the environment to ensure a safe home, outdoor space or work environment. The topics of driving and managing personal finances are delicate as they symbolise the person's sense of independence. When these tasks become compromised as a result of the progression of the illness, it is very important to involve the guidance and expertise of the medical doctor to assist with implementing the necessary next steps to ensure the safety of the individual.

The importance of self-care

A person receiving a dementia diagnosis needs to continue to live as healthy a lifestyle as possible, as well as embrace everything that they can still do. Establishing a regular exercise routine, healthy eating plan and quality time spent with friends, family and colleagues is important to maintaining a balanced life.

Concurrently, carers need to find ways to preserve their energy to fulfil their day-to-day tasks. That means becoming more protective of 'me time' and personal commitments as well as surrounding themselves with people and projects that add positivity to their lives. Learning to say no and becoming selective of where, how, and with whom they invest their time is key.

Becoming an advocate for change

In addition to becoming a Certified Dementia Care Consultant, one of my greatest accomplishments is having founded McGill University's Dementia Education Program[i] in 2017. The programme works in collaboration with several McGill University partners, including the Division of Geriatric Medicine, the Research Centre for Studies in Aging, the Steinberg Centre for Simulation and Interactive Learning, and the Faculty of Medicine and Health Sciences. I am collaborating with a team of dedicated multidisciplinary healthcare professionals to develop programmes that educate and support family carers, along with healthcare professionals and medical students of the future, with a focus on patient-centred care.

i This program includes in-class workshops, public education seminars and webinars. A free webcast and podcast series, McGill Cares, a Dementia Companion Guide for people living with dementia and their carers, and a Dementia Activity Booklet are available at www.mcgill.ca/dementia.

Conclusions

Alzheimer's disease and other types of dementia have no cure yet. As the population ages and more people are diagnosed, we need to ensure that the general public becomes better educated about dementia. This starts with health and social care systems that must also be agents of change in their own right. This system is multi-layered and complex. Having a foundation built on informed, reliable and support-driven information and guidance is a priority that demands attention and action.

The 2022 World Alzheimer Report will be dedicated to the journey following diagnosis, a natural next step to this report and looking at best practice models globally, barriers and facilitators, research and innovation.

Chapter 17
Re-evaluation of diagnosis over time

Serge Gauthier

Key points

- Long-term follow-up of people with dementia is needed as new symptoms and physical signs may appear and lead to a change in the original diagnosis and prognosis.
- Some causes of dementia may be partially reversible.
- Dementia due to conditions other than Alzheimer's disease may require additional clinical and laboratory assessments.
- As research is progressing on the biological definition of Alzheimer's disease, similar efforts are needed for non-Alzheimer dementias.

General background

The diagnosis of dementia is primarily clinical and based on the information obtained from the clinical history and physical examination, supplemented by laboratory tests. Over time, new symptoms will emerge, new physical signs will be detectable, and the suspected cause of the dementia may change. This is particularly true with atypical presentations of dementia such as progressive aphasia which may progress into frontotemporal dementia or Alzheimer's disease, dementia with changes in motor tone affecting the neck or one arm may lead to a diagnosis such as Progressive Supra-Nuclear Palsy (PSP) or Cortico Basal Degeneration (CBD), and for a new group of amyloid negative persons who clinically appear like they have Alzheimer's disease. Even more common is dementia with Lewy bodies, with a mix of Alzheimer and Parkinson symptoms. These various diagnostic categories are discussed in the following essays, preceded by an overview on how to manage a change in diagnosis. The need to follow longitudinally, including autopsy studies, people who look like they have Alzheimer`s disease but do not have excessive amyloid in their brain is explained in the final essay of this Chapter.

Reversible dementia or treatable causes of dementia

The clinical diagnosis of dementia may change under certain clinical circumstances. Frequent nutritional deficiencies such as vitamin B1 (thiamine) or B12 can cause dementia symptoms that can be reversed with treatment. Side effects of medications or drug combinations or substance abuse may cause reversible cognitive impairment, evident when the drug is discontinued. In addition, cognitive impairment secondary to autoimmune inflammatory conditions, such as vasculitis, or infectious diseases, such as chronic meningitis, are also treatable with the administration of immunosuppressive or antibiotics, respectively. Finally, neurosurgical interventions can reverse dementia in normal pressure hydrocephalus, subdural haematoma or non-malignant brain tumours (1–3). Therefore, an individual's initial assessment to rule out treatable causes of dementia should be an integral part of the evaluation. A non-exhaustive list of treatable causes of dementia is provided in Table 1.

Table 1. A non-exhaustive list of treatable causes of dementia

- Drug abuse
- Toxic effects of drugs
- Depression
- Metabolic causes
- Thyroid disease
- Vitamin B12 deficiency
- Calcium disturbance
- Liver disease
- Normal pressure hydrocephalus
- Subdural haematoma
- Neoplasm
- Diabetes
- Thyroid disease
- Parathyroid disease
- Cushing's disease
- Addison's disease
- B12, thiamine and nicotinic acid
- Respiratory disease
- Anaemia
- Head injury
- Space-occupying lesions
- Syphilis
- Encephalitis
- HIV

Change in diagnosis

Neurodegenerative dementias do not always follow predictable patterns of progression. While in typical dementia, amnestic individuals frequently exhibit apraxia, aphasia or dysexecutive symptoms as secondary features during the disease course, anterograde amnesia may be the very first manifestation of other conditions. In atypical dementia cases, the diagnosis may also change (4). People meeting the criteria for behavioural frontotemporal dementia may develop motor neuron diseases meeting typical amyotrophic lateral sclerosis phenotype, frequently with bulbar involvement. Psychotic symptoms are particularly observed in carriers of expansions of the C9ORF72 (5).

Cases initially dominated by a cognitive syndrome meeting criteria of behavioural variant of frontotemporal dementia may develop in 24–48 months, with significant aphasia or extrapyramidal symptoms meeting criteria either for the primary aphasia or progressive supranuclear palsy or corticobasal syndrome (6,7). By contrast, behavioural manifestations may arise in those with initial language or motor symptoms. The overlapping between behavioural, language and extrapyramidal syndromes provides insights related to the propagation of brain pathology across cortical regions (6,8,9).

Survey results

The 1,111 multidisciplinary clinicians who replied to the survey indicated that most (69%) have a flexible schedule regarding follow-up visits based on the patient and family needs, 20% followed up every six months, and very few (4%) did so annually (Chart 1). When asked about being at ease with re-evaluating the diagnosis over time as new symptoms emerged, 56% were confident for all types of dementias, 27% for the more common types of dementia, and 17% would refer the person to a specialist.

When asked whether follow-up appointments took place after the initial diagnosis of dementia, most of the 2,327 persons with cognitive complaints or their carers indicated that it took place within two to six months. This was in both high-income countries (HIC) (43%) and low-income countries (LIC) (42%). In the low-income countries, a higher percentage of respondents received a follow-up appointment within one month (30%), compared to high-income countries (14%). In contrast, 13% of those in low-income countries never had a follow-up in comparison to only 3% in high-income countries. In high income countries, 16% had their follow-up appointment 6 months after their initial diagnosis, compared to 8% for those from lower income countries (Chart 2).

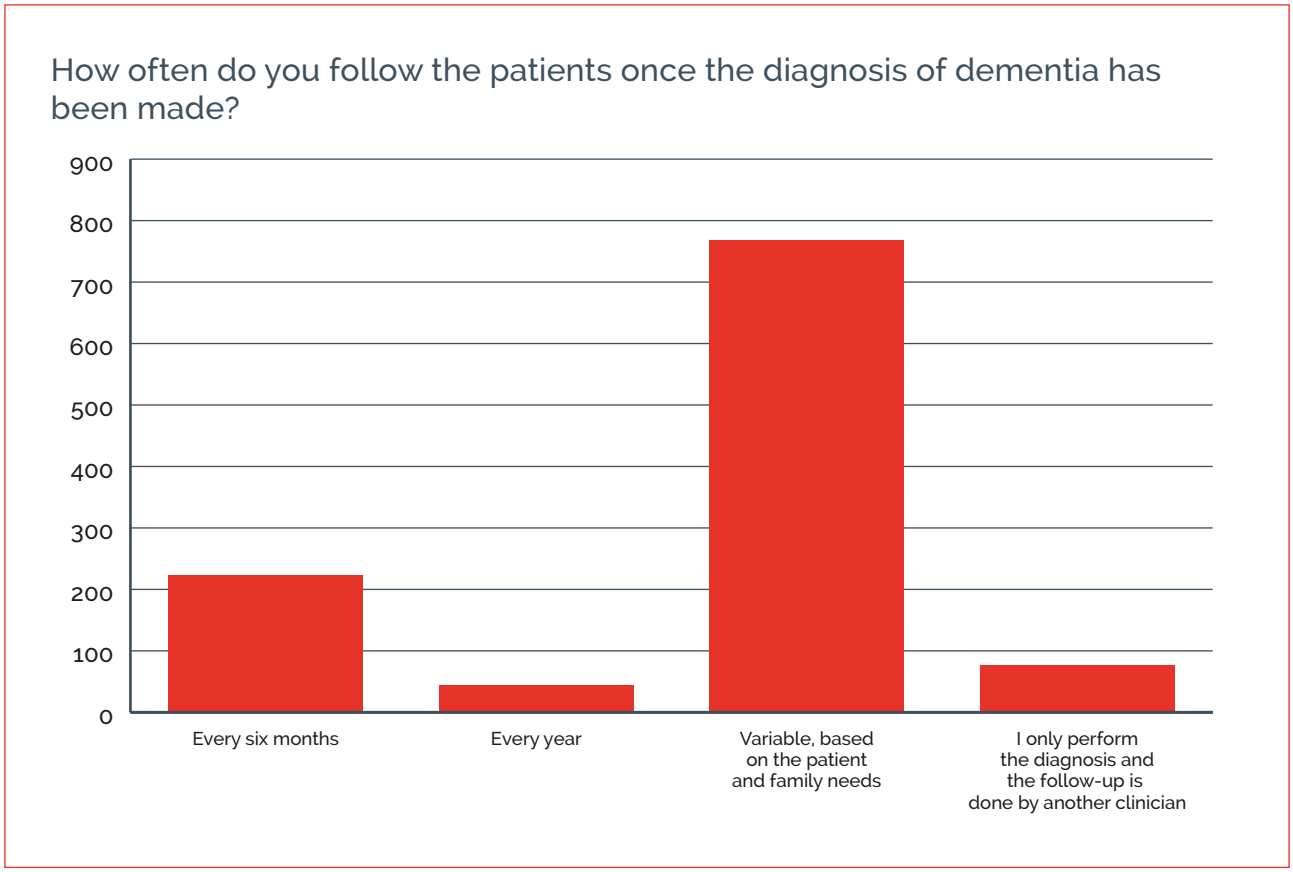


Chart 1. Clinician responses.

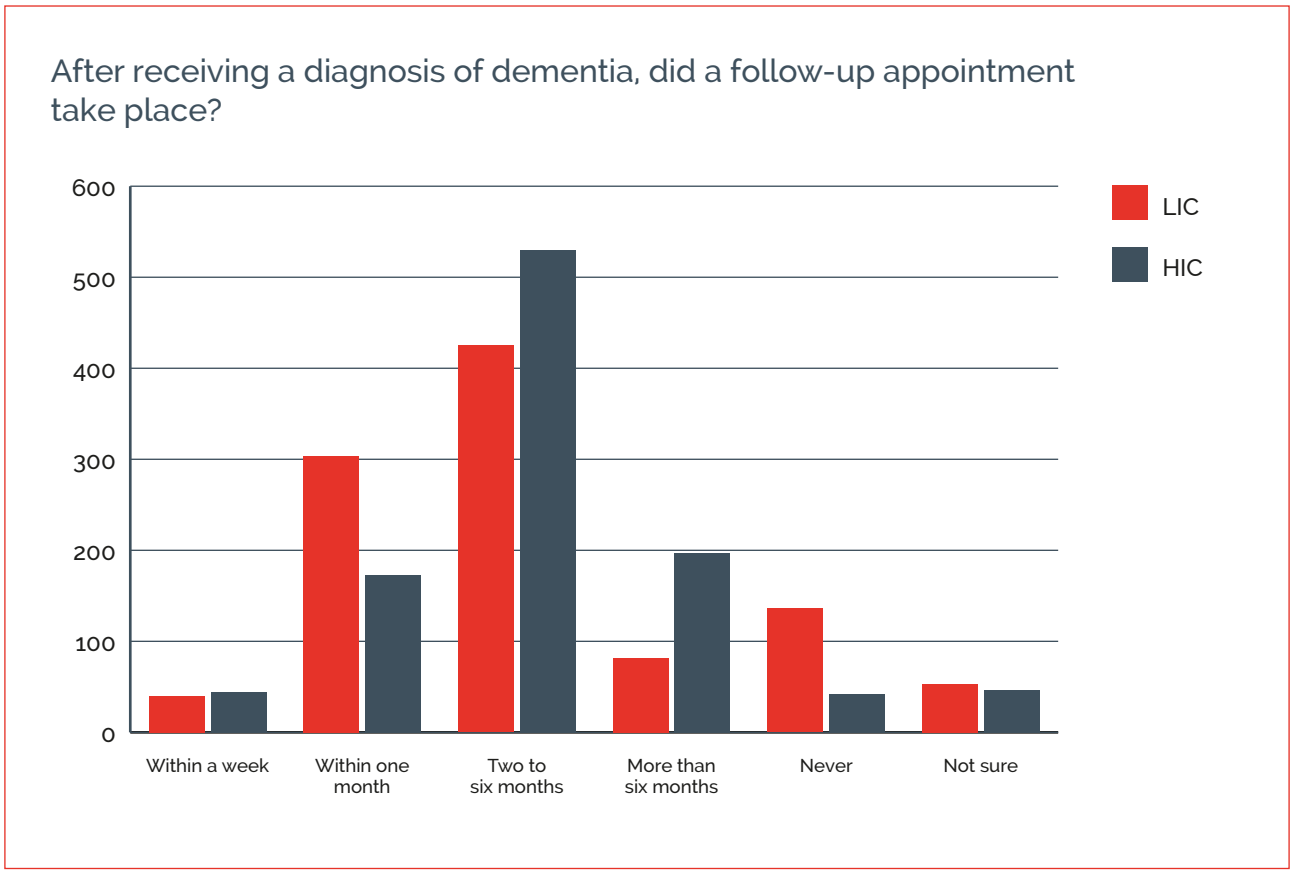


Chart 2. People with dementia and carer responses.

Expert essay

How to tell people with dementia that their diagnosis has changed over time

Paulo Caramelli

Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, BRAZIL

The diagnosis of dementia is clinical. It depends on proper identification of the characteristic syndrome, namely cognitive and/or behavioural impairment leading to functional decline, which is not explainable by delirium or by a major psychiatric disorder (1).

Identification of dementia syndrome can be challenging, especially among people with high education levels, where diagnostic sensitivity may be limited at the early stages, as well as among individuals with low educational level, where diagnostic specificity may be initially restricted (2). In this sense, the clinician may consider postponing a dementia diagnosis in situations where there is uncertainty, and this, to avoid any negative effects on the affected individual and their family. It is also important to bear in mind that dementia can be reversible (3) and, in these cases, the initial diagnosis may be revised. Nevertheless, in all these circumstances, follow-up assessments increase diagnostic confidence, allowing adequate care management and support.

Definition of the aetiology of dementia is the second step in the diagnostic workup and is usually more challenging. Blood tests and neuroimaging exams (structural and functional) are the routine ancillary procedures. In recent years, specific diagnostic biomarkers based on biological fluids (for example, plasma and cerebrospinal fluid) and molecular imaging (such as, positron emission tomography with amyloid and tau tracers) have increased diagnostic accuracy of Alzheimer's disease (4), the most common cause of dementia worldwide. Biomarkers for other illnesses related to dementia are also under investigation, with promising results (5). However, diagnosis is not 100% precise and co-pathologies are common, especially among older people, where vascular lesions or brain accumulation of up to four pathological proteins may occur in a significant proportion of people (6,7).

An important additional challenge in the diagnosis and follow-up of individuals with dementia is when the initial aetiological diagnosis proves to be incorrect over the course of the illness. It can happen in scenarios where the clinicians do not have access to specific Alzheimer's disease biomarkers, particularly important for the diagnosis of non-amnestic or atypical cases of Alzheimer's disease, where, for example, a behavioural-dysexecutive phenotype may be misdiagnosed as behavioural variant frontotemporal dementia (FTD) (8).

This situation can also emerge during the longitudinal assessment of non-Alzheimer's disease cases, for which some clinical overlaps are present. A good example applies to the diagnosis of frontotemporal dementia, which encompasses language presentations (primary progressive aphasia variants) and a behavioural variant, besides the associations with motor phenotypes, namely, progressive supranuclear palsy, corticobasal syndrome and motor neuron disease (9). Individuals presenting one of these clinical syndromes may evolve to a second phenotype after months or years. For instance, non-fluent primary progressive aphasia may be the initial clinical manifestation of progressive supranuclear palsy (10). Even genetic cases may modify their cognitive and behavioural profile over time, admitting a different clinical diagnosis. For instance, an individual with genetic frontotemporal dementia (progranulin mutation) initially presented with one of the typical language presentations of the syndrome, yet two years later, manifested prominent changes in behaviour, consistent with the diagnosis of behavioural variant frontotemporal dementia (11). The two examples above illustrate the phenotypical heterogeneity found in frontotemporal dementia and in other degenerative dementias.

How can the clinician respond to such modifications of diagnosis that may emerge with time and adequately communicate it to people with dementia and their families? Interestingly, in a recent Dutch study where the consultations of people with dementia were audio recorded and clinicians were prompted to ask questions from a prepared list of 25 topics, only 10% of people or their partners began a discussion within one of the listed topics and, when this occurred, they usually asked about the least frequently addressed issues (12). These results indicate that clinicians' expectations about what is important to be discussed may not coincide with the opinions of people with dementia and their families. Hence, a key point is to initially ask them what they want to know about their brain health problem. Clinicians need to

understand the individual and familial context, the doubts and worries, and to address all questions openly and in the clearest possible way.

Bear in mind that the ancillary methods (such as blood tests and structural neuroimaging) currently available in most settings allow the clinician to determine with high diagnostic confidence if the dementia is potentially reversible or not, as well as to figure out if the aetiology is most likely degenerative or non-degenerative. This latter aspect is crucial when discussing the prognosis and providing the necessary direction regarding advanced care planning and personal decisions that the person with dementia may need to make (13). Moreover, we must acknowledge that the medical diagnostic process is not necessarily without errors. This applies to most medical specialties (14).

Diagnostic disclosure of dementia and related conversations should be delivered in a clear way, from the explanation about the syndrome to how the specific aetiology has been considered. Wording must be intelligible, taking into consideration the cultural, educational, and social background of the person with dementia and their family. The clinician should remember that is preferable to say 'I'm not sure' or 'the diagnosis is not yet defined' when facing a complex situation, emphasising the importance of follow-up and repetition of complementary tests, if necessary, to increase diagnostic certainty. Clear information that the diagnosis may change with the emergence of more typical signs and symptoms after some time, or that a second clinical syndrome can appear in the context of specific forms of dementia (for example, frontotemporal dementia), should also be provided. It is important to highlight that in many instances, pharmacologic and non-pharmacologic treatments aimed at dementia symptoms shall be recommended regardless of the aetiological diagnosis. In this sense, the clinician must ensure that the person receives the best available care and support.

References

1. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement 2011;7:263–9. https://doi.org/10.1016/j.jalz.2011.03.005.
2. Calil V, Elliott E, Borelli WV, Barbosa BJAP, Bram J, De Oliveira Silva F, et al. Challenges in the diagnosis of dementia insights from the united kingdom–brazil dementia workshop. Dement e Neuropsychol 2020;14:201–8. https://doi.org/10.1590/1980-57642020dn14-030001.
3. Takada LT, Caramelli P, Radanovic M, Anghinah R, Hartmann APBJ, Guariglia CC, et al. Prevalence of potentially reversible dementias in a dementia outpatient clinic of a tertiary university-affiliated hospital in Brazil. Arq Neuropsiquiatr 2003;61:925–9. https://doi.org/10.1590/S0004-282X2003000600007.
4. Henriques AD, Benedet AL, Camargos EF, Rosa-Neto P, Nóbrega OT. Fluid and imaging biomarkers for Alzheimer's disease: Where we stand and where to head to. Exp Gerontol 2018;107:169–77. https://doi.org/10.1016/j.exger.2018.01.002.
5. Solje E, Benussi A, Buratti E, Remes AM, Haapasalo A, Borroni B. State-of-the-art methods and emerging fluid biomarkers in the diagnostics of dementia – a short review and diagnostic algorithm. Diagnostics 2021;11:788. https://doi.org/10.3390/diagnostics11050788.
6. Suemoto CK, Ferretti-Rebustini REL, Rodriguez RD, Leite REP, Soterio L, Brucki SMD, et al. Neuropathological diagnoses and clinical correlates in older adults in Brazil: A cross-sectional study. PLoS Med 2017;14. https://doi.org/10.1371/journal.pmed.1002267.
7. Karanth S, Nelson PT, Katsumata Y, Kryscio RJ, Schmitt FA, Fardo DW, et al. Prevalence and Clinical Phenotype of Quadruple Misfolded Proteins in Older Adults. JAMA Neurol 2020;77:1299–307. https://doi.org/10.1001/jamaneurol.2020.1741.
8. Paquin V, Therriault J, Pascoal TA, Rosa-Neto P, Gauthier S. Frontal Variant of Alzheimer Disease Differentiated from Frontotemporal Dementia Using in Vivo Amyloid and Tau Imaging. Cogn Behav Neurol 2020;33:288–93. https://doi.org/10.1097/WNN.0000000000000251.
9. Bang J, Spina S, Miller BL. Frontotemporal dementia. Lancet 2015. https://doi.org/10.1016/S0140-6736(15)00461-4.
10. Caramelli P, Hosogi-Senaha ML. Man with problems with reading and calculating. In: Rosa-Neto P, editor. Case Stud. Dement. Common Uncommon Present., S. Case Studies in Dementia. Cambridge, UK: Cambridge University Press; 2011, p. 238–44. https://doi.org/10.1017/CBO9780511997433.034.
11. Takada LT, Bahia VS, Guimarães HC, Costa TVMM, Vale TC, Rodriguez RD, et al. GRN and MAPT Mutations in 2 Frontotemporal Dementia Research Centers in Brazil. Alzheimer Dis Assoc Disord 2016;30:310–7. https://doi.org/10.1097/WAD.0000000000000153.
12. Fruijtier AD, Visser LNC, Bouwman FH, Lutz R, Schoonenboom N, Kalisvaart K, et al. What patients want to know, and what we actually tell them: The ABIDE project. Alzheimer's Dement Transl Res Clin Interv 2020;6. https://doi.org/10.1002/trc2.12113.
13. Phenwan T, Sixsmith J, McSwiggan L, Buchanan D. A narrative review of facilitating and inhibiting factors in advance care planning initiation in people with dementia. Eur Geriatr Med 2020;11:353–68. https://doi.org/10.1007/s41999-020-00314-1.
14. Gunderson CG, Bilan VP, Holleck JL, Nickerson P, Cherry BM, Chui P, et al. Prevalence of harmful diagnostic errors in hospitalised adults: A systematic review and meta-analysis. BMJ Qual Saf 2020;29:1008–18. https://doi.org/10.1136/bmjqs-2019-010822.

Expert essay

Progressive Supranuclear Palsy: clinical diagnosis

Leonardo Cruz de Souza,[1,2] Sarah Teixeira Camargos,[1,3] Paulo Caramelli,[1,2] Francisco Cardoso[1]

[1] School of Medicine, The Federal University of Minas Gerais, Belo Horizonte, MG, BRAZIL
[2] Cognitive and Behavioral Neurology Group, Neurology Service, The Federal University of Minas Gerais, Belo Horizonte, MG, BRAZIL.
[3] Movement Disorders Unit, Neurology Service, The Federal University of Minas Gerais, Belo Horizonte, MG, BRAZIL

Progressive Supranuclear Palsy (PSP) is a rare neurodegenerative disorder presenting with parkinsonism of insidious onset, other neurological features and progressive course. The incidence of PSP increases with age, and some studies suggest that men are more affected than women (1). Its prevalence varies across studies, ranging from 5 to 18 cases per 100,000 people (2). Despite its low prevalence, PSP is the most frequent cause of atypical parkinsonism.

Pathologically, PSP is a tauopathy classified as a form of frontotemporal lobe degeneration (2). A neuropathological exam usually reveals neurofibrillary tangles and/or neuropil threads in the brainstem and in the basal ganglia, usually associated to gliosis and neuronal loss (2).

PSP was first described by Steele, Richardson and Olszewski in 1964. Since then, it is recognised as a clinical syndrome with marked clinical heterogeneity (3). The original description is now referred as Richardson's syndrome (PSP-RS), which remains the most frequent phenotype (2,3). PSP-RS presents with early postural instability, vertical supranuclear gaze palsy, slow or hypometric saccades, levodopa-resistant bradykinesia, axial rigidity, dysarthria and dysphagia. The other associated phenotypes are PSP with predominant frontal presentation; PSP with corticobasal syndrome; PSP with predominant speech or language disorder; PSP with progressive gait freezing; PSP with predominant parkinsonism, and PSP with predominant cerebellar ataxia (3). This remarkable clinical heterogeneity represents a major diagnostic challenge, as the diagnosis of PSP may be confounded or overlap with other neurodegenerative disorders, such as Parkinson's disease, behavioural variant frontotemporal dementia, corticobasal syndrome and primary progressive aphasia.

In addition to motor features, PSP also presents with cognitive changes. Cognitive dysfunction in PSP has been classically described as a 'subcortical dementia', characterised by bradyphrenia and executive dysfunction due to frontal lobe involvement (4). However, more recently, it has been demonstrated that people with PSP have deficits in more complex cognitive abilities, such as conceptual thinking and social cognition (5,6).

In addition, people with PSP also have prominent behavioural changes. Apathy is the most frequent behavioural disorder, detected in up to 62% of people (7). Some symptoms related to frontal lobe dysfunction, such as eating disorders, impulsivity and stereotypic behaviour may also be observed (7).

The diagnosis is established on clinical grounds, according to the consensual diagnostic criteria proposed by the Movement Disorders Society (8) and requires detailed clinical history and neurological exam. Disease onset usually occurs at the seventh decade (1). People with PSP-RS report a history of recurrent, unprovoked falls and postural instability, which are present early in the disease course. Typically, they tend to fall backwards. They, as well as their carers, may also complain of cognitive and behavioural changes.

Careful neurological examination is the cornerstone of the diagnosis and usually demonstrates an abnormal response of postural reflexes. Other common findings are axial and symmetrical parkinsonism and pseudobulbar syndrome. The most typical feature of PSP-RS is the downward gaze palsy. Of note, it often appears after three or more years of disease onset. There are also other neuro-ophthalmological findings: slowing of saccades; reduced blinking; eyelid apraxia and blepharospasm. The vertical wrinkling of the forehead, known as the 'Procerus sign', is a clinical clue for the diagnosis of PSP, although it is not present in all people. Similarly, the 'applause sign' (the tendency to keep applauding after being instructed to only clap three times) may be observed in PSP people but lacks specificity (9).

Neuroimaging provides supportive evidence for the diagnosis, although these changes often appear late in the course of the disease. Structural brain magnetic resonance imaging (MRI) usually shows mild to moderate prefrontal atrophy, atrophy of the superior cerebellar peduncles, and marked midbrain atrophy. The latter, the most frequent sign on an MRI, is described as 'penguin', 'hummingbird' or a 'morning glory' sign. Notably, although rather specific, these findings lack sensitivity (2). Quantitative analysis of the pons: midbrain ratio increases the sensitivity to predict the diagnosis of PSP-RS (2).

Individuals with PSP usually exhibit impaired binding of pre-synaptic dopamine transporter in the striatum on functional imaging (1). However, this finding is also present in other parkinsonian disorders and is not useful for the differential diagnosis. On the other hand, there are no reliable wet biomarkers for PSP.

More recently, the advent of molecular neuroimaging (for example, positron emission tomography [PET]) with tau markers provide the in vivo pathophysiological diagnosis of tauopathy in people with different types of parkinsonism. However, while PET-tau is expensive and restricted to a few research centres, its clinical usefulness still lacks validation. In the perspective of disease-modifying treatments, it is possible that in vivo demonstration of tauopathy may be required as inclusion criteria for the selection of individuals in clinical trials.

PSP may be mistaken for other neurodegenerative diseases, especially in the initial stages, when the typical oculomotor features are lacking. The differential diagnosis may be a tough conundrum and involves Parkinson's disease and other forms of atypical parkinsonism, such as multiple system atrophy, corticobasal syndrome, dementia with Lewy bodies, and others. People with prominent behavioural symptoms may be misdiagnosed as behavioural variant frontotemporal dementia. Asymmetrical parkinsonism, absence of falls, psychosis and clinically relevant response to levodopa should lead to a reconsideration of the PSP diagnosis.

In summary, the diagnosis of PSP is based on accurate clinical history and neurological exam. Midbrain atrophy on structural brain MRI supports the diagnosis in suspected patients. The absence of reliable biomarkers and the clinical heterogeneity of PSP represent a diagnostic challenge. The next advances on biomarkers and molecular neuroimaging may provide valuable tools for the diagnosis and follow-up of people with PSP.

References

1. Donker Kaat L, Zheng Chiu W, J.W. Boon A, C. van Swieten J. Recent Advances in Progressive Supranuclear Palsy: A Review. Curr Alzheimer Res 2011;999:1–8. https://doi.org/10.2174/156721121225972050.
2. Boxer AL, Yu JT, Golbe LI, Litvan I, Lang AE, Höglinger GU. Advances in progressive supranuclear palsy: new diagnostic criteria, biomarkers, and therapeutic approaches. Lancet Neurol 2017;16:552–63. https://doi.org/10.1016/S1474-4422(17)30157-6.
3. Respondek G, Stamelou M, Kurz C, Ferguson LW, Rajput A, Chiu WZ, et al. The phenotypic spectrum of progressive supranuclear palsy: A retrospective multicenter study of 100 definite cases. Mov Disord 2014;29:1758–66. https://doi.org/10.1002/mds.26054.
4. Albert ML, Feldman RG, Willis AL. The 'subcortical dementia' of progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 1974;37:121–30.
5. Garcin B, Volle E, Funkiewiez A, Miller BL, Dubois B, Levy R. A mosquito bites and a butterfly flies: A specific response type of frontal patients in a similarity task. Neuropsychologia 2018;117:371–8. https://doi.org/10.1016/j.neuropsychologia.2018.06.022.
6. Toller G, Brown J, Sollberger M, Shdo SM, Bouvet L, Sukhanov P, et al. Individual differences in socioemotional sensitivity are an index of salience network function. Cortex 2018;103:211–23. https://doi.org/10.1016/j.cortex.2018.02.012.
7. Gerstenecker A, Duff K, Mast B, Litvan I. Behavioral abnormalities in progressive supranuclear palsy. Psychiatry Res 2013;210:1205–10. https://doi.org/10.1016/j.psychres.2013.08.045.
8. Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, et al. Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. Mov Disord 2017;32:853–64. https://doi.org/10.1002/mds.26987.
9. Schönecker S, Hell F, Bötzel K, Wlasich E, Ackl N, Süßmair C, et al. The applause sign in frontotemporal lobar degeneration and related conditions. J Neurol 2019;266:330–8. https://doi.org/10.1007/s00415-018-9134-y.

Expert essay

The silent minority of persons with Alzheimer-like symptoms but no amyloid build-up in their brain: what is their diagnosis?

Joseph Therriault,[1,2] Pedro Rosa-Neto,[1,2,3] Serge Gauthier[1,2,3]

[1] McGill Centre for Studies in Aging, Faculty of Medicine, McGill University, CANADA
[2] Department of Neurology & Neurosurgery, CANADA
[3] Department of Psychiatry, McGill University, CANADA

Introduction

Alzheimer's disease is defined by the accumulation of cerebral amyloid-β plaques and intracellular neurofibrillary tangles comprised of 3R+4R hyperphosphorylated tau (1), which are thought to lead to neurodegeneration. Accepted biomarker models of Alzheimer's disease derived from autosomal dominant (2) and sporadic (3) populations provide converging evidence that detectable amyloid-β abnormality precedes detectable tau abnormality by several years. Amyloid-β accumulation often occurs in the absence of symptoms, while the topographical distribution and magnitude tau accumulation and tau-mediated neurodegeneration are more closely related to the clinical presentation that characterises Alzheimer's disease. While details of the process remain poorly understood, multiple studies support the notion that elevated amyloid-β levels are required for the propagation of tau pathology from the medial temporal lobe to regions of the neocortex, associated with severe cognitive symptoms (4).

Multiple recent in vivo Alzheimer's disease biomarker studies support the notion that tau abnormality (T+) occurs almost exclusively in the presence of amyloid abnormality (A+) (5,6). T+ is more closely associated with N+ and with cognitive impairment. While the general pattern from these studies supports A+ as a requirement for T+, a non-negligible portion (generally <5%) of subjects are defined by elevated tau pathology (T+) without abnormal amyloid (A-) (5,6).

An especially interesting finding is the rare pattern of A-T+N+ in individuals who are diagnosed with probable Alzheimer's disease (6). According to 2018 NIA-AA criteria (1) as well as consensus neuropathological criteria for Alzheimer's disease (7), these individuals do not have Alzheimer's disease, which requires the presence of abnormal amyloid. An important question arises:

What is the diagnosis for individuals with the A-T+N+ profile and an Alzheimer phenotype?

The 2018 NIA-AA research framework for biological Alzheimer's disease labels the A-T+N+ biomarker profile in individuals with dementia as 'non-Alzheimer pathologic change with dementia'. This concept is supported by evidence that amyloid-β accumulation occurs years before tau and subsequent tau-mediated neurodegeneration (2,3).

If not Alzheimer's disease, where does the A-T+N+ biomarker profile point us to in cases of amnestic dementia? Several neuropathology studies have described a condition termed Neurofibrillary Tangle Predominant Dementia (NFTPD), characterised by neurofibrillary tangle accumulation (T+) in the absence of significant amyloid-beta plaques (A-), with a clinical phenotype that resembles probable Alzheimer's disease.

Outside of their different biomarker profiles, some differences exist between Alzheimer's disease and NFTPD which may give clues about its aetiology. People with NFTPD are generally older than people with Alzheimer's disease, their cognitive dysfunction is milder, their cognitive decline is typically slower, and they are very rarely APOE4

carriers (8). Autopsy studies suggest another important difference: aside from the absence of amyloid-β plaques, NFTs in NFTPD are more limited in both topography and magnitude than in Alzheimer's disease. NFTPD is characterised by extensive tau accumulation in allocortical regions, but only mild involvement of neocortical regions, typically extending only as far as Braak stages III or IV (8). In contrast, people with advanced Alzheimer's disease typically display tau accumulation in Braak stages V and VI.

Overall, NFTPD highlights important limitations of collapsing continuous biomarker measurements with topographical information into dichotomised categories. While they are T+, the milder spatial extent of their tauopathy suggests that it may not be identical to the T+ that characterises Alzheimer's disease. Furthermore, the lower magnitude of tau aggregation in this condition may indicate that despite surpassing a threshold for T+, the magnitude of tau pathology is not identical to what is observed in Alzheimer's disease.

Conceptual and methodological considerations

Despite differences in clinical and neuropathological data, it is difficult to conclude with certainty whether a biomarker profile of A-T+N+ equates with NFTPD in living individuals with amnestic dementia. One important possibility is that individuals with a A-T+N+ biomarker profile are not truly A-. For example, dichotomisation into positive/negative groups will by definition classify individuals just under the positive/negative threshold as negative. Despite the advantages of binary classification for diagnosis and clinical trial recruitment, binary cut points without biological bases may result in misclassifications. Correspondingly, it may be important to consider A biomarkers as continuous values in cases of suspected A-T+N+.

A related conceptual issue is that an A- status does not signify the absence of cerebral amyloid-β: rather, it signifies that this individual has not crossed a specific predetermined threshold of abnormality. It is conceivable that certain vulnerability factors in some individuals permit the Alzheimer's disease pathogenic process to unfold at lower concentrations of amyloid-β abnormality (9).

Remaining questions

A comprehensive understanding of A-T+N+ cases is limited by their low prevalence: estimates place NFTPD prevalence at between 0.7% and 5.8% of dementia cases (8), and population-based Alzheimer's disease biomarker studies estimate the prevalence of the A-T+N+ profile to be between 5–10% at age 80, with even lower prevalence at younger ages (10).

A number of questions remain unanswered. While A-T+N+ individuals will almost certainly not be eligible for anti-Aβ therapeutic trials, would they be eligible for anti-tau therapies? Special considerations of testing therapies in rare diseases may apply to these individuals.

Despite the limitations described above, Alzheimer's disease biomarkers are critical for separating individuals with the A-T+N+ profile accompanied by amnestic dementia from those with Alzheimer's disease. There is hope that given similar disease processes that anti-tau treatments designed for Alzheimer's disease may be beneficial to individuals with a A-T+N+ biomarker profile.

References

1. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's Dement. 2018;14(4):535–62.
2. Bateman RJ, Xiong C, Benzinger TLS, Fagan AM, Goate A, Fox NC, et al. Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease. N Engl J Med [Internet]. 2012;367(9):795–804. http://www.nejm.org/doi/abs/10.1056/NEJMoa1202753
3. Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013;12(2):207–16.
4. Jagust W. Imaging the evolution and pathophysiology of Alzheimer disease. Nat Rev Neurosci. 2018;
5. Jack CR, Wiste HJ, Botha H, Weigand SD, Therneau TM, Knopman DS, et al. The bivariate distribution of amyloid-$β$ and tau: relationship with established neurocognitive clinical syndromes. Brain. 2019;142(1):3230–42.
6. Therriault J, Pascoal TA, Benedet AL, Savard M, Chamoun M, Lussier F, et al. Frequency of biologically-defined AD in relation to age, sex, APOEε4 and cognitive impairment. Neurology. 2020;
7. Ball M, Braak H, Coleman P, Dickson D, Duyckaerts C, Gambetti P, et al. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. Neurobiol Aging. 1997;
8. Jellinger KA, Attems J. Neurofibrillary tangle-predominant dementia: Comparison with classical Alzheimer disease. Acta Neuropathol. 2007;113(2):107–17.
9. van der Kant R, Goldstein LSB, Ossenkoppele R. Amyloid-β-independent regulators of tau pathology in Alzheimer disease. Nat Rev Neurosci. 2020;21(1):21–35.
10. Jack CR, Wiste HJ, Weigand SD, Therneau TM, Knopman DS, Lowe V, et al. Age-specific and sex-specific prevalence of cerebral β-amyloidosis, tauopathy, and neurodegeneration in cognitively unimpaired individuals aged 50–95 years: a cross-sectional study. Lancet Neurol. 2017;16(6):435–44.

Expert essay

Dementia with Lewy Bodies

Ítalo Karmann Aventurato, Marcio L. F. Balthazar

Department of Neurology, University of Campinas, BRAZIL

Lewy bodies, an intracellular protein aggregate, were first described in the context of Parkinson's disease (1). Further studies revealed widespread cortical Lewy bodies in people presenting with progressive dementia (2). Due to its distinct clinical and pathologic findings, this form of dementia was proposed by Kosaka in 1976 to be a different cause of cognitive impairment (3,4), namely Lewy body disease. Later, this diagnostic category was recognised by the scientific community and came to be known as dementia with Lewy bodies (DLB).

Initially thought to be a rare cause of cognitive impairment, the discovery of α-synuclein (a protein) as the main component of Lewy bodies by Spillantini et al. in 1997 (5) as well as the development of α-synuclein immunohistochemistry staining (a way of visualizing the protein in the microscope) allowed greater sensitivity in the detection of the disease in post-mortem samples and revealed dementia with Lewy bodies to be the second most common cause of dementia (6).

Among people newly diagnosed with dementia, 3.1–7.1% fulfil the diagnostic criteria for dementia with Lewy bodies, with an overall incidence of 0.5–1.6 per 1000 person-years. Nonetheless, widespread cortical Lewy bodies can be found in 20–25% of the brains from people who died with dementia (7), as compared to 13.4% of those that died without cognitive impairment (8). These findings suggest that dementia with Lewy bodies may be underdiagnosed by current clinical criteria.

Diagnosis

Published in 2017, the Fourth consensus report of the dementia with Lewy bodies consortium establishes the current clinical criteria for the diagnosis and management of dementia with Lewy bodies (9), Table 1.

As an essential feature for the diagnosis of dementia with Lewy bodies, the person should be diagnosed with dementia, that is, a progressive cognitive decline that interferes with social and occupational functioning as well as activities of daily living. Other features include cognitive, psychiatric, motor and other symptoms and are classified as either core or supportive clinical features. Biomarkers (either imaging or laboratory exams) may further contribute to the diagnosis.

In summary, distinctive characteristics of dementia with Lewy bodies include but are not limited to fluctuating cognition; visual hallucinations; rapid eye movement (REM) sleep behaviour disorder; and parkinsonism (either bradykinesia, manifesting with slow and decreasing intentional movements, muscle rigidity or rest tremor). These will be further characterised in the following paragraphs.

Cognitive and neuropsychiatric symptoms

In contrast with Alzheimer's disease-related cognitive impairment, memory is relatively preserved in early disease. Cognitive decline is mostly seen regarding attention (such as being unable to follow a film or TV series), executive function (for example, loss of multitasking skills) and visuospatial skills (such as difficulties parking a car, more frequent GPS use, 'missing' the chair when sitting). The presence of fluctuations, waxing-and-waning, variable attention and cognitive activity in early stages is a core feature of dementia with Lewy bodies. These may present as spells of altered attention, incoherent speech, daytime sleepiness or staring into space with variable duration from minutes to hours, occurring rarely at first then increasing up to a daily basis.

Visual hallucinations, like seeing people, children and small animals, is commonly observed in the early stages and is also a hallmark of dementia with Lewy bodies (9). Later in the disease course, delusions (irrational, fixed beliefs) may become more prominent and disabling, often with paranoid content (10).

Changes in sleep should also be noted, as violent movements, agitation and shouting during sleep are the key symptoms of the REM sleep behaviour disorder. This is a very frequent phenomena in people with dementia with Lewy bodies and may predate the cognitive impairment by years (11). Although a bed partner report of violent behaviour and shouting is highly suggestive of this disorder, a polysomnographic study is needed for diagnostic confirmation (9).

Apathy, depression and anxiety are common symptoms in dementia with Lewy bodies and may be present before characteristic symptoms and cognitive decline (11).

Parkinsonism

Bradykinesia (slow body movements), muscle rigidity and resting tremor, as seen in Parkinson's disease, are also core features in dementia with Lewy bodies. However, unlike Parkinson's disease, these present concurrently or after the cognitive symptoms, usually isolated (that is either bradykinesia, rigidity or tremor) and symmetrically, affecting left and right limbs at the same time and with the same intensity (9).

Posture and gait difficulties are present during the disease course and occur earlier than seen in Parkinson's disease. Along with visuospatial disturbances and postural hypotension (as described in the upcoming sections), these features increase the risk of falling for people, potentially causing significant distress and clinical deterioration (12).

Dysautonomia symptoms

The loss of control over bodily functions, medically defined as dysautonomia, is an important phenomenon in dementia with Lewy bodies. Some of these symptoms may occur early in the disease course, such as constipation, and others are usually a concern in advanced stages, such as orthostatic hypotension (an abrupt decrease in blood pressure after one stands) and urinary incontinence (10).

Treatment

Currently, no treatment is available to cure dementia with Lewy bodies or to control the underlying process causing the disease. Nonetheless, pharmacological and non-pharmacological therapies may offer relief to the most distressing symptoms (13).

Pharmacological treatment

The use of acetylcholinesterase inhibitors, a group of medications for the treatment of Alzheimer's disease, has been shown to ameliorate cognitive performance and slow its decline. Among those, rivastigmine and donepezil have been studied in double-blind randomised trials with positive results (14).

Neuropsychiatric symptoms such as hallucinations and delusions are best treated by optimising the use of the drugs mentioned above. However, residual symptoms may persist and, in these cases, some antipsychotic drugs, namely quetiapine and clozapine, may be used with caution. Other antipsychotics, especially typical ones such as haloperidol, severely exacerbate parkinsonian symptoms and are contraindicated. Pimavanserin, a novel drug for the treatment of neuropsychiatric symptoms in Parkinson's disease, has been proposed as an alternative in people with dementia with Lewy bodies (15).

Other symptoms are treated similarly as with other diseases, such as with the use of blood-pressure raising medications in orthostatic hypotension, anti-depressants for anxiety and depressive symptoms (14).

Non-pharmacological treatment

Most studies have shown benefits with non-pharmacological approaches to dementia with Lewy bodies. Low cost and low likelihood of side effects make the use of some of these approaches very reasonable (15),

Carer education is fundamental in dementia. Plain language orientation regarding possible symptoms, disease progression and potential complications should always be available to carers. Special aspects of the disease, such as visuospatial impairment, posture instability and orthostatic hypotension, should be emphasised as they predispose the person to preventable burden.

Table 1. dementia with Lewy bodies clinical criteria (adapted from (9))

Essential: Dementia

Core clinical features:

- Fluctuating cognition with pronounced variations in attention and alertness
- Recurrent visual hallucinations
- REM sleep behaviour disorder
- Parkinsonism

Supportive clinical features:

- Severe sensitivity to antipsychotics
- Postural instability
- Repeated falls
- Syncope
- Severe autonomic dysfunction
- Increase somnolence
- Loss of the sense of smell
- Other hallucinations
- Delusions
- Apathy, depression, anxiety

Task-oriented occupational therapy, through motor practice and task adaptation, may enhance and slow the loss of fundamental abilities, such as activities of daily living. Supervised exercises and physical therapy reduce motor function decline, including gait and postural instability (15).

Prognosis

Cognitive decline seems to be faster in dementia with Lewy bodies than in Alzheimer's disease (16). As a consequence, quality of life in people with dementia with Lewy bodies is substantially decreased (17) and carer burden increased (18) when compared to their Alzheimer's disease counterparts.

Hospital admissions are also more frequent in dementia with Lewy bodies, mainly due to falls, pneumonia and cognitive fluctuations, frequently misinterpreted as delirium (19). Mortality is increased compared to the general population, with almost 4 times greater risk of death and an average survival of 4.7 years after diagnosis (20).

References

1. Lewy F. Paralysis agitans. 1. Pathologische Anatomie. Paralys Agit. 1912;920.
2. Okazaki H, Lipkin LE, Aronson SM. Diffuse intracytoplasmic ganglionic inclusions (Lewy type) associated with progressive dementia and quadriparesis in flexion. J Neuropathol Exp Neurol. 1961;20(2):237–44.
3. Kosaka K, Oyanagi S, Matsushita M, Hori A, Iwase S. Presenile dementia with Alzheimer-, Pick- and Lewy-body changes. Acta Neuropathol. 1976;36:3.
4. Kosaka K, editor. Dementia with Lewy Bodies [Internet]. Dementia with Lewy Bodies [Internet]. Tokyo: Japan; 2017 [citedJun 16]. Springer; 2017. http://link.springer.com/10.1007/978-4-431-55948-1.
5. Spillantini MG, Schmidt ML, Lee VMY, Trojanowski JQ, Jakes R, Goedert M. α-synuclein in Lewy bodies [8]. Nature. 1997;388(6645):839–40.
6. Hogan DB, Fiest KM, Roberts JI, Maxwell CJ, Dykeman J, Pringsheim T, et al. The prevalence and incidence of dementia with Lewy bodies: A systematic review. Can J Neurol Sci. 2016;43(S1):S83–95.
7. Galasko D. Lewy Body Disorders. Neurol Clin. 2017;35(2):325–38.
8. Bennett DA, Schneider JA, Arvanitakis Z, Kelly JF, Aggarwal NT, Shah RC, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology. 2006 Jul;66(12):1837–44.
9. McKeith IG, Boeve BF, DIckson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies [Internet]. Vol. 89, Neurology. Neurology; 2017 [cited 2021 Jul 13]. p. 88–100. https://pubmed.ncbi.nlm.nih.gov/28592453/.
10. Dementias GSNLB. Dementia With Lewy Bodies and Parkinson Disease Dementia. Contin Lifelong Learn NeurolApr; 2016;22:2.
11. McKeith IG, Ferman TJ, Thomas AJ, Blanc F, Boeve BF, Fujishiro H, et al. Research criteria for the diagnosis of prodromal dementia with Lewy bodies. Neurology. 2020;94(17):743–55.
12. Sanford A. Lewy Body Dementia. Clin Geriatr Med. 2018;34(4):603–15.
13. Sezgin M, Bilgic B, Tinaz S, Emre M. Parkinson's Disease Dementia and Lewy Body Disease. Semin Neurol. 2019;39(2):274–82.
14. Taylor JP, McKeith IG, Burn DJ, Boeve BF, Weintraub D, Bamford C, et al. New evidence on the management of Lewy body dementia. Lancet Neurol. 2020;19(2):157–69.
15. Connors MH, Quinto L, Mckeith I, Brodaty H, Allan L, Bamford C, et al. Non-pharmacological interventions for Lewy body dementia: A systematic review. Psychol Med. 2018;48(11):1749–58.
16. Kramberger MG, Auestad B, Garcia-Ptacek S, Abdelnour C, Olmo JG, Walker Z, et al. Long-Term Cognitive Decline in Dementia with Lewy Bodies in a Large Multicenter, International Cohort. Vol. 57, Journal of Alzheimer's Disease. 2017.
17. Boström F, Jönsson L, Minthon L, Londos E. Patients with dementia with Lewy bodies have more impaired quality of life than patients with Alzheimer disease. Alzheimer Dis Assoc Disord. 2007;21(2):150–4.
18. Ricci M, Guidoni SV, Sepe-Monti M, Bomboi G, Antonini G, Blundo C, et al. Clinical findings, functional abilities and caregiver distress in the early stage of dementia with Lewy bodies (DLB) and Alzheimer's disease (AD). Arch Gerontol Geriatr. 2009;49(2):49.
19. Murman DL, Kuo SB, Powell MC, Colenda CC. The impact of parkinsonism on costs of care in patients with AD and dementia with Lewy bodies. Neurology. 2003;61(7):944–9.
20. Savica R, Grossardt BR, Bower JH, Ahlskog JE, Boeve BF, Graff-Radford J, et al. Survival and causes of death among people with clinically diagnosed Synucleinopathies with parkinsonism: A population-based study. JAMA Neurol. 2017;74(7):839–46.

Expert essay

Alzheimer's disease: separating the clinical from the biological

Joseph Therriault,[1,2] Pedro Rosa-Neto,[1,2,3] Serge Gauthier[1,2,3]

[1] McGill Centre for Studies in Aging, Faculty of Medicine, McGill University, CANADA
[2] Department of Neurology & Neurosurgery, CANADA
[3] Department of Psychiatry, McGill University, CANADA

Introduction

The field of Alzheimer's disease research has undergone important conceptual changes in recent years, guided by the evolving understanding of Alzheimer's disease biology. This article will briefly review previous definitions of Alzheimer's disease before describing the current conceptualisation as a biological entity characterised by the accumulation of amyloid-β plaques and tau neurofibrillary tangles.

The first diagnostic criteria for Alzheimer's disease were introduced in 1984 (1). In the 1984 framework, individuals who had progressive memory impairment that led to dementia (without other attributable causes) were labelled as 'probable Alzheimer's disease'. Definitive diagnosis could only be given at autopsy in the presence of amyloid-β plaques and tau neurofibrillary tangles. While the 'probable Alzheimer's disease' diagnosis was associated with higher sensitivity and specificity for amyloid-β plaques and tau neurofibrillary tangles at autopsy, imperfect agreement between the two assured the need for the 'probable' term to be applied to living individuals, though it was often omitted (2).

Revisions in 2011, commissioned by the National Institute of Aging (NIA) and the Alzheimer's Association (AA), retained the core clinical features of probable Alzheimer's disease from 1984 and the notion of Alzheimer's disease as a clinico-pathological entity (3). Importantly, following the progress in research of other neurodegenerative diseases that resulted in dementia, Alzheimer's disease dementia was separated from all-cause dementia. The 2011 framework also integrated advances in in vivo biomarkers of amyloid-β and neurodegeneration, which could be used to support the clinico-pathological relationships.

In 2014, the International Working Group (IWG), an independent group of researchers, described Alzheimer's disease as a combination of clinical symptoms (amnestic dementia or a non-amnestic 'atypical' phenotype) in combination with biomarker evidence of Alzheimer's disease pathology (4). Thus, Alzheimer's disease remained an entity defined by symptoms, with biomarkers used to support the diagnosis.

In 2018, following rapid advances in tau biomarkers (specifically tau-PET), the NIA-AA revised its research framework to diagnose Alzheimer's disease based on the concurrent presence of both abnormal amyloid-β and tau biomarkers, regardless of cognitive symptoms (5). Therefore, the 2018 framework extends the neuropathological definition of Alzheimer's disease in place since the 1990s (6) by applying in vivo biomarkers of amyloid-β and tau to living individuals. In the recent biological research framework, individuals can be grouped according to their Amyloid-β/Tau/Neurodegeneration [A/T/(N)] biomarker status. A and T are biomarkers considered specific to Alzheimer's disease, while the (N) is stylised in parentheses to denote the fact that it is also a feature of other neurodegenerative diseases. In the 2018 framework, the 'probable Alzheimer's disease' clinical presentation of progressive amnestic multidomain cognitive impairment resulting in dementia is now termed 'Alzheimer Clinical Syndrome' (5).

Advantages of a biological framework

The immediately obvious advantage of the transition to a biological research framework is that Alzheimer's disease is now specific to a biological process, and not a set of clinical symptoms.

Multiple neurodegenerative processes can result in a clinical presentation that resembles the Alzheimer's disease phenotype; this is part of what makes an accurate Alzheimer's disease diagnosis based on clinical symptoms so challenging. Adopting a consistent biological definition of the disease helps ensure that different research groups are indeed discussing the same thing. The alternative clinical definition of progressive amnestic multidomain cognitive impairment collapses many different disease processes into one term. In fact, the 'probable Alzheimer's disease' clinical syndrome can be caused by other diseases. Differentiating

Alzheimer's disease from these other conditions will also allow for the recognition and treatment of other causes of cognitive decline.

A second important advantage of the biological research framework is that Alzheimer's disease can now be studied in asymptomatic persons. The abnormal protein accumulation that characterises biological Alzheimer's disease takes place over a longer time frame (estimated 10–20 years) than the time frame of Alzheimer's disease symptoms (4–8 years). There is hope that targeting biological Alzheimer's disease during the preclinical phase will result in better outcomes than the multiple trials conducted in individuals with symptomatic Alzheimer's disease.

Criticisms of the biological Alzheimer's disease framework

A common criticism levied against the biological definition of Alzheimer's disease is that biomarkers are either expensive, unavailable, or both. This is a fair criticism that reflects deeply rooted inequities in the access to medical care and systematic inequalities in healthcare technology. While this criticism is legitimate, the hope is that developments in blood-based biomarkers of Alzheimer's disease (7) will allow for Alzheimer's disease biomarker studies to be conducted at lower costs and without the need for highly specialised equipment.

Another criticism raised against the biological definition of Alzheimer's disease is that amyloid-β plaques and tau neurofibrillary tangles often occur in individuals without cognitive impairment, and therefore should not be used to define a disease. While it is correct that biological Alzheimer's disease can be detected in individuals without overt cognitive symptoms, this observation helps identify individuals at risk for the development of cognitive symptoms, with the hope of treating Alzheimer's disease before symptoms develop. Preclinical Alzheimer's disease (abnormal levels of amyloid-beta and tau in the absence of clinical symptoms) can be considered analogous to preclinical disease in other areas of medicine.

A third important criticism of the Alzheimer's disease biological framework is that it does not include other common pathologies. Again, while this is correct, it is important to emphasise that other pathologies such as vascular pathology, alpha synuclein, TDP-43 pathology, or processes such as neuroinflammation, do not define Alzheimer's disease among other neurodegenerative diseases. Moreover, biomarkers for these other processes await further validation.

Current applications

Informed by a biological framework for studying Alzheimer's disease, some clinical trials are recruiting individuals not based on the presence of amnestic dementia, but rather on abnormal levels of amyloid-β as determined by amyloid-PET (8). These studies, designed to lower concentrations of cerebral amyloid-β, are thought to have increased chances of meeting primary endpoints because the trials include individuals who stand to benefit from anti-Aβ therapies. Moreover, the biological Alzheimer's disease framework allows for the disambiguation of Alzheimer's clinical syndrome into different diseases which have the same symptoms but different biomarker profiles. Finally, it is crucial to emphasise that the current conceptualisation of Alzheimer's disease as a biological entity is to guide research and is not intended to have clinical applications at this time.

References

1. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of alzheimer's disease: Report of the NINCDS-ADRDA work group* under the auspices of department of health and human services task force on alzheimer's disease. Neurology 1984. https://doi.org/10.1212/wnl.34.7.939.
2. Knopman DS, Petersen RC, Jack CR. A brief history of 'Alzheimer disease': Multiple meanings separated by a common name. Neurology 2019;92:1053–9. https://doi.org/10.1212/WNL.0000000000007583.
3. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement 2011;7:263–9. https://doi.org/10.1016/j.jalz.2011.03.005.
4. Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing research diagnostic criteria for Alzheimer's disease: The IWG-2 criteria. Lancet Neurol 2014;13:614–29. https://doi.org/10.1016/S1474-4422(14)70090-0.
5. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's Dement 2018;14:535–62. https://doi.org/10.1016/j.jalz.2018.02.018.
6. Ball M, Braak H, Coleman P, Dickson D, Duyckaerts C, Gambetti P, et al. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. Neurobiol Aging 1997. https://doi.org/10.1016/S0197-4580(97)00057-2.
7. Karikari TK, Pascoal TA, Ashton NJ, Janelidze S, Benedet AL, Rodriguez JL, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. Lancet Neurol 2020;19:422–33. https://doi.org/10.1016/S1474-4422(20)30071-5.
8. Sperling RA, Rentz DM, Johnson KA, Karlawish J, Donohue M, Salmon DP, et al. The A4 Study: Stopping AD Before Symptoms Begin? Sci Transl Med 2014;6:228fs13--228fs13. https://doi.org/10.1126/scitranslmed.3007941.

Expert essay

Spectrum of Alzheimer's disease and the need for post-mortem examination

Raj N Kalaria,[1] Rufus Akinyemi[2]

[1] Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UNITED KINGDOM
[2] Neuroscience and Ageing Research Unit, Institute for Advanced Medical Research and Training, College of Medicine, University of Ibadan, NIGERIA

Early diagnosis of Alzheimer's disease is a key issue in the global fight against dementia. Numerous efforts are being made to search for reliable biomarkers for the accurate diagnosis of clinically defined Alzheimer's disease. Despite variability in clinical presentations of Alzheimer's disease and confounding atypical symptoms, biomarkers are necessary to improve the overall diagnosis as well as accelerate the development of effective disease-modifying treatments. To improve the definition and understand the progression of Alzheimer's disease at the forefront, body fluids including plasma and cerebrospinal fluid (CSF) are being extensively screened to monitor hallmark protein components of biologically defined Alzheimer's disease pathology, namely amyloid β (Aβ) and τau. Current developments suggest four fluid-based biomarkers are essential to indicate brain changes in the Alzheimer's disease process (1). These are the ratio of Aβ 42 to 40 amino acid peptides, a marker of plaque pathology, total-tau and phosphorylated tau (T-τau and P-τau, respectively), markers of Alzheimer's disease-related changes in τau metabolism, phosphorylation and secretion; and neurofilament light (NfL), a marker of neurodegeneration. Recent technological advances have enabled these to be measured in blood samples besides the cerebrospinal fluid. Remarkably, there is reasonable agreement between Alzheimer's disease proteins, or fragments thereof measured in cerebrospinal fluid and plasma, and the degree of pathology found at post-mortem. cerebrospinal fluid Aβ42, when used together with Aβ40 or P-τau, to predict the subsequent development of Alzheimer's disease dementia in people with mild cognitive impairment (MCI) with high accuracy (2,3). Even more remarkably, plasma P-τau 181 can predict specific Alzheimer's disease neuropathology years before post-mortem confirmation, thus supporting the use of this marker for prognosis in primary care and recruitment for clinical trials (4). Nevertheless, the widespread application as well as the sensitivity of these assays remain a challenge. Easily accessible and cost-effective blood-based biomarkers detecting the same Alzheimer's disease pathologies may revolutionise the diagnostic workup of Alzheimer's disease globally. Could it be as easy as testing fasting blood for sugar levels to confirm diabetes? Time will tell.

Neuroimaging has been earnestly used to demonstrate structural and functional changes associated with Alzheimer's disease. Different imaging modalities in the brain as well as retina have been used to scrutinise clinical criteria. The radiolabelled Pittsburgh compound B (PiB) is now widely used as a tracer for positron emission tomography (PET) imaging to demonstrate the presence of cerebral Aβ in the living brain as an indicator of the presence of Alzheimer's disease pathology. Similarly, ligands for the microtubule associated protein τau to demonstrate neurofibrillary pathology are also being used, but these latter advancements are still largely being properly evaluated. The specificity and sensitivity for Aβ or PiB PET are probably at their best, but several nagging concerns remain. For example, up to 20% of cognitively normal older individuals may retain substantial levels of PiB although current analysis shows on the whole baseline PiB positive status is associated with increased risk of cognitive impairment in healthy elderly and people with mild cognitive impairment(4). Conversely, up to 20% of clinically diagnosed dementia or Alzheimer's disease cases can be Aβ negative. These may also comprise various other types of dementias, including those primarily with vascular dementia. Post-stroke dementia was thought to uncover Alzheimer's disease-type of syndromes but just 20% of stroke survivors retain high enough levels of PiB to diagnose Alzheimer's disease in stroke people who developed dementia but in reality have mixed dementia (5).

Studies comparing clinical diagnoses with autopsy diagnoses indicate that, even at specialised memory or dementia clinics, up to 30% of people fitting into currently used clinical criteria for the diagnosis of Alzheimer's disease may be misdiagnosed. Similarly, the accuracy of clinical diagnosis seems even lower for other dementias, including dementia with Lewy bodies, frontotemporal dementia and vascular dementia. Frequencies of misdiagnosis are even greater in

general practice clinics handling primary care. Diagnosis of Alzheimer's disease in people with self-reported memory problems or with reported mild cognitive impairment can be highly heterogeneous although as many as 50% of people with mild cognitive impairment could have incipient Alzheimer's disease. However, the underlying aetiology is difficult to determine in these without screening for other biomarkers. This is further complicated by the fact that recent neuroimaging and pathological studies have suggested the existence of at least three distinct variants of Alzheimer's disease (6,7). These include the typical, limbic predominant and hippocampal sparing Alzheimer's disease types and there is likely a posterior cortical variant.

Despite refinements in criteria and use of more biomarkers, there is a cause for concern for the low accuracy of clinical diagnosis of Alzheimer's disease in predicting underlying characteristic brain pathology. For example, from 2005–2010, clinicopathological studies of the NACC database showed that in some 919 clinically diagnosed Alzheimer's disease cases, 25% did not match Alzheimer's disease pathological diagnosis. The sensitivity ranged 71–87% and the specificity 44–71%. Sensitivity was generally increased with more liberal clinical criteria and specificity was increased with more stringent criteria, but interestingly the opposite was true when neuropathological criteria were applied (8). When a clinical diagnosis was not confirmed by the minimum degree of Alzheimer's disease pathology, the most frequent primary neuropathological diagnoses were tangle-only dementia or argyrophilic grain disease, frontotemporal lobar degeneration, cerebrovascular disease, Lewy body disease and hippocampal sclerosis. When dementia was not clinically diagnosed as Alzheimer's disease, ~40% of the cases met or exceeded the minimum threshold levels of Alzheimer's disease pathology. In a recent analysis by Kalaria, Penantian and Hase (unpublished observations) of the NACC database, from a total of 14,131 cases of clinically diagnosed Alzheimer's disease, only 72% were confirmed pathologically with Braak staging (neurofibrillary pathology) V and VI. The remaining cases met various pathological diagnoses including vascular dementia. This shows that there is a 30% risk of including people living with Alzheimer's disease without the pathology of interest in clinical trials and estimates for epidemiological studies.

While misdiagnosis and overdiagnosis is a concern that may be resolved in the future with possible precision medicine or management, there is an urgent need for investigation of dementias which are Aβ negative or those that bear features of Alzheimer's disease syndrome. Such investigation could prove important to fill knowledge gaps in the entire spectrum of dementia. Thus, clinicians and ancillary medical discipline colleagues can encourage collection of such cases for biorepositories. There is an absolute need for brain tissues from individuals suffering from various types of disorders. However, we also need to know the norm. Thus, there is an urgent need for brain donations from healthy ageing individuals who might have lived a physically balanced life but may still have been afflicted by age-related problems.

“While misdiagnosis and overdiagnosis is a concern that may be resolved in the future with possible precision medicine or management, there is an urgent need for investigation of dementias which are Aβ negative or those that bear features of Alzheimer's disease syndrome.

Without doubt, the current knowledge of the spectrum of dementia has come from post-mortem examination and brain banking. For example, we would not be at this juncture if amyloid material or fibrils were not first extracted from cerebral vessels retained at post-mortem from individuals with Alzheimer's disease. Without the sequenced Aβ peptide(s) or A4 peptide, we could not have advanced in the neurobiology of Alzheimer's disease evident today. Brain banks have been important biorepositories of central nervous system tissue. They store research samples of whole brains, biopsies and spinal cord, and body fluids including cerebrospinal fluid and blood. Brain banking is a rapidly developing field of science with a promising future of enabling research to bring creative solutions on board for central nervous system disorders through collection, characterisation, management, and accessibility of human brain tissue for analysis (9). The majority of these are established in high income countries with well-connected networks in North America, Europe, Australasia and SE Asia/Pacific with recent efforts also emerging in developing regions including Africa (10). However, international collaboration among brain banks can foster networking, interactions among researchers, standardisation of criteria and protocols as well as access to diverse tissue samples for robust research. This has the potential to engage in cutting-edge translational research which can lead to personalised (or precision) medicine globally.

References

1. Zetterberg H, Blennow K. Moving fluid biomarkers for Alzheimer's disease from research tools to routine clinical diagnostics. Mol Neurodegener 2021;16:10. https://doi.org/10.1186/s13024-021-00430-x.
2. Mattsson N, Lonneborg A, Boccardi M, Blennow K, Hansson O. Geneva Task Force for the Roadmap of Alzheimer's B. Clin Validity Cerebrospinal Fluid Abeta 2017;42:196–213.
3. Hansson O, Seibyl J, Stomrud E, Zetterberg H, Trojanowski JQ, Bittner T, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimer's Dement 2018;14:1470–81. https://doi.org/10.1016/j.jalz.2018.01.010.
4. Hansson O. Biomarkers for neurodegenerative diseases. Nat Med 2021;27:954–63. https://doi.org/10.1038/s41591-021-01382-x.
5. Mok V, Leung EYL, Chu W, Chen S, Wong A, Xiong Y, et al. Pittsburgh compound B binding in poststroke dementia. J Neurol Sci 2010;290:135–7. https://doi.org/10.1016/j.jns.2009.12.014.
6. Murray ME, Graff-Radford NR, Ross OA, Petersen RC, Duara R, Dickson DW. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: A retrospective study. Lancet Neurol 2011;10:785–96. https://doi.org/10.1016/S1474-4422(11)70156-9.
7. Whitwell JL, Dickson DW, Murray ME, Weigand SD, Tosakulwong N, Senjem ML, et al. Neuroimaging correlates of pathologically defined subtypes of Alzheimer's disease: A case-control study. Lancet Neurol 2012;11:868–77. https://doi.org/10.1016/S1474-4422(12)70200-4.
8. Beach TG, Monsell SE, Phillips LE, Kukull W. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005-2010. J Neuropathol Exp Neurol 2012;71:266–73. https://doi.org/10.1097/NEN.0b013e31824b211b.
9. Kliouеva N, Bovenberg J, Huitinga I. Banking brain tissue for research. Handb Clin Neurol 2018;145:9–12. https://doi.org/10.1016/B978-0-12-802395-2.00002-X.
10. Akinyemi RO, Salami A, Akinyemi J, Ojagbemi A, Olopade F, Coker M, et al. Brain banking in low and middle-income countries: Raison D'être for the Ibadan Brain Ageing, Dementia And Neurodegeneration (IBADAN) Brain Bank Project. Brain Res Bull 2019;145:136–41. https://doi.org/10.1016/j.brainresbull.2018.08.014.

Conclusions

There is a need for longitudinal follow-up of people with a dementia diagnosis not only for the comprehensive management of their condition, but also to reassess the diagnosis which may change over time. Clinicians are advised to be on the lookout for new symptoms and physical signs that may indicate a co-morbid event such as a stroke, but also a change of perspective on the cause of the dementia.

There may be rare circumstances where the initial diagnosis of dementia is no longer appropriate, since the person's symptoms have resolved. The term 'pseudo-dementia' can be found in the older medical literature. This should not be considered a misdiagnosis but rather a natural evolution of symptoms explained by reversible causes such as depression, substance abuse, or a systemic disorder.

As more and more biological characterisations of the probable cause of dementia takes place using biomarkers, people who appear to have Alzheimer's disease but are amyloid negative will need closer follow-up to clarify the underlying cause of their condition, which may alter prediction for progression and treatments.

Additional references

1. Little MO. Reversible Dementias. Clin Geriatr Med. 2018;34(4):537-62. https://www.ncbi.nlm.nih.gov/pubmed/30336987
2. Day GS. Reversible Dementias. Continuum (Minneap Minn). 2019;25(1):234-53. https://www.ncbi.nlm.nih.gov/pubmed/30707195
3. Ryan DH. Misdiagnosis in dementia: Comparisons of diagnostic error rate and range of hospital investigation according to medical speciality. International Journal of Geriatric Psychiatry. 1994;9(2):141-7. https://onlinelibrary.wiley.com/doi/abs/10.1002/gps.930090208
4. Slavin MJ, Sachdev PS, Kochan NA, Woolf C, Crawford JD, Giskes K, et al. Predicting Cognitive, Functional, and Diagnostic Change over 4 Years Using Baseline Subjective Cognitive Complaints in the Sydney Memory and Ageing Study. Am J Geriatr Psychiatry. 2015;23(9):906-14. https://www.ncbi.nlm.nih.gov/pubmed/25441053.
5. Rohrer JD, Isaacs AM, Mizielinska S, Mead S, Lashley T, Wray S, et al. C9orf72 expansions in frontotemporal dementia and amyotrophic lateral sclerosis. The Lancet Neurology. 2015;14(3):291-301. https://pubmed.ncbi.nlm.nih.gov/25638642/.
6. Sikora J, Stein C, Ubellacker D, Walker A, Tippett DC. Longitudinal decline in spoken word recognition and object knowledge in primary progressive aphasia. Medicine (Baltimore). 2021;100(22):e26163. https://www.ncbi.nlm.nih.gov/pubmed/34087875.
7. Kertesz A, Blair M, McMonagle P, Munoz DG. The diagnosis and course of frontotemporal dementia. Alzheimer Dis Assoc Disord. 2007;21(2):155-63. https://www.ncbi.nlm.nih.gov/pubmed/17545742.
8. Woodward M, Jacova C, Black SE, Kertesz A, Mackenzie IR, Feldman H, et al. Differentiating the frontal variant of Alzheimer's disease. Int J Geriatr Psychiatry. 2010;25(7):732-8. https://www.ncbi.nlm.nih.gov/pubmed/19823987.
9. Sakae N, Josephs KA, Litvan I, Murray ME, Duara R, Uitti RJ, et al. Neuropathologic basis of frontotemporal dementia in progressive supranuclear palsy. Mov Disord. 2019;34(11):1655-62. https://www.ncbi.nlm.nih.gov/pubmed/31433871.

Part V
Particular circumstances

Chapter 18
Limited access to healthcare resources

José A. Morais

Key points

- Low- and middle-income countries face a greater challenge making the diagnosis of dementia in a timely fashion due to human and technological restrictions.
- Well-structured virtual educational programmes may facilitate quick dissemination to the public about dementia risk factors and warning signs.
- Data gathering on the prevalence of dementia is a crucial step to inform stakeholders.
- Formulation of policies and national dementia strategies are needed to improve diagnostics and the living condition of people with dementia in all countries.

General background

From a global perspective, dementia has no boundaries, and it does not discriminate. It affects people of every gender, culture, ethnicity, religion, citizenship, sexual orientation and ability. It does not have any preference when it comes to geographical location, be it remote and uncrowded or urban and densely populated. It affects individuals from all levels of education, professional and work backgrounds as well as financial status.

When it comes to accessing healthcare resources for dementia, there are, however, many boundaries in place around the world: a lack of awareness about the signs and symptoms of the disease; resource-poor countries; transportation systems; language barriers; specialised healthcare experts and diagnostic tools; health insurance; access to free public healthcare and/or financial assistance, home care support services and residential long-term care. The recent COVID-19 pandemic has also highlighted the important role that modern day technology such as cellular phones, iPads and computers play in a restriction-bound environment. Unfortunately, millions of people around the world may not have the privilege to own such resources nor have access to them.

The ever-evolving progression of dementia demands that the person living with the illness, as well as their carers, have access to healthcare resources. By the time the disease has evolved to its full manifestation, the majority of people will require full-time care. There is currently no universal public healthcare system in the world that can provide all of the components needed to respond to this reality. As a result, care management and decision-making responsibilities fall squarely into the hands of the carers. Sadly, the numerous boundaries highlighted above can make a significant difference in a person's quality of life, the individual living with dementia as well as that of their carer. This is a direct outcome of whether they have access to essential healthcare resources.

> **From a global perspective, dementia has no boundaries, and it does not discriminate. It affects people of every gender, culture, ethnicity, religion, citizenship, sexual orientation and ability.**

Two of the essays below present the challenges that people from rural, low- and middle-income countries face when dealing with a dementia diagnosis while the third one is dedicated specifically to the diagnostic issues faced in Africa.

Expert essay

Dementia diagnosis in rural areas

Huali Wang

Dementia Care and Research Center, Peking University Institute of Mental Health, Beijing, CHINA

An estimated 55 million people worldwide have dementia, and this number is projected to increase with the growth of the ageing population. In contrast to the enormous number of people living with dementia, diagnostic coverage for dementia is estimated to be only 5–10% in low- and middle-income countries (1). The situation is even worse in rural areas (2). Globally, a large percentage of the population resides in rural areas. Delineating the sociocultural and biological barriers, and exploring the solutions for access to care, are essential steps to address the health disparity in the timely diagnosis of dementia in rural areas.

In rural communities, early dementia diagnosis may be impeded by numerous factors, including cultural obstacles, scarcity of professionals, inadequate access to memory clinics and support services, and geographic distancing.

In rural areas, families may attribute symptoms of dementia to the process of ageing. A multi-centre survey conducted in city-based memory clinics found that seeking diagnosis was delayed for an average of two years from the time families observed symptoms of dementia (3). The delay may be even longer than that, as symptoms may have been dismissed. Some families considered symptoms as something to be ashamed of (4). They would prefer to cover up the problems associated with dementia. Cultural values of resilience and independence can be barriers to seeking mental health services in these areas (5). The values of self-reliance and independence may contribute to health service underutilisation among rural carers of people living with dementia. Families tend to seek help when people living with dementia present prominent behavioural problems and cause difficulties in managing their personal lives. Another common belief that dementia cannot be cured may contribute to the nihilism among older adults and family carers in rural areas. The concerns of cognitive symptoms and the post diagnosis care may influence the actions of seeking a diagnosis (6).

Globally, the number of healthcare workers specialising in dementia is limited, especially within rural communities. Among the underrepresented population, 85% of dementia diagnosis was made by nondementia specialist physicians.

In rural communities, early dementia diagnosis may be impeded by numerous factors, including cultural obstacles, scarcity of professionals, inadequate access to memory clinics and support services, and geographic distancing.

The use of dementia specialty care was low, particularly for Hispanics and Asians (7). Nurses may also play significant roles in the diagnostic periods for people with early-stage cognitive impairment (6). Most healthcare workers regarded memory loss as part of the normal ageing process in rural areas and reported that it does not need any specific treatment. Other healthcare workers could recognise signs and symptoms of dementia but focused on managing other medical problems at the expense of assessing cognitive decline and mental health (8).

In addition, healthcare workers in rural areas have not received specific training on assessing and diagnosing dementia. Lack of knowledge regarding appropriate diagnostic tools among these healthcare professionals may reinforce the challenges of dementia diagnosis. Healthcare workers with specialised training are more likely to use neuropsychological tests, blood tests, urine tests, and brain imaging to diagnose dementia. In contrast, healthcare workers without specific training assessed and diagnosed dementia based on history and physical examination alone (8), even though screening instruments, such as AD8, community screening instrument – dementia (CSI-D), Mini-cog, Rowland Universal Dementia Assessment Scale (RUDAS), have been validated to be applicable for people with different schooling levels (9–12). Compared with dementia specialists, nondementia specialists are more likely to use 'unspecified' dementia diagnoses (7). Sometimes, city-based clinicians who have limited experience with older immigrants may experience difficulties assessing

dementia due to language barriers and difficulties related to the involvement of the family or an interpreter (4). These factors may also impede the early detection and diagnosis of dementia and its aetiological subtype.

'Our village doctor is only responsible for minor physical problems. They never diagnose dementia in practice. If an older adult cannot manage his or her daily living, he or she has to be cared for by family members. We all know he or she has dementia. Very few of them are brought to city hospitals because there is no medicinal cure for the disease. Sometimes, when experts from big cities come and provide consultation in city hospitals, these patients might be brought to the clinic for further check-up and advice on medications.'

A retired 72-year-old woman with middle-school education, living in the village for ten years.

Memory clinics are considered the optimal setting for dementia diagnosis. Currently, most memory clinics are in urban areas (13). Access to memory clinics may be restricted by geographic distancing. Transportation challenges may become barriers to accessing dementia services. Also, when older adults are referred to memory clinics in cities, they may not be familiar with test situations of cognitive assessment. What's more, a lack of continuity and poor information exchange in the chain of care seem to reinforce the challenges of dementia diagnosis in rural areas (4).

Additionally, underserved populations are less likely to receive a timely diagnosis of mild cognitive impairment (14). One of the reasons is that the assay for Alzheimer's disease biomarkers is not well accepted. The situation is similar in rural areas where the infrastructure is lacking. MRI scanners are not available in rural health and often people referred for a scan must travel to city hospitals. People are also concerned with the idea of a lumbar puncture (15), especially those living in rural areas. Some even believe that cerebrospinal fluid is the essence of the mind, and extraction of it may make cognitive function worse. These misconceptions about biomarker examinations may further account for the underdiagnosis of dementia in rural areas, especially for mild cognitive impairment.

'Our hospital plans to set up a memory clinic. However, we find that there is a great shortage of professionals to provide service. We will send young doctors to a well-known memory centre for further training on assessment, diagnostic, and treatment algorithms. In our city, there are only two scanners installed in the general hospitals. Our hospital is a psychiatric hospital. Although we see a lot of elderly patients, MRI scanning is not a routine examination for diagnosis. Lumbar puncture is not routinely performed. We do not know that it could support dementia diagnosis. Another challenge is that family members of the patients may consider it harmful for the mind. We need more education on using biomarkers for dementia diagnosis'.

A psychiatric hospital director in a low-resource city, where older patients are usually referred.

References

1. Alzheimer's Disease International (ADI). World Alzheimer Report 2011: The benefits of early diagnosis and intervention. World Alzheimer Report 2011. 2011.
2. Chen R, Hu Z, Chen RL, Ma Y, Zhang D, Wilson K. Determinants for undetected dementia and late-life depression. Br J Psychiatry. 2013;203(3):203–8.
3. Zhao M, Lv X, Tuerxun M, He J, Luo B, Chen W, et al. Delayed help seeking behavior in dementia care: Preliminary findings from the Clinical Pathway for Alzheimer's Disease in China (CPAD) study. Int Psychogeriatrics. 2016;28(2):211–9.
4. Sagbakken M, Spilker RS, Nielsen TR. Dementia and immigrant groups: a qualitative study of challenges related to identifying, assessing, and diagnosing dementia. BMC Health Serv Res. 2018 Dec;18(1):910.
5. Caxaj CS. A Review of Mental Health Approaches for Rural Communities: Complexities and Opportunities in the Canadian Context. Can J Community Ment Heal. 2016;34(September):29–45.
6. Mattos MK, Nilsen ML, Lingler JH. Experiences Surrounding an Early-Stage Cognitive Diagnosis in Rural-Dwelling Older Adults. Res Gerontol Nurs. 2018 Jul;11(4):181–9.
7. Drabo EF, Barthold D, Joyce G, Ferido P, Chang Chui H, Zissimopoulos J. Longitudinal analysis of dementia diagnosis and specialty care among racially diverse Medicare beneficiaries. Alzheimer's Dement. 2019 Nov;15(11):1402–11.
8. Kamoga R, Rukundo GZ, Wakida EK, Nakidde G, Obua C, Buss SS. Dementia assessment and diagnostic practices of healthcare workers in rural southwestern Uganda: a cross-sectional qualitative study. BMC Health Serv Res. 2019 Dec;19(1):1005.
9. Xie Y, Gao Y, Jia J, Wang X, Wang Z, Xie H. Utility of AD8 for cognitive impairment in a chinese physical examination population: A preliminary study. Sci World J. 2014;2014(1):3–7.
10. Prince M, Acosta D, Ferri CP, Guerra M, Huang Y, Jacob KS, et al. A brief dementia screener suitable for use by non-specialists in resource poor settings-the cross-cultural derivation and validation of the brief Community Screening Instrument for Dementia. Int J Geriatr Psychiatry. 2011;26(9):899–907.
11. Brodaty H, Connors H. Screening for Dementia in Primary Care : A Comparison of the GPCOG and the MMSE. 2016;2052:323–30.
12. Nielsen TR, Jørgensen K. Cross-cultural dementia screening using the Rowland Universal Dementia Assessment Scale: A systematic review and meta-analysis. Int Psychogeriatrics. 2020;
13. Wang H, Xie H, Qu Q, Chen W, Sun Y, Zhang N, et al. The continuum of care for dementia: needs, resources and practice in China. J Glob Health. 2019 Dec;9(2):020321.
14. Tsoy E, Kiekhofer RE, Guterman EL, Tee BL, Windon CC, Dorsman KA, et al. Assessment of Racial/Ethnic Disparities in Timeliness and Comprehensiveness of Dementia Diagnosis in California. JAMA Neurol. 2021;94158(6):657–65.
15. Aldayel AY, Alharbi MM, Almasri MS, Alkhonezan SM. Public knowledge and attitude toward lumbar puncture among adults in Riyadh, Saudi Arabia: A cross-sectional study. SAGE Open Med. 2019;7:205031211987106.

Expert essay

Estimating prevalence of dementia in low- and middle-income countries

Nicolas Farina,[1] Cleusa P. Ferri[2]

[1] Brighton and Sussex Medical School, UNITED KINGDOM
[2] Universidade Federalde Sao Paulo, BRAZIL

It is widely acknowledged that dementia is underdiagnosed in many low- and middle-income countries (1,2), and when diagnosis does take place, it is typically many years after its onset. This is due to many complex reasons, including lack of knowledge about the condition, fear of diagnosis, and nihilism. While these barriers are not country specific, within low- and middle-income countries, dementia diagnosis occurs in the context of having under-resourced healthcare systems, lack of trained healthcare professionals, and inequalities to access of care. The inability to receive a clinical diagnosis prevents people from receiving treatment and care, while denying them the recognition that there is a medical explanation to their impairment. Another consequence of underdiagnoses is our inability to rely on health service statistics of dementia to be an accurate reflection of those living with the condition in many low- and middle-income countries.

Researchers internationally have made great strides in developing our understanding of dementia prevalence in low- and middle-income countries, with previous iterations of the World Alzheimer Report contributing to the synthesis and interpretation of the literature (3–5). Such reviews highlight that there are still many low- and middle-income countries that have limited or no estimates of dementia prevalence, and therefore it is important to fill these gaps, even if incrementally. Importantly, we should recognise that countries (like the term 'low- and middle-income countries') are not homogeneous groups. Factors such as ethnicity, sex and education levels may all play a part in the risk of dementia, and hence recruiting participants from a single region may prevent us from making generalisations within and between countries. Brazil is a good example of this, where the majority of dementia prevalence estimates are derived from samples originating almost exclusively from the South East region (6).

Accurate estimates of dementia prevalence in individual country settings are essential, primarily because they can shine a light on the size of the problem, but also act as the foundation for other estimates of incidence, mortality, costs and care needs. In addition, there is an inherent value of being able to highlight local data to policymakers, maximising potential buy-in while minimising the potential disregard of evidence because it is not relevant. International cross-country initiatives such as the 10/66 Dementia Research Group project, the HCAP Network-Harmonized Cognitive Assessment Protocol and the STRiDE project – Strengthening responses to dementia in developing countries (STRiDE)[i] aims to generate meaningful data to inform a country's dementia policies.

STRiDE has developed a pragmatic approach to estimating the prevalence of dementia. One of the key strategies to achieve this is by adopting a diagnostic approach that is not reliant on clinicians. Instead, trained researchers would use a standardised set of cognitive and functional measures, and dementia prevalence estimates would be calculated using a validated algorithm. This should not be viewed as unreasonable, considering that dementia (and its subtypes) is regularly clinically diagnosed by symptoms alone. STRiDE has opted for the use of the brief 10/66 algorithm, which has identified potential cases of dementia in line with clinical diagnosis, across a range of settings with little evidence of cultural or education bias (7,8). However, STRiDE also goes far beyond just identifying how many people might have dementia, and instead seeks to understand how dementia impacts people's lives in low- and middle-income countries. This means that instead of being primarily focused on cognitive outcomes and factors that potentially have led to an increased risk of dementia, the project is interested in how people are living with dementia now. The merit of such an approach is that it adds value when engaging with policymakers about the need for support for people with dementia, demonstrating the profound impact of dementia within the context of a given country. This includes quality of life, general (or physical) health, elder abuse and experienced stigma, but also carer burden, financial impact and services accessed. STRiDE

i For more information about STRiDE please visit www.stride-dementia.org

is due to collect prevalence data in Indonesia and South Africa (pandemic dependent), although the methodology and tools used within the project will be widely shared to enable other countries to replicate or adapt this model.

Despite fantastic initiatives already existing, it is important that countries continue to invest in the accurate monitoring and estimation of dementia prevalence to ensure resources are properly directed to meet the needs of those living with dementia and their carers.

References

1. Nakamura AE, Opaleye D, Tani G, Ferri CP. Dementia underdiagnosis in Brazil [Internet]. Vol. 385, The Lancet. Elsevier; 2015 [cited 2021 Jul 8]. p. 418–9. http://www.thelancet.com/article/S0140673615601532/fulltext
2. Alzheimer's Disease International. World Alzheimer Report 2016. Improving healthcare for people with dementia. London, UK; 2016.
3. International AD. World Alzheimer's Report 2013: An analysis of long term care for dementia [Internet]. 2013 [cited 2021 Jul 1]. https://www.alz.co.uk/research/WorldAlzheimerReport2013.pdf
4. Alzheimer's Disease International. World Alzheimer's Report 2015: The Global Impact of Dementia. London, UK; 2015.
5. International AD. World Alzheimer Report. 2009 [cited 2021 Jul 8]; www.deutsche-alzheimer.de
6. Farina N, Ibnidris A, Alladi S, Comas-Herrera A, Albanese E, Docrat S, et al. A systematic review and meta-analysis of dementia prevalence in seven developing countries: A STRiDE project. Glob Public Health [Internet]. 2020 [cited 2021 Jul 8];15(12):1878–93. https://pubmed.ncbi.nlm.nih.gov/32658604/
7. Abdin E, Vaingankar JA, Picco L, Chua BY, Prince M, Chong SA, et al. Validation of the short version of the 10/66 dementia diagnosis in multi-ethnic Asian older adults in Singapore. BMC Geriatr [Internet]. 2017 Apr 21 [cited 2021 Jul 8];17(1). https://pubmed.ncbi.nlm.nih.gov/28431511/
8. Stewart R, Guerchet M, Prince M. Development of a brief assessment and algorithm for ascertaining dementia in low-income and middle-income countries: The 10/66 short dementia diagnostic schedule. BMJ Open [Internet]. 2016 [cited 2021 Jul 8];6(5). https://pubmed.ncbi.nlm.nih.gov/27225649/

Expert essay

Early diagnosis of dementia: a complex problem requiring a multidimensional approach for India

Suvarna Alladi,[1] Jayeeta Rajagopalan[2]

[1] Professor of Neurology, National Institute of Mental Health and Neurosciences [NIMHANS], INDIA
[2] Early Career Researcher, Strengthening Responses to Dementia in Developing Countries [STRiDE], National Institute of Mental Health and Neurosciences [NIMHANS], INDIA

Early diagnosis of dementia is crucial for providing care to persons with dementia and their families. In diverse and low- and middle-income countries like India, the diagnostic journey is complex and often fraught with numerous challenges. From being a relatively unknown disease a few decades ago, dementia has now become a major source of disability. A rise in life expectancy has contributed to a high burden of dementia in India. This rise, however, has not been met with a proportionate increase in awareness or availability of healthcare services. The lack of awareness, stigmatising attitudes towards persons with dementia, and the absence of a coordinated system of care in India are major barriers to receiving a dementia diagnosis. This significantly impacts quality of life of persons with dementia and their families.

It is estimated that 5.29 million people are living with dementia in India currently (1). However, only 1 in 10 people with dementia receive any diagnosis, treatment, or care (2). In the majority of cases, families do not look for help, waiting until significant behavioural disturbances emerge in order to seek care. Even when support is sought, the type of healthcare service that families look for substantially influences the possibility of receiving an early diagnosis or a diagnosis at all. Health-seeking behaviours in India are highly heterogeneous, varying across geographic areas, socioeconomic groups and influenced significantly by the availability and accessibility of services within a given region. In rural India, families from lower-socioeconomic groups may communicate concerns to a community health worker or visit a traditional medical practitioner. In urban areas where there is a larger concentration of private hospitals, the well-educated are likely to visit their general physician, or directly consult a specialist for a diagnosis due to the absence of a structured referral system. This diversity in health seeking behaviours contributes to a large proportion of people with dementia falling through the gaps, continuing to remain undetected and undiagnosed. Therefore, there is a need to improve care coordination between modern and traditional health systems, strengthen referral networks within the existing public health infrastructure, create effective partnerships between private and public health sectors and develop a multi-level feedback loop that allows for tertiary level specialist centres to support service delivery for complex conditions like dementia.

Another significant concern that impacts dementia diagnosis in India is that only specialists like neurologists, psychiatrists or geriatricians are currently trained to diagnose and manage dementia. Dementia is not emphasised in the undergraduate medical degree curriculum. In addition, very few multidisciplinary memory clinics exist throughout the country (1). In this context, of considerable shortage of specialists and limited expertise, general physicians can play a crucial role in recognising dementia.

The process of making a dementia diagnosis in itself is multifaceted and requires a comprehensive understanding of cognitive, behavioural and functional deficits that involve the use of standardised tests. The majority of tests have been developed for use in predominantly English speaking and formally educated people. In countries like India that are characterised by linguistic diversity and educational heterogeneity, diagnosis requires availability of culturally appropriate tools. Screening tools to diagnose dementia have been adapted (3) and the Indian Council of Medical Research-Neuro Cognitive Tool Box (ICMR-NCTB) (4) has been developed in many Indian languages and for people who are illiterate/low literate. There are also efforts to implement physician training modules to diagnose and manage dementia. Training cadres of community/lay health workers to identify and/or screen for dementia can also be an effective way to address specialist shortages and reduce underdiagnosis, particularly in underserved areas. Such task-shifting strategies have been trialled for mental health conditions in India (5,6) and have demonstrated relative success. The accurate diagnosis of dementia also involves use of laboratory investigations and brain imaging to determine the subtype of dementia and detect reversible causes such as nutritional deficiencies, stroke and thyroid diseases

that are still common in India. Biomarker-based diagnosis of dementia is frequently advocated in developed countries but poses challenges for widespread implementation in India due to a lack of availability, costs and requirement of expertise for interpretation (7).

The costs involved in the diagnostic process are sizeable and present as another major obstacle to receiving a diagnosis, especially for low- and middle-income families. Substantial distances to facilities, long waiting times and overcrowding further deter an individual or their family members from seeking help. In addition, costs associated with diagnostics and indirect costs result in significant out-of-pocket payments.

Indeed, out-of-pocket payments is the major contributor of healthcare expenditure in India (8) and social protection mechanisms to cover costs encountered are therefore essential. The Ayushman Bharat scheme – a national government health insurance scheme to support the economically disadvantaged focuses significantly on hospitalisation. However, the government is working towards strengthening primary care services by transforming existing infrastructure into Health and Wellness centres. These centres will include provision of elder care services as well as cover costs for essential drugs and diagnostics. This is a step forward towards universal health coverage, and the future of this scheme relies significantly on overcoming challenges that hamper effective implementation.

The COVID-19 pandemic has further complicated dementia diagnosis due to the implementation of widespread infection-prevention measures and a system overwhelmed with COVID-19 related care. While constant efforts were made by hospitals and NGOs like Alzheimer's and Related Disorders Society of India (ARDSI) to reach out to families both in-person and through telemedicine (9,10), there are substantial concerns on how to ensure people with dementia do not go undetected as the current pandemic continues, or in the event of future health emergencies.

Dementia diagnosis in India remains a complex problem, influenced by several factors ranging from low awareness, infrastructure gaps and costs associated with help-seeking. Concentrated efforts need to be taken to address these vulnerabilities in our health system, and placing people with dementia and their families at the centre of these efforts is crucial. Strategies that take into account the diverse and low-resource nature of such settings is a way forward to facilitate early and accurate diagnosis of dementia and ensuring they receive the care they need.

References:

1. Alzheimer's and Related Disorder's Society of India. Dementia India Report. 2010. Available at: http://ardsi.org/downloads/main report.pdf
2. Nulkar A, Paralikar V, Juvekar S. Dementia in India – a call for action. J Glob Heal Reports 2019;3. https://doi.org/10.29392/joghr.3.e2019078.
3. Ganguli M, Ratcliff G, Chandra V, Sharma S, Gilby J, Pandav R, et al. A hindi version of the MMSE: The development of a cognitive screening instrument for a largely illiterate rural elderly population in india. Int J Geriatr Psychiatry 1995;10:367–77. https://doi.org/10.1002/gps.930100505.
4. Iyer GK, Paplikar A, Alladi S, Dutt A, Sharma M, Mekala S, et al. Standardising Dementia Diagnosis across Linguistic and Educational Diversity: Study Design of the Indian Council of Medical Research-Neurocognitive Tool Box (ICMR-NCTB). vol. 26. Cambridge University Press;26(2): 172-86; 2020. https://doi.org/10.1017/S1355617719001127.
5. Nimgaonkar AU, Menon SD. A task shifting mental health program for an impoverished rural Indian community. Asian J Psychiatr 2015;16:41–7. https://doi.org/10.1016/j.ajp.2015.05.044.
6. Buttorff C, Hock R, Weiss H, Naik S, Araya R, Kirkwood B, et al. Economic evaluation of a task-shifting intervention for common mental disorders in India. Bull World Health Organ 2012;90:813–21. https://doi.org/10.2471/blt.12.104133.
7. Sathianathan R, Kantipudi S. The dementia epidemic: Impact, prevention, and challenges for India. Indian J Psychiatry 2018;60:165–7. https://doi.org/10.4103/psychiatry.IndianJPsychiatry_261_18.
8. National Health Systems Resource Centre. National Health Accounts Estimates for India (2015-16). Ministry of Health and Family Welfare. 2018. Available from: https://main.mohfw.gov.in/sites/default/files/NHA_Estimates_Report_2015-16_0.pdf
9. Rajagopalan J, Arshad F, Hoskeri RM, Nair VS, Hurzuk S, Annam H, et al. Experiences of people with dementia and their caregivers during the COVID-19 pandemic in India: A mixed-methods study. Dementia Aug 2021. https://doi.org/10.1177%2F14713012211035371
10. Rajagopalan J, Hurzuk S, Arshad F, Alladi S, Dm MD. The COVID-19 Long-Term Care situation in India International Long-Term Care Policy Network, CPEC-LSE, 30th May 2020.

Expert essay

The challenges of diagnosing dementia in Africa[i]

Rufus O. Akinyemi,[1,2] Olabode O. Oguntiloye[1]

[1] Department of Neurology, University College Hospital, Ibadan, NIGERIA
[2] Neuroscience and Ageing Research Unit, Institute for Advanced Medical Research and Training, College of Medicine, University of Ibadan, NIGERIA

Introduction

There is a huge gap between the current rate of diagnosis of dementia in Africa compared to the World Health Organization's Global action plan on dementia target of diagnosing at least 50% of those living with dementia in 50 countries at the minimum by 2025 (1). In fact, it is estimated that up to 75% of those living with dementia globally have not been diagnosed and no doubt most of these people live in low- and middle-income countries (2) including African countries. The rate of diagnosis of dementia in low- and middle-income countries is estimated to be less than 10%. This is especially worrisome as the elderly population is increasing in Africa. The reasons for this alarming underdiagnosis are many, and they include, little knowledge and understanding of symptoms and signs of dementia, odd beliefs and stigmatisation of those living with dementia, poor health-seeking behaviour, lack of diagnostic tools and services, language barriers, reluctance on the part of health workers to diagnose a disease with enormous burden that has no cure, poor access to neurology and geriatric specialists, poor awareness and insufficient support services post diagnosis (3–6).

Little knowledge of the symptoms of dementia

In a questionnaire survey from eastern Africa assessing the knowledge of undergraduate students (going through various health programmes) on dementia, it was reported that up to 53.4% believed that memory loss was only an ageing phenomenon (3). Furthermore, the study showed that 32% of the students had poor knowledge of dementia, 41% had moderate knowledge, leaving only 26.8% with good knowledge (3). Even among healthcare workers, some believe that 'memory loss' is part of the normal ageing process that requires no specific treatment (6). The inadequate awareness of dementia in the general population is a barrier to a timely visit to the hospital for prompt and proper diagnosis of cognitive impairment and dementia.

Odd beliefs and stigmatisation of people with symptoms of dementia

A systematic review of contemporary views on dementia in sub-Saharan Africa revealed that some people believe that dementia is related to witchcraft; some believe it is a curse from God or ancestors, while others belief it is a curse from the devil (7). Another systematic review from sub-Saharan Africa demonstrated that these weird beliefs strongly influence people's perception of dementia and other mental health disorders (8). No doubt, these 'supernatural' concepts or beliefs fuel stigmatisation and discrimination against the people living with dementia. Although higher levels of education appear to reduce discrimination against people with dementia, other individuals, despite their educational attainment in healthcare, may still hold tenaciously to odd beliefs regarding dementias (8).

Reluctance of health workers to diagnose dementia

Healthcare workers are important in the diagnostic process of dementia but unfortunately, there is a high level of apathy and reluctance among many, either due to the level of their training, perception about the disease, ignorance of the modalities available to make a diagnosis, or the fact that there is no cure for dementia. In a study assessing the diagnostic practices with regards to dementia among healthcare workers, it was observed that only healthcare workers with specialised training could confidently make a clinical diagnosis of dementia using history-taking, neuropsychiatric

i ROA is supported by the UK Royal Society/African Academy of Sciences FLAIR Grants FLR/R1/191813 and FCG/R1/201034, and GCRF Networking Grant from the UK Academy of Medical Sciences and Global Brain Health Institute/Alzheimer's Association/Alzheimer's Society UK Grant GBHI ALZ UK-21-724204 as well as grant U01HG010273 from the National Institutes of Health (NIH), USA as part of the H3Africa Consortium.

exam, and relevant investigations. Other healthcare workers may be able to recognise signs and symptoms of dementia, but focus instead on managing other medical problems and disregard the assessment of cognitive decline and mental health since they are not confident in making the diagnosis of dementia (6).

Poor health-seeking behaviour

The health-seeking behaviour of a population is determined by various factors which vary somewhat from one region to another in Africa. Very important among these factors are level of education, religious beliefs, socioeconomic status, gender, age, family size, and availability of healthcare services. Another important factor that perpetuates poor health-seeking behaviour is the inability to pay for healthcare services, since most people pay out-of-pocket due to low coverage of health insurance schemes (9). Generally, those with low level education, low economic status, large family sizes are less likely to seek medical care when ill. This low drive to seek medical care is worse when it has to do with a disease that is perceived to be age-related or alluded to spiritual attack, such as dementia.

Lack of culturally appropriate diagnostic tools and facilities, and trained personnel

In Africa, cognitive tools are often influenced by educational status, language differences and cultural beliefs. There is also a lack of diagnostic facilities, including neuroimaging which is sometimes needed for accurate phenotyping. Facilities dedicated to the care of people living with dementia are also inadequate when compared to the Western world where there are memory clinics and specialised diagnostic centres with diagnostic services and post diagnosis care (1). This is so crucial among those who reside in rural settings who have to travel long distances to access healthcare. Few healthcare workers have acquired knowledge and skills to function as specialists in neurology, geriatrics, psychiatry and other important aspects of healthcare to cater to the needs of people living with dementia.

Poor awareness and insufficient support services post diagnosis

A good number of healthcare workers across Africa are not aware of any support services that people with dementia can be enrolled in to continue their care. This is due to the level of training acquired and information available to most healthcare workers who are not specialists, as the level of advocacy for those living with dementia in Africa is quite low compared to high-income countries. The support services available to people living with dementia are also quite insufficient. This might be the reason why most people living with dementia who initially accessed care at a hospital in Eastern Africa ended up in the religious and traditional homes after two encounters there, due to lack of skill to manage their condition and low improvement in quality of life (10).

Summary

There is a need for training and retraining of healthcare workers, development of simple diagnostic tools and tests that are resistant to the influence of language and education, advocacy in the society to support people living with dementia, and formulation of policies and national dementia strategies that will improve diagnostics and the living condition of those living with dementia across African countries.

References

1. Guerchet M, Mayston R, Lloyd-Sherlock P, Prince M, Aboderin I, Akinyemi R, et al. Dementia in Sub-Saharan Africa: Challenges and opportunities. Alzheimer Disease International. LondonSep; Alzheimer's Disease International (ADI); 2017. 1–69 p.
2. International AD. Dementia statistics [Internet]. Available from; [cited 2021 Jun 28]. https://www.alzint.org/about/dementia-facts-figures/dementia-statistics/
3. Musoke P, Olum R, Kembabazi S, Nantaayi B, Bongomin F, Kaddumukasa M. Assessment of the Knowledge and Attitude Towards Dementia Among Undergraduate University Students in Uganda. Adv Med Educ Pract. 2021;Volume 12:635–46.
4. George-Carey R, Adeloye D, Chan KY, Paul A, Kolčić I, Campbell H, et al. An estimate of the prevalence of dementia in Africa: A systematic analysis. J Glob Health [Internet]. 2012 Dec;2(2):2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3529309/
5. Giebel C. 'current dementia care: What are the difficulties and how can we advance care globally?' BMC Health Serv Res. 2020;20(1):20.
6. Kamoga R, Rukundo GZ, Wakida EK, Nakidde G, Obua C, Buss SS. Dementia assessment and diagnostic practices of healthcare workers in rural southwestern Uganda: a cross-sectional qualitative study. BMC Health Serv Res. 2019 Dec;19(1):1005.
7. Brooke J, Ojo O. Contemporary views on dementia as witchcraft in sub-Saharan Africa: A systematic literature review. J Clin Nurs. 2020;29(1–2):20–30.
8. Spittel S, Maier A, Kraus E. Awareness challenges of mental health disorder and dementia facing stigmatisation and discrimination: A systematic literature review from Sub-Sahara Africa. J Glob Health [Internet]. 2019 Oct;9(2):30. http://www.jogh.org/documents/issue201902/jogh-09-020419.htm
9. Latunji OO, Akinyemi OO. Factors Influencing Health-Seeking Behaviour Among Civil Servants in Ibadan, Nigeria. Ann Ibadan Postgrad Med [Internet]. 2018;16(1):52–60. http://www.ncbi.nlm.nih.gov/pubmed/30254559%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC6143883
10. Kakongi N, Rukundo GZ, Gelaye B, Wakida EK, Obua C, Okello ES. Exploring pathways to Hospital Care for Patients with Alzheimer's disease and related dementias in rural South Western Uganda. BMC Health Serv Res. 2020;20(1):20.

Conclusions

There are some great equalisers in life that make us realise that no matter who or where we are, we are more alike than we are different. Dementia is one of those equalisers. An estimated 55 million people worldwide have dementia, and that number continues to grow every day. It is a condition that does not care about gender, culture, ethnicity, religion, citizenship or sexual orientation. It pays no heed to education, achievements, contributions or how much money a person has. In essence, it is impervious to anything that makes you… you.

However, when delving a little deeper, you come to understand that things are not created equal after all. For people in low- and middle-income countries, and in rural areas, dementia falls prey to an often understaffed or underfunded healthcare system that does not provide enough access, nor adequate dementia training or dementia-centric care management and support. When coupled with people's lack of awareness of the signs; language barriers that impede critical testing; cultural biases that make one want to hide symptoms; reluctance to travel long distances for medical appointments; and a lack of facilitating modern technology, a person may be far advanced in their condition and consequently have a significantly diminished quality of life.

In Africa, in addition to the constraints listed above, cultural beliefs about dementia, stigmatisation, a reluctance by healthcare workers to diagnose dementia and a lack of tools to do so adequately remain key challenges. STRiDE – strengthening responses to dementia in developing countries – has developed a new pragmatic approach that does not rely on clinicians. Rather, trained researchers will use a standardised set of cognitive and functional measures to estimate dementia prevalence. It is a step in the right direction as countries need to invest in the development of resources to support dementia diagnosis and care.

Chapter 19
Low education

José A. Morais

Key points

- The diagnosis of cognitive impairment and dementia can be challenging but the circumstances of low-educated individuals amplifies the difficulties.
- A modified, patient-centric approach to the assessment is needed among such populations.
- A variety of specific cognitive tests have been developed and are available to assist clinicians in the diagnosis of dementia.

General background

Cognitive impairment and dementia are on the rise due largely to the ageing of the population. Among the most consistent factors associated with the maintenance of cognitive function is education, likely through an effect of increased cognitive reserve. This refers to the actual differences in cognition that may increase one's tolerance of age-related changes and disease related to pathology. In this regard, all efforts should be made to encourage young generations to continue their education for the longest time possible. The reality is that low education and illiteracy are very prevalent global issues, especially in low- and middle-income countries. This poses specific challenges when assessing the possibility of cognitive impairment.

As examined in the essay below by Nitrini and Brucki, many adjustments and considerations would need to be made to the current standard assessment tools, including developing and defining the psychometrics of some specific ones.

Expert essay

How to assess the possibility of dementia in people with low education or illiteracy

Ricardo Nitrini,[1] Sonia Maria Dozzi Brucki[2]

[1] Department of Neurology, Faculdade de Medicina, Universidade de São Paulo, São Paulo, BRAZIL
[2] Department of Neurology, Hospital Santa Marcelina, São Paulo, BRAZIL

Low education is still a widespread condition in less developed countries and among immigrants in developed countries. Low education is one of the main non-genetic risk factors for dementia, mainly due to low cognitive reserve.

There are still 781 million illiterate adults in the world (1). Many other individuals have learned to read or write but cannot use these abilities to follow a written command or write a simple message. In a Brazilian study, when using the short version of the Test of Functional Health Literacy in Adults, functional illiteracy was detected in 92.5% of the individuals who completed three years of schooling or less, whereas 54.7% of those with 4 to 7 years of education had an inadequate performance (2).

First attempts to diagnose dementia in low-educated individuals

The initial efforts involved decreasing the cut-off score of the usual tests, such as the Mini-Mental State Exam (MMSE) (3). This test is still widely used globally, but the MMSE has several hindrances for low-educated individuals including counting or spelling backwards as well as writing and reading. The now widely used MoCA test is considered even more inappropriate for low-educated individuals.

Other test batteries were designed for diagnosing dementia in low-educated individuals. Two of the most well-known are the RUDAS (Rowland Universal Dementia Assessment Scale) (4) and CASI-S (Cognitive Abilities Screening Instrument-Short Form) (5).

The RUDAS has been used in a variety of sociocultural backgrounds and translated into many languages. It consists of six items: body orientation, praxis, drawing, judgment, memory, and language. The pooled sensitivity was 82% and specificity of 83% for dementia detection, with low or no influence of educational level (4).

The CASI-S is a short test developed to evaluate low-educated individuals. It includes the following subtests: registration of three words, temporal orientation, verbal fluency (four-legged animals in 30 seconds) and recall of the three words. It was influenced by the education level in Brazil, although it does not require reading, writing, drawing, or calculating. But it is easy and brief to use in clinical settings (5).

The main limitation of these tests is a unique score, with no division by domains with differentiated scores.

Diagnosis of dementia at any educational level

The diagnosis of all-cause dementia is characterised by a decline in at least two domains in the cognitive or behavioural (neuropsychiatric) function that interferes with functional activities and is not explained by major psychiatric disorder or delirium (6). Both history-taking from the individual and a knowledgeable informant as well as an objective cognitive assessment should be used (6).

Personal experience with a test designed for low-educated individuals

In the early 1990s, we realised that the tests used in centres from the developed world were not appropriate for the population of older adults that came to our hospital. We designed the Brief Cognitive Screening Battery (7,8), which contains the Figure Memory Test (FMT), (link available in reference 8).

A sheet of paper with ten black and white drawings of simple objects is presented to the individual, who should identify and name the objects (without having been told that they needed to be memorised). Then the sheet of paper is removed from view, and the individual is asked to remember the figures. Two other similar attempts are done, but in these instances, the person is asked to memorise the figures. The last recall is a measure

of encoding or learning. After two interference tests, semantic verbal fluency (animals in one minute) and clock-drawing test (CDT), delayed recall (without cues) is evaluated. Finally, the ability to recognise the ten previously shown figures among 20 figures (with ten distractors) is assessed.

This test takes about 8 minutes to be administered to a healthy volunteer and does not have a total score, but it can diagnose impairments of memory, language, executive functions, and visuospatial abilities.

The delayed recall of the Figure Memory Test showed the highest accuracy for the diagnosis of dementia in several studies, with the same cut-off score (≤5) for all education levels. That is especially important as an impairment of delayed recall is one of the first and most frequently seen signs of the most common form of dementia: amnestic Alzheimer's disease. A coloured version of this battery has been used together with other tests for diagnosing dementia in immigrants or low-educated individuals living in European countries. The delayed recall subtest, with the same cut-off score (≤5), showed the highest accuracy among other tests included in that battery (9).

Alzheimer's disease usually progresses to affect executive functions, language, or behaviour. Semantic verbal fluency, an executive test based on lexical-semantic information, is one of the best tests for assessing executive function in low-educated individuals. Cut-offs should be adapted according to years of schooling: ≤9 for individuals who are illiterate, ≤12 for individuals with 1–7 years, and ≤13 for those with 8 or more years of education (8).

The naming of the drawings and semantic verbal fluency can detect language impairment

The clock drawing test is not a good model for diagnosing dementia in low-educated individuals, although it is important for the interference phase of Figure Memory Test. The use of the clock drawing test in the Brief Cognitive Screening Battery is partially justified because in Brazil, as well as in many other countries, there is heterogeneous educational background in the population, and the clock drawing test may help when examining individuals with higher education. Healthy individuals who are illiterate or low-educated usually draw the circle, but numbers may be missing or placed outside of the clock circle (score ≥4) (8).

Together with the Brief Cognitive Screening Battery, we use the Functional Activity Questionnaire (FAQ) (10), with ten simple questions, with the cut-off of ≥5 for the diagnosis of dementia. The Functional Activity Questionnaire is even more reliable when the informant has a high education. As the Functional Activity Questionnaire is being completed while the Brief Cognitive Screening Battery is being administered, it does not add any additional time to the evaluation.

We and others have performed studies with the Brief Cognitive Screening Battery and Functional Activity Questionnaire in Brazil for years. We always found them easy to use and well-received by the individuals being examined in urban epidemiological studies and remote rural areas of the Amazon basin.

References

1. Unesco. A new generation: 25 years of efforts for gender equality in education [Internet]. Global Education Monitoring Report. 2020. https://en.unesco.org/gem-report/2020genderreport
2. Carthery-Goulart MT, Anghinah R, Areza-Fegyveres R, Bahia VS, Dozzi Brucki SM, Damin A, et al. Desempenho de uma população brasileira no teste de alfabetização funcional para adultos na área de saúde. Rev Saude Publica [Internet]. 2009 Aug [cited 2021 Jul 8];43(4):631–8. https://pubmed.ncbi.nlm.nih.gov/19488667/
3. Katzman R, Zhang M, Ouang-Ya-Qu, Wang Z, Liu WT, Yu E, et al. A Chinese version of the mini-mental state examination; Impact of illiteracy in a Shanghai dementia survey. J Clin Epidemiol [Internet]. 1988 [cited 2021 Jul 8];41(10):971–8. https://pubmed.ncbi.nlm.nih.gov/3193141/
4. Nielsen TR, Jørgensen K. Cross-cultural dementia screening using the Rowland Universal Dementia Assessment Scale: A systematic review and meta-analysis. Int Psychogeriatrics. 2020.
5. Damascene A, Delicio AM, Mazo DFC, Zullo JFD, Scherer P, Ng RTY, et al. Validation of the Brazilian version of mini-test CASI-S. Arq Neuropsiquiatr. 2005;63(2 B):416–21.
6. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement [Internet]. 2011 [cited 2021 Jul 8];7(3):263–9. https://pubmed.ncbi.nlm.nih.gov/21514250/
7. Nitrini R, Helena Lefèvre B, Mathias SC, Caramelli P, Carrilho PEM, Sauaia N, et al. Testes neuropsicológicos de aplicação simples para o diagnóstico de demência. Arq Neuropsiquiatr [Internet]. 1994 [cited 2021 Jul 8];52(4):457–65. http://www.scielo.br/scielo.php?script=sci_arttext&nrm=iso&lng=pt&tlng=pt&pid=S0004-282X1994000400001
8. Nitrini R, Bucki SMD, Yassuda MS, Fichman HC, Caramelli P. The Figure Memory Test: diagnosis of memory impairment in populations with heterogeneous educational background. Dement Neuropsychol [Internet]. 2021 Apr [cited 2021 Jul 8];15(2):173–85. http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1980-57642021000200173&tlng=en
9. Nielsen TR, Vogel A, Waldemar G. Comparison of performance on three neuropsychological tests in healthy Turkish immigrants and Danish elderly. Int Psychogeriatrics [Internet]. 2012 Sep [cited 2021 Jul 8];24(9):1515–21. https://pubmed.ncbi.nlm.nih.gov/22717281/
10. Pfeffer RI, Kurosaki TT, Harrah CH, Chance JM, Filos S. Measurement of functional activities in older adults in the community. Journals Gerontol [Internet]. 1982 [cited 2021 Jul 8];37(3):323–9. https://pubmed.ncbi.nlm.nih.gov/7069156/

Conclusions

Individuals of any age bring with them their own personalised conditions. Consequently, the diagnosis of cognitive impairment and dementia, especially at the earliest onset, may be challenging. These difficulties are compounded for low-educated or illiterate individuals.

A modified, patient-centric approach in the assessment process is needed, as are sensitivity, understanding and expertise on behalf of the healthcare professionals when working with these populations.

Specific tests have been developed (Rowland Universal Dementia Assessment Scale, Cognitive Abilities Screening Instrument – Short version, Brief Cognitive Screening Battery with Figure Memory Test and the Functional Activity Questionnaire) and are available to assist clinicians in their diagnostic process. The Figure Memory Test component of the Brief Cognitive Screening Battery 1 was shown to be useful in diverse cultures, thus showing promise for its general use.

Chapter 20
Sex, gender and cultural factors

José A. Morais

Key points

- Evidence suggests that minority groups and women are not diagnosed with dementia in as timely a manner as others.
- There is insufficient awareness of how sex and gender influence the diagnostic journey.
- Precision medicine with the inclusion of sex and gender factors will optimise not only the diagnostic pathway, but also patient experience.
- For effective and culturally optimal diagnosis and care, health and social care providers must comprehend, and be responsive to, the specific characteristics and needs of Indigenous Peoples with dementia.

Background for clinicians

Diagnosing dementia is a complex procedure that necessitates healthcare professionals to process a large volume of information. Our own personal and cultural biases inform us as people, though when considering scientific evidence, it is our imperative to be as objective, accurate and efficient as possible. Anything less, and the health and well-being of those who trust and rely on our expertise will be impacted. Among the many potential biases that can influence us as clinicians, there exist those inherent or underlying ones we carry that may significantly impact our diagnosis and treatment, namely our attitude towards such factors as sex, gender and ethnocultural differences.

The essays below will address timely issues such as racial and ethnic disparities when diagnosing dementia as well as equity, diversity, and inclusion from a Canadian perspective. Considerations on sex and gender in the diagnosis of dementia are also addressed. Differences to be aware of when diagnosing dementia in Arabic countries and in Indigenous populations worldwide are discussed.

> “ Among the many potential biases that can influence us as clinicians, there exist those inherent or underlying ones we carry that may significantly impact our diagnosis and treatment, namely our attitude towards such factors as sex, gender and ethnocultural differences.

Expert essay

Racial and ethnic disparities in the diagnosis of dementia

Elena Tsoy,[1] Katherine L. Possin[1,2]

[1] Department of Neurology, Memory and Aging Center, University of California San Francisco, San Francisco, California, UNITED STATES
[2] Global Brain Health Institute, University of California San Francisco, San Francisco, California, UNITED STATES

With rising life expectancy, the global burden of dementia is expected to increase exponentially. Whereas high-income countries (HICs) are projected to experience an approximately 56% rise in older adult populations in the next 30 years, this growth is anticipated to exceed 150% in low-and middle-income countries (LMICs) (1). Moreover, in many high-income countries, including the United States and several European Union nations, the number of racially and ethnically diverse older adults is expected to increase dramatically in the coming decades (2,3). With age being the main risk factor for dementia, these rapid demographic changes require a prompt and effective response from healthcare systems to address the needs of diverse older adults.

Most experts agree that early diagnosis of dementia is a healthcare priority (4), and its benefits are numerous. These include opportunities to identify aetiological causes, inform and coordinate medical care, enable planning for the future, address possible safety issues, and connect families to interventions. It also allows for the identification of appropriate candidates for clinical trials of potentially disease-modifying therapies that are anticipated to benefit people in early stages (5). In turn, missed or late diagnosis may result in devastating outcomes for individuals and their families, including lost opportunities for treatment, complications of comorbid medical conditions, increased healthcare expenditures, adverse effects on patient safety, and increased carer burden (4).

Evidence and consequences of diagnostic disparities

Diagnostic practice recommendations for early diagnosis of dementia and its prodromal phase, mild cognitive impairment, underline the importance of a comprehensive work-up. This can vary by setting and needs of each person but typically includes evaluation by a dementia specialist, cognitive examination, and laboratory and neuroimaging studies to help identify underlying aetiology including potential non-neurodegenerative causes (6). For most people with dementia, their evaluation does not approximate this standard (5), and commonly, no diagnosis is made. The rates of underdiagnosis are inversely related to income of countries, from around 60% in high-income countries to above 90% in low- and middle-income countries (7). Furthermore, older adults in LMICs frequently experience substantial disability and poor general health due to unaddressed modifiable risk factors and unmanaged chronic disease (8). In high-income countries, racial and ethnic minorities are at higher risk of underdiagnosis than the majority (frequently White/Caucasian) population, as documented by studies from Denmark, Norway, the United Kingdom, and the United States (3,5). Moreover, even when racially and ethnically diverse older adults do receive a diagnosis, they are more likely to be diagnosed at a later stage and receive a less comprehensive diagnostic evaluation than the ethnic majority group (3,5), making them more vulnerable to adverse outcomes associated with late or inaccurate diagnosis.

Diagnostic disparities in dementia have wide-ranging consequences for individuals and their families including, perhaps most critically, access to support and treatment that are most effective in earlier stages (5). Indeed, racial and ethnic minorities have been reported to be less likely to be prescribed cholinesterase inhibitors and to access fewer services (9), which is possibly directly related to upstream diagnostic disparities early in the disease process. Moreover, later or missed diagnosis of dementia among racially and ethnically diverse older adults may indirectly result in inaccurate representation of these communities in epidemiological studies on prevalence and incidence rates of dementia that are critical sources of information for public health policy (5). Finally, diagnostic disparities likely play a crucial role in underrepresentation and often exclusion of diverse older adults in clinical trials, which in turn puts these individuals at risk for future treatment disparities, particularly if a disease-modifying agent is approved.

What is driving diagnostic disparities?

Much more research is needed to elucidate the patient-level and system-level factors that underlie racial and ethnic disparities in the diagnosis of dementia (3). Patient-level factors include low awareness of dementia, limited health literacy, language and communication barriers, cultural and familial perceptions of dementia and ageing, stigma of mental illness, and distrust of healthcare services (3,5). System-level factors, in turn, are comprised of the historical and structural inequities and include lack of culturally appropriate services and tools, shortage of dementia specialists particularly in low resource areas, inadequate training of general healthcare professionals in the recognition of dementia, bias in referral practices to specialists, and time- and cost-related barriers to access quality care that may disproportionally affect underrepresented groups (3). Furthermore, these patient- and system-level factors must be understood in the context of the structural racism that is experienced by many racial and ethnic groups, which has resulted in the accumulation of disadvantage and higher risk of poor health outcomes in general (3). The combination of these factors drives racial and ethnic diagnostic disparities and represent a critical area for research and intervention to reduce inequities in the timely and accurate diagnosis of dementia amongst racially and ethnically diverse older adults.

Future directions

Racial and ethnic disparities in the diagnosis of dementia are a major research and public health priority. We urgently need to better understand the causes of these disparities, develop targeted interventions that are amenable to scale, and implement the interventions with attention to what works and what can be sustained in diverse communities. We propose a multi-pronged approach that includes culturally tailored campaigns to increase public awareness about brain health and reduce stigma, policies to increase the diversity of the general practitioner and dementia specialty healthcare workforce, better education and training for general practitioners on dementia recognition and care, outreach by dementia specialist providers to facilitate referral of underserved patient groups, adequate reimbursement and time for providers to diagnose and manage dementia, and improved access to effective dementia care models that provide critical support for individuals, carers, and general practitioners following diagnosis. We emphasise this last point, that improved diagnosis must always be linked to quality care (10), because without this link, the providers will not be motivated to diagnose, and the benefits of diagnosis will not be realised. Collaborative efforts among researchers, clinicians, community partners, and policymakers are essential to achieve equity in dementia diagnosis.

References

1. Alzheimer's Disease International. World Alzheimer's Report 2015: The Global Impact of Dementia. London, UK; 2015.
2. Bureau UC. Demographic Turning Points for the United States [Internet]. [cited 2021 Jul 9]. https://www.census.gov/library/publications/2020/demo/p25-1144.html
3. Alzheimer Europe. The development of intercultural care and support for people with dementia from minority ethnic groups. 2018;92.
4. Bradford A, Kunik ME, Schulz P, Williams SP, Singh H. Missed and delayed diagnosis of dementia in primary care: Prevalence and contributing factors [Internet]. Vol. 23, Alzheimer Disease and Associated Disorders. Alzheimer Dis Assoc Disord; 2009 [cited 2021 Jul 9]. p. 306–14. https://pubmed.ncbi.nlm.nih.gov/19568149/
5. Tsoy E, Kiekhofer RE, Guterman EL, Tee BL, Windon CC, Dorsman KA, et al. Assessment of Racial/Ethnic Disparities in Timeliness and Comprehensiveness of Dementia Diagnosis in California. JAMA Neurol. 2021;94158(6):657–65.
6. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. JAMA – J Am Med Assoc [Internet]. 2019 Oct 22 [cited 2021 Jul 9];322(16):1589–99. https://pubmed.ncbi.nlm.nih.gov/31638686/
7. Lang L, Clifford A, Wei L, Zhang D, Leung D, Augustine G, et al. Prevalence and determinants of undetected dementia in the community: A systematic literature review and a meta-analysis [Internet]. Vol. 7, BMJ Open. BMJ Open; 2017 [cited 2021 Jul 9]. https://pubmed.ncbi.nlm.nih.gov/28159845/
8. World Health Organization. World report on ageing and health. :246.
9. Cooper C, Tandy AR, Balamurali TBS, Livingston G. A systematic review and meta-analysis of ethnic differences in use of dementia treatment, care, and research [Internet]. Vol. 18, American Journal of Geriatric Psychiatry. Am J Geriatr Psychiatry; 2010 [cited 2021 Jul 9]. p. 193–203. https://pubmed.ncbi.nlm.nih.gov/20224516/
10. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Vol. 396, The Lancet. Lancet Publishing Group; 2020. p. 413–46.

Expert essay

Equity, diversity, and inclusion in dementia diagnosis: a Canadian perspective

Ngozi Iroanyah,[1] Marie Y. Savundranayagam,[2] Reanne G. Mundadan,[2] Saskia Sivananthan[1]

[1] Alzheimer Society of Canada, CANADA
[2] Faculty of Health Sciences, Western University, CANADA

Canada, like other western nations, has experienced unprecedented demographic changes in its age-based population. Since 2016, the number of adults over the age of 65 has outnumbered those 0–14 years of age (1). Moreover, there has been an increase in both the rate of immigration and differences in countries of origin for newcomers, resulting in 1 in every 5 Canadians now identifying as foreign born, and 1 in every 5 Canadians also identifying as a visible minority (2). As dementia is poised to impact almost a million Canadians by 2030 (3) focused attention is crucial to understand the needs and experience of these racially diverse communities when accessing dementia care services and programmes.

Unlike other western nations, there is little Canadian data or resources available for the needs and experiences of people living with dementia and their carers from racially diverse communities, particularly from a population-level perspective (4,5). Specific studies found that racially diverse communities have a higher prevalence of dementia and face disproportionate challenges due to a lack of culturally safe carer and community support, and poor system-level awareness of their education needs and health-seeking behaviours (4,6). These gaps in knowledge can further exacerbate the burden of care felt in these communities, including increased isolation, stigma and delays in seeking a diagnosis.

Receiving a timely dementia diagnosis has been shown to help decrease the progression of the condition, yet the decision-making process to seek a diagnosis for people experiencing dementia complaints from racialised backgrounds is complex. It operates on cultural and structural levels. Cultural barriers are both knowledge- and society-related. Knowledge-related barriers include misidentification of the causes of dementia to spiritual, psychological, and other physical health or social origins (7,8), beliefs that dementia is part of normal ageing, misinterpreting changes in behaviour and personality, and not perceiving a need to seek a diagnosis or support (9). Society-related cultural barriers can include fear of shame, ostracisation, and stigma within families and communities (8,10). Cultural expectations about family carers can create barriers to seeking a diagnosis; they can place a large onus on the family to provide for the needs of elders, thus contributing to delays in seeking a diagnosis (11).

Importantly, cultural barriers do not occur in isolation. They can be strongly influenced by structural barriers that are part of broader social contexts that inform access to healthcare services. Specifically, structural barriers can cause hesitancy engaging with the healthcare system due to systemic discrimination, difficulty navigating health services that are not culturally appropriate, and lack of resources in the language of choice (7,9).

While these studies highlight some barriers experienced by racially diverse communities, more in-depth analysis needs to take place to understand the experiences and barriers faced by physicians providing care to these communities. In Canada, primary care physicians are gatekeepers for those seeking a dementia diagnosis, making this information particularly relevant to physicians' provision of care. Primary care physicians have been shown to have difficulty with accurately diagnosing dementia when their patients do not speak English or French, or have potential low literacy and education (12). Moreover, many of the widely used assessment tools for the diagnosis of dementia are not culturally

appropriate. Education, language, ethnocultural factors can affect performance on neuropsychological testing, leading to false-positives and false-negatives (13,14). Lastly, primary care physicians may have their own biases about dementia. They may have been reluctant to confirm a diagnosis based on assumptions that people do not want to receive a diagnosis due to associated stigma or their own views that a diagnosis was not useful.

> **Primary care physicians have been shown to have difficulty with accurately diagnosing dementia when their patients do not speak English or have potential low literacy and education. Moreover, many of the widely used assessment tools for the diagnosis of dementia are not culturally appropriate.**

The following recommendations can enable a planned and systematic pathway to seeking a diagnosis and accessing supports. Community level recommendations include implementing and encouraging anti-stigma campaigns that are culturally safe and appropriate, along with psychoeducation, vigilant screening, culturally-friendly dementia services, and awareness building (15). For example, community agencies can provide tailored information and support to immigrants and at-risk communities. Interventions targeted at building knowledge and awareness can be customised to the needs of racially diverse groups. These could include multilingual informational pamphlets about dementia and culturally-appropriate services (11).

Clinicians should also be attentive to the subtle signs of possible dementia, including missed appointments or mismanaged chronic conditions (12). To prevent false-positive and false-negative dementia misclassification by the brief cognitive assessments in ethnically diverse groups, clinicians should also consider encouraging older adults to bring a companion or carer to the appointment. They may be in a position to inform the clinician of culturally relevant issues (12), participate in informant-rated cognition and potential test specific biases (13). Informant reports from cultural perspectives can also complement cognitive testing to improve the accuracy of a dementia diagnosis (14).

Incorporating these recommendations into dementia-friendly communities can help to normalise dementia so that individuals and their carers from these communities can be confident in obtaining a timely dementia diagnosis.

As the primary national organisation that provides education and support for people living with dementia, the Alzheimer Society of Canada continues to play a crucial role in implementing these recommendations and has taken a more active approach to relationship building and understanding the experiences of ethnically diverse communities is essential. In partnership with the College of Family Physicians of Canada, the Alzheimer Society of Canada launched the first national survey focused on understanding the needs of racially diverse people living with dementia, and a companion survey to family physicians providing care to these communities. Concurrent with the survey, targeted community outreach and awareness raising is occurring within racially diverse communities. Data from the survey will be shared back with the communities to support their own decision-making and advocacy, a step rarely taken but crucial for building those communities' capacity. Phase two will involve leveraging existing relationships and supports as a starting point, while recognising the need for co-creation of culture-first (instead of language-first) resources.

As the population of people living with dementia continues to grow and diversify, more data and research will be essential to develop better resources and supports that focus on building knowledge and confidence in communities that have long experienced structural barriers in the healthcare system. This must be the first step in a long-term, multi-year, multimedia strategy to provide dementia care programmes and services.

References

1. Statistics Canada. Age and sex, and type of dwelling data: Key results from the 2016 Census The Daily Statistics Canada Catalogue no. 11-001-X. Stat Canada Cat no 11-001-X [Internet]. 2017 [cited 2021 Jul 9];Ottawa. https://www150.statcan.gc.ca/n1/daily-quotidien/170503/dq170503a-eng.htm
2. Statistics Canada. Immigration and ethnocultural diversity: Key results from the 2016 Census. Dly [Internet]. 2017 [cited 2021 Jul 9];(Catalogue no. 11-001-X):1–8. https://www150.statcan.gc.ca/n1/daily-quotidien/171025/dq171025b-eng.htm
3. Report summary Prevalence and monetary costs of dementia in Canada (2016): a report by the Alzheimer Society of Canada. Heal Promot chronic Dis Prev Canada Res policy Pract. 2016 Oct 1;36(10):231–2.
4. McCleary L, Persaud M, Hum S, Pimlott NJ, Cohen CA, Koehn S, et al. Pathways to dementia diagnosis among South Asian Canadians. Dementia [Internet]. 2013 Apr 26 [cited 2021 Jul 9];12(6):769–89. https://journals.sagepub.com/doi/abs/10.1177/1471301212444806
5. O'Connor D, Phinney A, Hulko W. Dementia at the Intersections: A unique case study exploring social location. J Aging Stud. 2010 Jan 1;24(1):30–9.
6. Co M, Couch E, Gao Q, Mac-Ginty S, Das-Munshi J, Prina M. Access to Health Services in Older Minority Ethnic Groups with Dementia: A Systematic Review [Internet]. Vol. 69, Journal of the American Geriatrics Society. J Am Geriatr Soc; 2021 [cited 2021 Jul 9]. p. 822–34. https://pubmed.ncbi.nlm.nih.gov/33230815/

7. Mukadam N, Cooper C, Livingston G. A systematic review of ethnicity and pathways to care in dementia [Internet]. Vol. 26, International Journal of Geriatric Psychiatry. John Wiley & Sons, Ltd; 2011 [cited 2021 Jul 9]. p. 12–20. https://onlinelibrary.wiley.com/doi/full/10.1002/gps.2484
8. Mukadam N, Cooper C, Livingston G. Improving access to dementia services for people from minority ethnic groups [Internet]. Vol. 26, Current Opinion in Psychiatry. Curr Opin Psychiatry; 2013 [cited 2021 Jul 9]. p. 409–14. https://pubmed.ncbi.nlm.nih.gov/23454888/
9. Parker M, Barlow S, Hoe J, Aitken L. Persistent barriers and facilitators to seeking help for a dementia diagnosis: A systematic review of 30 years of the perspectives of carers and people with dementia [Internet]. Vol. 32, International Psychogeriatrics. Cambridge University Press; 2020 [cited 2021 Jul 9]. p. 611–34. https://www.cambridge.org/core/journals/international-psychogeriatrics/article/abs/persistent-barriers-and-facilitators-to-seeking-help-for-a-dementia-diagnosis-a-systematic-review-of-30-years-of-the-perspectives-of-carers-and-people-with-dementia/F5A64C2
10. Koehn S. 'It is not a disease, only memory loss': Exploring the complexity of access to a diagnosis of dementia in a cross-cultural sample. exploring the complexity of access to a diagnosis of dementia in a cross-cultural sample. In: Evidence-informed Approaches for Managing Dementia Transitions: Riding the Waves. Academic Press; 2020. p. 29–52.
11. Koehn S, McCleary L, Garcia L, Spence M, Jarvis P, Drummond N. Understanding Chinese-Canadian pathways to a diagnosis of dementia through a critical-constructionist lens. J Aging Stud. 2012 Jan 1;26(1):44–54.
12. Amjad H, Roth DL, Sheehan OC, Lyketsos CG, Wolff JL, Samus QM. Underdiagnosis of Dementia: an Observational Study of Patterns in Diagnosis and Awareness in US Older Adults. J Gen Intern Med [Internet]. 2018 Jul 1 [cited 2021 Jul 9];33(7):1131–8. https://pubmed.ncbi.nlm.nih.gov/29508259/
13. Ranson JM, Kuźma E, Hamilton W, Muniz-Terrera G, Langa KM, Llewellyn DJ. Predictors of dementia misclassification when using brief cognitive assessments. Neurol Clin Pract [Internet]. 2019 Apr 1 [cited 2021 Jul 9];9(2):109–17. https://pubmed.ncbi.nlm.nih.gov/31041124/
14. Sayegh P, Knight BG. Assessment and diagnosis of dementia in hispanic and non-hispanic white outpatients. Gerontologist [Internet]. 2013 Oct [cited 2021 Jul 9];53(5):760–9. https://pubmed.ncbi.nlm.nih.gov/23348889/
15. Martinez-Ruiz A, Huang Y, Gee S, Jamieson H, Cheung G. Individual risk factors for possible undetected dementia amongst community-dwelling older people in New Zealand. Dementia [Internet]. 2020 Jul 10 [cited 2021 Jul 9];19(3):750–65. https://journals.sagepub.com/doi/abs/10.1177/1471301218786277?journalCode=dema

Expert essay

Optimal Alzheimer's disease detection and diagnosis under the sex and gender lens: a crucial step towards precision neurology

Maria Teresa Ferretti,[1] Antonella Santuccione Chadha,[2] Annemarie Schumacher Dimech,[3] Maria Florencia Iulita,[1] Julie Martinkova,[4] Laura Campo,[5] Harald Hampel[6]

1 Women's Brain Project, SWITZERLAND
2 Biogen International, SWITZERLAND
3 University of Lucerne, SWITZERLAND
4 Department of Neurology, Charles University, Second Faculty of Medicine and Motol University Hospital, CZECH REPUBLIC
5 Eli Lilly and Company, UNITED STATES
6 Sorbonne University, GRC n° 21, Alzheimer Precision Medicine (APM), AP-HP, Pitié-Salpêtrière Hospital, FRANCE

Alzheimer's disease pathophysiology emerges decades before the first clinical signs and symptoms appear. The clinical continuum of the disease is therefore characterised by a long asymptomatic, preclinical stage and a complex trajectory. It is important to detect the first biological indicators and diagnose affected individuals as early as possible, to effectively implement secondary preventative strategies, to provide access to potential (pharmacological and non-pharmacological) disease-modifying treatments, and to allow individuals and their families to plan for the future.

Sex (biological) and gender (socio-cultural) differences in Alzheimer's disease are particularly relevant in the individual's diagnostic pathway and medical journey.

Definition of sex and gender

Sex: genetically determined differences resulting from the expression of sex chromosomes (XX/XY)

Gender: socio-cultural construct determining feminine and masculine expected behaviours and norms in a particular society

In this essay, we highlight gaps that could be addressed by specific advocacy and policy actions to enable accurate, reliable and precise diagnosis and treatment for both sexes, a crucial step towards precision neurology.

Lifetime risk and need for personalised prevention

Datasets consistently show that approximately two-thirds of people with Alzheimer's disease are women (2). Although differences in indicators of Alzheimer's disease risk by sex are controversial and vary by country, the lifetime risk of dementia is higher in women (2). This highlights the importance of a timely diagnosis as well as of understanding and managing risk factors early in women.

Of the 12 modifiable risk factors identified by the Lancet Commission in 2020 (3), several are more common in women, including low level of education and depression. Also, sex- and gender-specific risk factors have been proposed for both men and women (see Table 1) and might be leveraged for personalised prevention.

Access to healthcare and gender considerations

The diagnostic process is directly related to health awareness and healthcare access. Differences between men and women in interpreting symptoms, as well as accessing and receiving healthcare, include:

Socio-economic factors: Examples of these include lower level of education, lower income, poverty, less health coverage, old age, and multimorbidity. These represent barriers to healthcare access and a timely diagnosis, where women are typically overrepresented (4).

Table 1. Modifiable risk factors of Alzheimer's disease under the sex and gender lens

Modifiable risk factors identified by The Lancet Commission (in **bold**, factors which were shown to be different in men and women)	Potential female-specific risk factors	Potential male-specific risk factors
• **Lower level of education** • **Hypertension** • **Obesity** • Hearing loss • **Smoking** • **Depression** • Physical inactivity • Social isolation • **Diabetes** • **Excessive alcohol consumption** • **Traumatic Brain Injury** • Air pollution	• Age-related decline in female sex hormones • Early menopause • Pregnancies and pregnancy complications • Shorter reproductive period • Migraine • Traumatic Brain Injury by domestic violence	• Androgen depleting treatments for prostate cancer • Age-related decline in male sex hormones (andropause)

Stigma: Women living with Alzheimer's disease face a 'triple jeopardy' (5) of barriers from stigma related to old age, cognitive decline, and gender stereotypes and bias, which can create a hurdle to acknowledge and talk about their symptoms and seek professional help.

Carer role: Approximately two-thirds of informal carers are women, often juggling their carer role with other family and professional responsibilities. On the one hand, because women tend to be more engaged in household and other managing tasks, it may be easier for family members to identify behavioural changes in women rather than men. However, as the Alzheimer's disease diagnostic journey can take years, necessitating a significant investment in terms of time and personal resources, this can generate a specific problem for women carers who lack the required time and family support (6).

Help-seeking behaviour: Men engage in healthcare-seeking behaviour less than women and only when symptoms are severe; the World Health Organization reports that women tend to talk about mental health issues with their general practitioner (GP) while men are more likely to seek specialist help. This difference in help-seeking behaviour could also have an impact on delayed diagnosis or misdiagnosis (7).

Not only do these gender factors affect access to healthcare and early diagnosis, they also have an impact on clinical trial access., (8,9).

Sex and gender considerations in the clinical diagnosis of Alzheimer's disease

According to published studies, mild cognitive impairment (MCI) is more common in men (2); its diagnosis however is often missed in women or occurs at an advanced pathological stage. This is partly due to sex differences in neuropsychological tests, which rely heavily on verbal memory, and where women perform on average better than men, despite equal amounts of Alzheimer's disease pathology. Adjusting cut-offs based on sex-specific considerations can detect approximately 20% more women who missed out an MCI diagnosis (10).

In addition to biological differences, MCI is often overlooked in women as gender stereotypes tend to steer diagnosis towards depression rather than MCI due to Alzheimer's disease. When treating mental health problems, doctors were more likely to diagnose depression in older women than men presenting the same symptoms (5).

Sex differences in biomarkers for Alzheimer's disease diagnosis

Biomarker-aided (fluid, imaging, and digital) diagnosis is increasingly used to diagnose Alzheimer's disease. The use of biomarkers has the potential to overcome gender biases and leverage sex differences for a more precise diagnosis.

There is growing evidence that the levels of several currently used biomarkers differ between men and women (11). Cerebrospinal fluid (CSF) concentration of neurofilament light chain, a biomarker for neurodegeneration, has been shown to be higher in men, while tau, another biomarker for neurodegeneration, was higher in women. In addition, several PET-imaging studies show that tau levels in the brain accumulate at higher levels and faster in women. This suggests that sex-specific cut-offs, for both diagnostic and prognostic value, should be carefully examined.

Several PET-imaging studies show that tau levels in the brain accumulate at higher levels and faster in women. This suggests that sex-specific cut-offs, for both diagnostic and prognostic value, should be carefully examined.

Several digital biomarkers, tools, smart technology, wearables and apps are under development and validation for early detection of cognitive impairment and signs of decline. Their use could help accelerate early diagnosis and follow-up of Alzheimer's disease. Initial evidence suggests even digital biomarkers differ significantly between men and women. Therefore, considering sex and gender differences will also be crucial in the development of digital solutions.

Finally, in the near future, improved validation of blood-based biomarkers will allow for inexpensive, regular and timely screening and early detection of at-risk individuals, even in primary care. It will therefore be important to also consider sex-related aspects in the application of such biomarkers.

To enable precision medicine, multidimensional data needs to be analysed and interpreted via predictive algorithms. In this context, sex and gender are crucial factors affecting the overall predictive power of clinical models. Indeed, it has been shown that including sex in predictive algorithms improves their efficiency (12).

Both sex (biological) and gender (socio-economic) factors can influence access to healthcare and accurate diagnosis of Alzheimer's disease. However, there is insufficient awareness of sex and gender influence on the diagnostic journey by the medical community and society overall.

Considering sex- and gender-specific factors is a key step to improve access to and precision of diagnosis of Alzheimer's disease, especially during early stages. A paradigm shift towards precision neurology will optimise the diagnostic pathway and the individual's medical journey.

Recommendations

- Promote awareness campaigns to address 'triple jeopardy' barriers older adult women face and reduce stigma.
- Determine evidence-based sex-specific cut-offs for cognitive/clinical/biomarker testing, using both standard and digital solutions.
- Increase awareness of sex and gender differences at societal and professional levels.
- Healthcare providers from primary care physicians to academia, from generalists to specialists, need to be educated and informed.
- Make gender equity in medicine a priority for governments, regulators, and policymakers.
- Implement multi-stage, sex-specific brain health screening and diagnostic process for people at risk over the age of 50.
- Promote sex- and gender-specific prevention campaigns such as cognitive training for women with lower education or early menopause.

References

1. Ferretti MT, Iulita MF, Cavedo E, Chiesa PA, Dimech AS, Chadha AS, et al. Sex differences in Alzheimer disease – The gateway to precision medicine [Internet]. Vol. 14, Nature Reviews Neurology. Nat Rev Neurol; 2018 [cited 2021 Jul 9]. p. 457–69. https://pubmed.ncbi.nlm.nih.gov/29985474/
2. Alzheimer's Disease International. World Alzheimer's Report 2015: The Global Impact of Dementia. London, UK; 2015.
3. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Vol. 396, The Lancet. Lancet Publishing Group; 2020. p. 413–46.
4. Mejia-Arango S, Garcia-Cifuentes E, Samper-Ternent R, Borda MG, Cano-Gutierrez CA. Socioeconomic Disparities and Gender Inequalities in Dementia: a Community-Dwelling Population Study from a Middle-Income Country. J Cross Cult Gerontol [Internet]. 2021 Mar 1 [cited 2021 Jul 9];36(1):105–18. https://pubmed.ncbi.nlm.nih.gov/33247379/
5. Bamford S-M. Women and Dementia-Not forgotten. 2011 [cited 2021 Jul 9]; www.ilcuk.org.uk
6. Cañabate P, Martínez G, Rosende-Roca M, Moreno M, Preckler S, Valero S, et al. Social Representation of Dementia: An Analysis of 5,792 Consecutive Cases Evaluated in a Memory Clinic. J Alzheimer's Dis [Internet]. 2017 [cited 2021 Jul 9];58(4):1099–108. / pmc/articles/PMC5523907/

7. Gough B, Novikova I. Mental health, men and culture: how do sociocultural constructions of masculinities relate to men's mental health help-seeking behaviour in the WHO European Region? (2020) [Internet]. 2020 [cited 2021 Jul 9]. 1–72 p. https://www.euro.who.int/en/publications/abstracts/mental-health,-men-and-culture-how-do-sociocultural-constructions-of-masculinities-relate-to-mens-mental-health-help-seeking-behaviour-in-the-who-european-region-2020
8. Ferretti MT, Martinkova J, Biskup E, Benke T, Gialdini G, Nedelska Z, et al. Sex and gender differences in Alzheimer's disease: current challenges and implications for clinical practice: Position paper of the Dementia and Cognitive Disorders Panel of the European Academy of Neurology. Eur J Neurol [Internet]. 2020 Jun 1 [cited 2021 Jul 9];27(6):928–43. https://pubmed.ncbi.nlm.nih.gov/32056347/
9. Abdelnour C, Valero S, Rosende-Roca M, Lafuente A, Hernandez I, Tartari JP, et al. Gender and sex bias in clinical trial recruitment in Alzheimer's disease: Findings from Fundació ACE. Alzheimer's Dement [Internet]. 2020 Dec [cited 2021 Jul 9];16(S10):e041234. https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1002/alz.041234
10. Sundermann EE, Maki P, Biegon A, Lipton RB, Mielke MM, Machulda M, et al. Sex-specific norms for verbal memory tests may improve diagnostic accuracy of amnestic MCI. Neurology [Internet]. 2019 Nov 12 [cited 2021 Jul 9];93(20):E1881–9. https://pubmed.ncbi.nlm.nih.gov/31597708/
11. Ferretti M, Dimech A, Santuccione A. SEX AND GENDER DIFFERENCES IN ALZHEIMER'S DISEASE: the women's brain. Elsevier Academic Press; 2021. https://www.elsevier.com/books/sex-and-gender-differences-in-alzheimers-disease/ferretti/978-0-12-819344-0
12. Van Maurik IS, Slot RER, Verfaillie SCJ, Zwan MD, Bouwman FH, Prins ND, et al. Personalized risk for clinical progression in cognitively normal subjects – The ABIDE project. Alzheimer's Res Ther [Internet]. 2019 Apr 16 [cited 2021 Jul 9];11(1). https://pubmed.ncbi.nlm.nih.gov/30987684/

Expert essay

Access to diagnostic evaluations in people with symptoms suggesting dementia in the Arab world

Hamed Al Sinawi

Department of Behavioural Medicine, Sultan Qaboos University, OMAN

The Arab world is made up of 22 countries distributed between the Atlantic coast of Northern Africa to the Arabian Gulf, with a total population of approximately 280 million. A report by the World Health Organization (WHO) estimated that the prevalence of people with dementia in the Arab world would increase 125% by 2050 (Dementia: A public health priority, WHO 2012).

Like other parts of the globe, the number of older adults in the Arab world has been increasing gradually and the number of people living with dementia in these countries is expected to reach 4.4 million by the year 2030 (1).

This means that such countries would need to consider dementia as a global health issue and start developing guidelines and policies to improve detection and management. It is worth noting that by 2021, out of the 22 countries, only three had a national plan.[i]

Despite a significant variation in income levels, Arab countries share common values, social customs, cultural and religious beliefs (Islam being the most widely practiced religion followed by Christianity and Judaism). In many Arab communities, the elders are considered a source of spiritual blessing, religious faith, wisdom, and love. Such values may influence help-seeking behaviour when a person develops cognitive impairment and becomes unable to fulfil social expectations (2). When an older person requires assistance, the family may hire a carer or a nurse at home; if the family is unable to afford to pay for a carer or nurse, a family member, usually a spouse or a daughter, becomes the main carer (3).

While Arabic is the formal language, different variations are spoken ranging from formal and literary to vernacular. This raises the question: how can psychological tests be written and understood by people from different countries? This will not only affect how the test is interpreted, but also its validity and its appropriateness to be used in another Arabic-speaking country (4).

The diagnostic process

In many Arab countries, the diagnosis of dementia is often not made or is delayed until it reaches the advanced stages. This is attributed to several factors such as stigma, lack of awareness, and access to dedicated services for diagnosis and treatment.

Stigma

Stigma towards people with dementia is a worldwide phenomenon and is not limited to the general public but also extends to healthcare workers. According to the 2019 World Alzheimer Report, both the public and some healthcare professionals in many countries consider dementia a normal part of ageing. Families will mostly consult a healthcare professional when someone starts exhibiting challenging behaviours.

In Arabic, the term *kharaf* is used to describe dementia and means 'the one who has lost his mind' (4). There has been a recent attempt to change that to a less stigmatising definition which translates to cognitive impairment. However, many people find this too academic, and some health workers have adopted the term 'Alzheimer's like' to describes other forms of dementia. Recent health education campaigns are gradually contributing toward a better awareness about dementia.

Clinical memory services

Clinical services that provide both assessment and management to people with dementia vary across Arab countries based on the availability of resources and the clinicians' training and background in each country. That said, as a general rule, neurologists, psychiatrists, and geriatrics specialists are consulted after initial assessment from primary care physicians. In some countries where clinicians have North American-based post-graduate training, behavioural neurologists with the combined expertise of neurology and psychiatry are also involved in the assessment and

i For more information please see From Plan to Impact IV (ADI, 2021) https://www.alzint.org/resource/from-plan-to-impact-iv/

management of people with dementia. The number of experienced psychologists in neurocognitive assessment is incredibly limited and cognitive assessments scales that have been translated to Arabic and validated are equally scarce. Traditionally, the Mini-Mental Status Examination (MMSE) is used as the standard scale for assessment, however copyright issues restrict its use to specific centres. Albanna et al., conducted a study in Qatar on the validation of the Arabic versions of the MMSE and Mini-Cog screening tests when used together. Results found that the combination improved the balance between sensitivity and specificity rather than using either measure alone (5). In Egypt, a validation study of the Addenbrooke's Cognitive Examination III (ACE III) was conducted by Qaseem et al., and a cut-off score for mild cognitive impairment was established (6). Chayya et al., from Lebanon validated the Arabic version of the Rowland Universal Dementia Assessment Scale (RUDAS) and concluded that it is a reliable short screening test with good psychometric properties among different types of older adults, regardless of their demographic characteristics and depressed states. This finding is of particular interest when assessing people with limited educational backgrounds (7).

When it comes to neuroimaging, most centres that assess people with dementia follow international guidelines such as those from National Institute for Health and Care Excellence (NICE). However, the lack of widespread neuroimaging technology restricts its use to tertiary care centres (8).

Post diagnosis services vary across the region; some countries provide psycho-education and support groups for carers, others conduct formal training for carers covering topics related to physical and psychological care, improving communication and dealing with different behavioural problems.

Dementia care in the era of COVID-19

The COVID-19 pandemic had a significant worldwide impact on the services available to people with dementia. Measures such as physical distancing and lockdown restrictions were introduced as ways to reduce the risk of spreading the infection and of protecting older adults. This led to fewer available medical appointments for people with dementia. Eventually, this situation incurred additional delays in providing diagnostic and follow-up assessments. People with dementia experienced significant deterioration of cognitive abilities while they and their carers also endured increased loneliness and isolation. Pandemic conditions also contributed to carer burnout because of regulated social interaction with others. Other factors, including a lack of internet literacy coupled with limited accessibility to high-speed internet servers, hindered the use of virtual clinics in many countries. At a governmental level, the economic impact of COVID-19, as well as the focus on physical care and well-being, have likely diverted attention from developing appropriate dementia plans.

The way forward

Despite the significant growth of available dementia services in some Arab countries, further improvement in terms of ongoing health education campaigns, early diagnosis advocacy, clinical research focused on validating cognitive assessment scales and developing post diagnosis services that are practical, affordable, and culturally appropriate to improve the quality of care of people with dementia and their carers (9) are still lacking. Providing home care for the person with dementia can be exhausting and several studies from the Arab world reported high levels of carer burnout. This points to the need for a more structured carer support system to improve their quality of life as well as that of the person with dementia.

References

1. Yaghmour SM, Bartlett R, Brannelly T. Dementia in Eastern Mediterranean countries: A systematic review. Dementia [Internet]. 2019 Nov 1 [cited 2021 Jul 9];18(7–8):2635–61. https://pubmed.ncbi.nlm.nih.gov/29336168/
2. Kirkinci M. DIVINE DETERMINING (FATE AND DESTINY) AND MAN'S WILL IN ISLAM – Rahmath Pathippagam [Internet]. Sozler Publications (Turkey); 2000 [cited 2021 Jul 9]. https://rahmath.net/product/divine-determining-fate-and-destiny-and-mans-will-in-islam/
3. Abyad A. Alzheimer's the Road Ahead in the Middle East. J Alzheimer's Dis Park [Internet]. 2016 Jun 15 [cited 2021 Jul 9];6(3):1–2. https://www.omicsonline.org/open-access/alzheimers-the-road-ahead-in-the-middle-east-2161-0460-1000241.php?aid=75780
4. Zeinoun P, Iliescu D, El Hakim R. Psychological Tests in Arabic: A Review of Methodological Practices and Recommendations for Future Use [Internet]. Vol. 1, Neuropsychology Review. Springer; 2021 [cited 2021 Jul 9]. p. 1–19. https://link.springer.com/article/10.1007/s11065-021-09476-6
5. Albanna M, Yehya A, Khairi A, Dafeeah E, Elhadi A, Rezgui L, et al. Validation and cultural adaptation of the Arabic versions of the Mini–Mental status examination – 2 and Mini-Cog test. Neuropsychiatr Dis Treat [Internet]. 2017 Mar 14 [cited 2021 Jul 9];13:793–801. https://pubmed.ncbi.nlm.nih.gov/28352179/
6. Qassem T, Khater MS, Emara T, Rasheedy D, Tawfik HM, Mohammedin AS, et al. Validation of the Egyptian-Arabic Version of the Addenbrooke's Cognitive Examination III (ACE-III) in Diagnosing Dementia. Dement Geriatr Cogn Disord [Internet]. 2020 Oct 1 [cited 2021 Jul 9];49(2):179–84. https://pubmed.ncbi.nlm.nih.gov/32417842/
7. Chaaya M, Phung TKT, El Asmar K, Atweh S, Ghusn H, Khoury RM, et al. Validation of the Arabic Rowland Universal Dementia Assessment Scale (A-RUDAS) in elderly with mild and moderate dementia. Aging Ment Heal [Internet]. 2016 Aug 2 [cited 2021 Jul 9];20(8):880–7. https://pubmed.ncbi.nlm.nih.gov/25984584/
8. Fasfous AF, Al-Joudi HF, Puente AE, Pérez-García M. Neuropsychological Measures in the Arab World: A Systematic Review [Internet]. Vol. 27, Neuropsychology Review. Neuropsychol Rev; 2017 [cited 2021 Jul 9]. p. 158–73. https://pubmed.ncbi.nlm.nih.gov/28624899/
9. El-Metwally A, Toivola P, Al-Rashidi M, Nooruddin S, Jawed M, Alkanhal R, et al. Epidemiology of Alzheimer's Disease and Dementia in Arab Countries: A Systematic Review. Behav Neurol [Internet]. 2019 [cited 2021 Jul 9];2019. https://pubmed.ncbi.nlm.nih.gov/31772681/

Expert essay

Understanding diagnosis of dementia in Indigenous populations

Jennifer D. Walker,[1] Lynden (Lindsay) Crowshoe,[2] Julia Rowat,[3] Gabrielle Bruser[3]

[1] McMaster University, Ontario, CANADA
[2] University of Calgary, Alberta, CANADA
[3] Laurentian University, Ontario, CANADA

The emergence of dementia is a significant concern for Indigenous populations worldwide. The limited available research points to higher rates of dementia compared with non-Indigenous populations (1). These higher rates are rooted in colonial disruption and collective trauma that affect diverse Indigenous nations worldwide. However, despite observed higher rates, underdiagnosis and misdiagnosis are serious concerns due to notable structural barriers and healthcare systems that are under-resourced and ill-equipped for the needs of Indigenous populations. Existing diagnostic guidelines and approaches must be evaluated for how well they attend to Indigenous cultural knowledges, Indigenous experiences with colonisation, and determinants of Indigenous Peoples' health.

Indigenous communities and populations often have limited access to dementia care resources (2). This is particularly true for Indigenous People living in rural and remote communities who often need to travel long distances to visit a physician (2). In addition, many older Indigenous People speak an Indigenous language as their first language, which has implications for diagnosis and care. With a widespread lack of health services offered in these languages, older Indigenous adults often struggle to communicate with physicians, making it increasingly difficult to recognise the signs and symptoms of dementia (2). Additional healthcare resources for Indigenous populations will facilitate improved access to diagnosis, but it is equally critical that systemic barriers arising from racism and discrimination be addressed. For urban Indigenous populations, although there may be a greater availability of formalised healthcare services, systemic racism rooted in healthcare systems create a significant barrier to accessing healthcare (3), therefore preventing or delaying a diagnosis of dementia. Fears of experiencing racism or discrimination in healthcare service settings can prevent individuals from seeking medical help for symptoms of dementia. Indigenous families may avoid accessing healthcare due to a lack of trust in colonial institutions, and a lack of culturally-relevant, or culturally-appropriate care (3).

“ For urban Indigenous populations, although there may be a greater availability of formalised healthcare services, systemic racism rooted in healthcare systems create a significant barrier to accessing healthcare, therefore preventing or delaying a diagnosis of dementia.

Disparate access to primary healthcare and neuroimaging services among Indigenous populations, accompanied by restrictive diagnostic criteria (4), have contributed to the underdiagnosis of dementia in Indigenous populations. Emerging clinical guidelines and diagnostic resources offer the opportunity to address the health and healthcare disparity that Indigenous Peoples with dementia experience. Recommendations from the Fifth Canadian Consensus Conference on the diagnosis and treatment of dementia (CCCDTD); highlight the importance of targeted case-finding by primary healthcare professionals who should be 'vigilant for potential symptoms' and subsequent anatomical neuroimaging in most situations (4). Current recommendations in Canada also propose using an 'objective assessment' such as the Montreal Cognitive Assessment (MoCA) or the Mini-Mental State Examination (MMSE) to aid in the diagnosis of dementia (4). However, research findings from Indigenous-engaged dementia research projects raise concerns that standard Western biomedical assessments do not accurately detect dementia in Indigenous populations (5,6). In response to these concerns, culturally-relevant cognitive assessment tools have been developed to aid in accurate case-finding of dementia in Indigenous communities and populations. These include the Kimberley Indigenous Cognitive Assessment (KICA) in Australia (7), the Māori

Assessment of Neuropsychological Abilities (MANA) in New Zealand (8), and the Canadian Indigenous Cognitive Assessment (CICA) (6) in Canada. While these resources are promising, any success will require strategic engagement with Indigenous communities, healthcare providers and health system policymakers to enable effective uptake and implementation.

It is critical for healthcare providers to comprehend that dementia is influenced by intergenerational social traumas experienced as pervasive poverty, accumulative psychosocial adversities, racism, cultural genocide and social exclusion. Key knowledge includes how historical and ongoing colonisation and discrimination towards Indigenous People in Canada has a lasting impact on the health of Indigenous populations, resulting in higher rates of chronic illness and comorbidities within Indigenous populations compared to non-Indigenous populations (9). Further, chronic illnesses also influenced by colonisation, such as diabetes and hypertension, have been identified as risk factors for the development of dementia (10). This increases the complexity of medical needs in a population that is already underserved by the healthcare system. As a result, the presence of multiple chronic illnesses not only increases the complexity of disease but may confound potential dementia diagnoses. For effective and culturally safe diagnosis and care, healthcare providers must fully comprehend and be responsive to the very complex social and cultural realities of Indigenous Peoples that influence dementia. Ignoring this reality is not only a missed opportunity for diagnostic clarity and appropriate critical management approaches, but it is also an erasure revealing complicity in perpetuating colonial violence towards Indigenous Peoples.

In alignment with equity-oriented care, a potential model to inform a framework for addressing diagnostic barriers for Indigenous populations may emerge from the Educating for Equity Care Framework that was developed with a focus on diabetes in Indigenous populations but has generalisable principles for other conditions. According to Crowshoe et al., (11), the principles offered by this framework emphasise that: 'colonisation is the predominant cause of health inequity for Indigenous People.' Furthermore, 'healthcare equity is providing appropriate resources according to need and addressing differential treatment arising from system and individual factors' while 'empowerment is building capacity within individuals to address social determinants influencing health outcomes,' and that 'culture, by respecting its diverse perspectives and experiences, is a facilitator of the clinical relationship and patient capacity.'

It is critical for healthcare providers to comprehend that dementia is influenced by intergenerational social traumas experienced as pervasive poverty, accumulative psychosocial adversities, racism, cultural genocide and social exclusion.

By understanding the key structural challenges and enablers for Indigenous populations, we can develop better responses to the unique needs of Indigenous adults with dementia, as well as the needs of their carers. The standardised approaches used in non-Indigenous populations have limitations that render them ineffective for the accurate diagnosis and monitoring of dementia in Indigenous populations. The uptake of culturally-safe cognitive assessment tools and equity-oriented approaches will aid in more accurate case-finding, thus improving detection and diagnosis of dementia in Indigenous populations. With an improved understanding of dementia prevalence, appropriate and accessible infrastructure can be developed alongside policies and community-level healthcare services appropriate for Indigenous People around the world.

References

1. Warren LA, Shi Q, Young K, Borenstein A, Martiniuk A. Prevalence and incidence of dementia among indigenous populations: A systematic review. Int Psychogeriatrics 2015;27:1959–70. https://doi.org/10.1017/S1041610215000861.
2. Jacklin K, Pace JE, Warry W. Informal dementia caregiving among Indigenous Communities in Ontario, Canada. Care Manag Journals 2015;16:106–20. https://doi.org/10.1891/1521-0987.16.2.106.
3. Kitching GT, Firestone M, Schei B, Wolfe S, Bourgeois C, O'Campo P, et al. Unmet health needs and discrimination by healthcare providers among an Indigenous population in Toronto, Canada. Can J Public Heal 2020;111:40–9. https://doi.org/10.17269/s41997-019-00242-z.
4. Ismail Z, Black SE, Camicioli R, Chertkow H, Herrmann N, Laforce R, et al. Recommendations of the 5th Canadian Consensus Conference on the diagnosis and treatment of dementia. Alzheimer's Dement 2020;16:1182–95. https://doi.org/10.1002/alz.12105.
5. Jacklin K, Walker J. Cultural understandings of dementia in indigenous peoples: A qualitative evidence synthesis. Can J Aging 2020;39:220–34. https://doi.org/10.1017/S071498081900028X.

6. Walker JD, O'Connell ME, Pitawanakwat K, Blind M, Warry W, Lemieux A, et al. Canadian Indigenous Cognitive Assessment (CICA): Inter-rater reliability and criterion validity in Anishinaabe communities on Manitoulin Island, Canada. Alzheimer's Dement Diagnosis, Assess Dis Monit 2021;13:1. https://doi.org/10.1002/dad2.12213.
7. LoGiudice D, Smith K, Thomas J, Lautenschlager NT, Almeida OP, Atkinson D, et al. Kimberley Indigenous Cognitive Assessment tool (KICA): Development of a cognitive assessment tool for older indigenous Australians. Int Psychogeriatrics 2006;18:269–80. https://doi.org/10.1017/S1041610205002681.
8. Dudley MD. Māori Assessment of Neuropsychological Abilities (MANA): A cognitive, functional and wellbeing screening tool for dementia in older Māori. Alzheimer's Dement 2020;16. https://doi.org/10.1002/alz.040110.
9. Walker JD. Aging and frailty in first nations communities. Can J Aging 2020;39:133–44. https://doi.org/10.1017/S0714980817000319.
10. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 2020;396:413–46. https://doi.org/10.1016/S0140-6736(20)30367-6.
11. Crowshoe LL, Henderson R, Jacklin K, Calam B, Walker L, Green ME. Educating for Equity Care Framework: Addressing social barriers of Indigenous patients with type 2 diabetes. Can Fam Physician 2019;65:25–33.

Conclusions

The scientific and medical communities are not immune to long-standing personal and cultural biases. At the heart of this Chapter is how such bias may hinder an accurate and timely diagnosis of dementia. Across the globe, this collection of essays points to the racial, ethnic, demographic, language, gender, education and socioeconomic factors that influence this diagnostic disparity, while also acknowledging that early diagnosis is a healthcare priority that must be addressed. Providing medical access to individuals with dementia and services for their families is essential as are solutions to develop targeted interventions to improve care provided and quality of life. As worldwide life expectancy increases, these are critical factors to consider today and for the future.

That is why there is such a rallying cry for change and recommendations that include campaigns to increase public awareness about brain health and reduce its associated stigma as well as outreach to underserved groups, all to help overcome systemic barriers in place. This includes adapting standardised assessment tests to account for educational and cultural differences. Under- or late diagnosis adds a tremendous burden on individuals with dementia, their carers and the healthcare system in general. An improved understanding of dementia is needed to reform infrastructure in a meaningful and necessary way, as well as integrate consequential policy changes.

Chapter 21
Impact of a world pandemic on the diagnosis of dementia

Claire Webster

Key points

- The COVID-19 pandemic has delayed access to diagnostic assessments and follow-up health and social care services.
- Social isolation has worsened dementia-related symptoms even in the absence of COVID-19.
- There is expected to be an underreporting of COVID-19-associated deaths in people with dementia.

General background

The global health crisis that is the COVID-19 pandemic will likely have lasting economic, logistical and health-care system consequences. Whilst attention has been rightfully focused on combatting this infectious disease, such dedicated efforts have greatly strained healthcare resources. One of the outcomes of this worldwide crisis is that individuals and their families have had to wait to obtain dementia diagnostic assessments, thus many remain undiagnosed. At the time of writing, it is too early to fully appreciate the full extent of COVID-19-related deaths in people with dementia, but in some western countries, like` Canada, the majority of deaths in long-term care facilities during this period were in fact people with dementia. The expert essays within this Chapter address the human repercussions of the pandemic on people with dementia and their families; the epidemiologic impact in Italy where the virus struck early and hard, and its adverse correlation to dementia treatment and services; and lastly, a first look at the pathological impact of COVID-19 on the brain of people with dementia.

Survey results

Among the 1,111 multidisciplinary clinicians who responded to this survey, 94% indicated that pre-pandemic waiting times for an initial assessment for suspected dementia was less than six months. However, 90% responded that additional delays had been incurred due to pandemic-related restrictions. Fortunately, 23% had no interruption in diagnostic services while 70% had partial and only 7% experienced a total interruption.

Among the 2,327 people with dementia and carers who replied to the survey, 812 had in-person access to a clinician when they presented symptoms as well as a multitude of options available via remote access (Chart 1). Notably, 163 of the respondents indicated that they were not provided any options for communication with a clinician. Among those with an in-person or virtual appointment, 72% of respondents attended, suggesting that over a quarter did not.

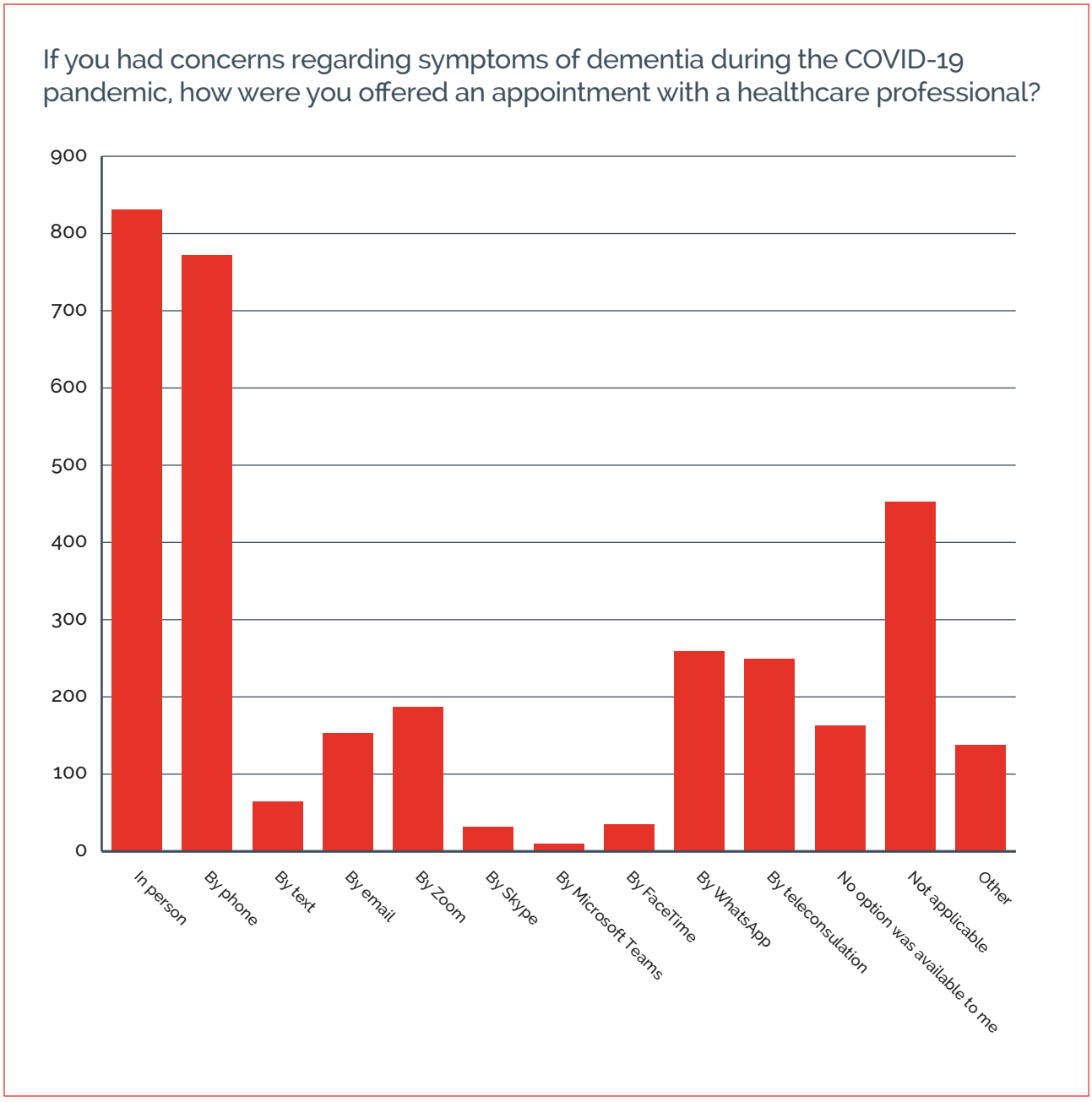


Chart 1. People with dementia and carer responses.

Expert essay

Understanding the impact of COVID-19 on people with dementia and their carers[i]

Juanita-Dawne Bacsu,[1] Megan E. O'Connell,[1] Claire Webster,[2] Lisa Poole,[3] Mary Beth Wighton,[3] Saskia Sivananthan,[4] Allison Cammer,[1] Mahsa Azizi,[1] Karl Grewal,[1] Shoshana Green,[1] Rory Gowda-Sookochoff,[1] Raymond J. Spiteri[1]

1 University of Saskatchewan, CANADA
2 Caregiver Crosswalk, CANADA
3 Dementia Advocacy Canada, CANADA
4 Alzheimer Society of Canada, CANADA

Introduction

There is an urgent need to understand the experiences of people living with dementia and their carers during the COVID-19 pandemic. Compared to other groups, people with dementia have an increased risk of contracting COVID-19, a higher risk of hospitalisation, and a greater risk of severe complications or mortality from COVID-19 (1). Globally, statistics show that up to 75% of COVID-19 deaths in care facilities have been people living with dementia (2). Moreover, the pandemic has significantly restricted and delayed access to dementia diagnosis and memory assessment services. In England, statistics show a steady decrease in dementia diagnosis rates, declining from 67.6% in February 2020 to 63.2% in July 2020 (3). These numbers indicate that more people are remaining undiagnosed with dementia. However, a timely diagnosis is critical as it enables people with dementia to acquire relevant information and support services, plan for the future, engage in cognitive health promotion activities, and access pharmaceutical treatments to improve their quality of life.

In response to COVID-19, several governments worldwide imposed lockdown measures and physical distancing restrictions to reduce the spread of the virus. These measures included limitations on social gatherings and travel outside of the home, visitation bans in long-term care facilities, and restricted/terminated access to healthcare services and supports. However, such constraints are having adverse effects on people with dementia and their carers. Research shows that carers of people with dementia are overwhelmed by the additional caregiving needs that the pandemic has imposed on them. Despite this, research focusing on recognising how COVID-19 has defined the experiences and needs of people living with dementia is currently scarce. Given that, the purpose of this investigation was to examine the impact of COVID-19 on people with dementia and their carers, and thus, inform services and future COVID-19 policies.

Methods

Two methods were employed for this research including a scoping review and an analysis of Twitter data (4,5). The scoping review was conducted to synthesise peer-reviewed COVID-19 literature on people with dementia published between January 2020 and September 2020. Search terms included a combination of words such as: coronavirus, COVID-19, SARS-CoV-2, dementia and 'Alzheimer's disease.' Six databases were searched: Scopus, PubMed, CINAHL, EMBASE, Web of Science, and Google Scholar. Of the 420 initial records, 21 articles were included in the review.

For the Twitter analysis, tweets were collected using the GetOldTweets application in Python from February 15, 2020 to September 7, 2020. Search terms included keywords for dementia (namely Alzheimer's, Lewy body disease, etc.) and COVID-19 (coronavirus, etc.). From the initial 20,800 tweets, filters were used to exclude irrelevant tweets. The remaining 5,063 tweets were exported to an Excel document for analysis and divided among 7 coders with an additional coder managing inter-coder reliability during thematic analysis.

i This work was supported by Team 15 in the Canadian Consortium on Neurodegeneration in Aging (CCNA) which is supported by the Canadian Institutes of Health Research with funding from several partners, including the Saskatchewan Health Research Foundation, the Centre for Aging and Brain Health, and the Alzheimer Society of Canada (ASC).

Results

Based on the analysed research, five themes emerged: i) lockdown and confinement challenges; ii) separation and loss; iii) unpaid sacrifices of formal carers; iv) COVID-19 confusion, despair, and declining psychological health; and v) informal carer fatigue and burnout.

Lockdown and confinement challenges

A prevalent theme that emerged was the issue of COVID-19 lockdown and confinement challenges. These difficulties included changes to daily routines, physical inactivity and limited or terminated access to health services and supports. These may have included dementia diagnosis and memory assessment services, home care, day care, meal programmes, respite care, healthcare specialists, exercise programmes, cognitive therapy, and adequate long-term care housing. Loneliness and mental health struggles were also at the forefront of the shared comments. The challenges that lockdown presented are illustrated in the following tweets:

'… My mother cannot get care support as she does not currently have a dementia diagnosis because all her appointments have been cancelled since March. There have been no COVID deaths in the local hospital for weeks…'

'… the hardest part is being stuck 24/7 in the house with my mom who has severe dementia. It is hell! She had a day care but it closed. I can't get respite bc [sic] I'm terrified of exposing her to covid [sic]. I fight loneliness, depression and boredom everyday [sic]!'

Separation and loss

Another major theme was the psychological sense of loss and separation resulting from the actual physical barriers imposed during the pandemic. Specific instances of separation included separation due to death, during the dying process, and those resulting from visitation bans in care facilities such as long-term residences or hospitals. Underlying these instances of physical separation is a clear psychological disconnect accompanied by feelings of loss. This is also evident when related to a heightened awareness of accelerated cognitive decline in the person with dementia during the pandemic. This theme of separation and loss is depicted in the following tweets:

'My husband passed away... victim of COVID protocol! He had dementia, didn't understand why I couldn't visit him. He lost hope, 36 lbs in 23 days; could not be saved. This is so cruel to do to our seniors/ he was a veteran!!! WRONG!!!'

'Let me tell you what this covid [sic] lockdown did, it killed my daddy. He had dementia and he was still doing good, then the lockdown, we weren't there to hold him and to help feed him. When we went to see him, he was a shell, there was nothing left of him…'

Unpaid sacrifices of formal care providers

The theme of unpaid sacrifices made by formal carers (such as long-term care facility workers, care aides, nurses, and more) was especially predominant throughout the tweets. Formal care providers identified numerous personal sacrifices made for work and to provide care during the pandemic. For instance, these formal carers described sacrificing their participation at family events, parenting responsibilities, and social activities to help protect individuals with dementia and family members from potential exposure to the virus. Carers universally expressed an emotional connection to people with dementia as well as a sense of duty in providing care, noting that this was 'more than simply a job.' In turn, many conveyed concerns for the health of their own families due to exposures at work. Limited personal protective equipment and social distancing challenges were two of the reasons for this. They also made trade-offs to help ensure the safety of the people they were caring for by limiting their outside contacts. These sacrifices are highlighted in the following tweets:

'I'm a nurse with COVID, probably from reusing dirty N95s and working with dementia patients who could not grasp the need to wear a mask and social distance.'

'I'm a mental health nurse working in a dementia specialist nursing home. My fight is to keep corona [sic] out of the building. There are many of us who will be in hiding to protect our residents…'

COVID-19 confusion, despair, and declining neuropsychological health

Another theme that surfaced was confusion about COVID-19 itself by people living with dementia. As a result, feelings of despair and declining psychological health set in. Many tweeters described how they had difficulties understanding COVID-19 as displayed or personally experienced. The negative psychological repercussions included depression, agitation, anxiety, difficulties sleeping, and cognitive decline. Tweets reported that people living with dementia often could not understand the changes imposed by the pandemic response, such as the visitation bans, social distancing, personal protective equipment, and lockdowns. They required constant education, reminders, and reassurance. The convergence of COVID-19 confusion, despair, and worsening psychological health are underscored in the following tweets:

'Hardest thing to hear is my mom trying to explain to my grandmother, who has dementia, that we can't see her because of the corona. My grandmother repeating that she is in jail. Asking where we are.

'…Or live alone with dementia and all the trouble I have. I can't even drive myself to a doctor. I don't remember all the rules myself. I'm terrible at wearing a mask. Someone pointed out I had it inside out at the covid [sic] testing place. I'm gonna [sic] die, I hope. I'm [sic] tired of life.'

Carer fatigue and burnout

Carer fatigue and burnout was yet another major theme identified in the literature and shared tweets. Here, informal carers were faced with challenges related to increased workloads, financial difficulties, social isolation, fear of COVID-19 exposure, mental health issues, and terminated and/or limited access to healthcare services and support. In essence, lockdown measures substantially limited or cut off services such as home care, day care, respite, and other appropriate care home options. As such, many described the difficulty of dealing with household chores, social isolation, and the increased responsibilities, which frequently led to carer fatigue and feelings of mental, emotional, and physical burnout. The tweet below perfectly reveals how burnout is being confronted:

'Another horrifying day. We are in isolation with my beloved 93 year old Mom. She has descended into terrifying hallucinations and extreme anger because of dementia. We can't get her into nursing care because of COVID...'

There is an imminent need for definitive government leadership and measures to back dementia initiatives during the pandemic. More specifically, governments must rethink a one-size-fits-all response to COVID-19 policy and use a collaborative approach to support people with, or seeking a diagnosis of, dementia. Lockdown policies and the ensuing lack of services have created a support vacuum and have rendered it imperative to make these resources available again. With little access to these healthcare support systems, people with dementia and their carers have now reached crisis point. Moreover, dementia diagnosis and memory assessment must be reprioritised to provide critical healthcare and information during the pandemic. In developing COVID-19 policies and programmes, there is a vital need for collaborative research and co-creation methods to ensure maximum impact.

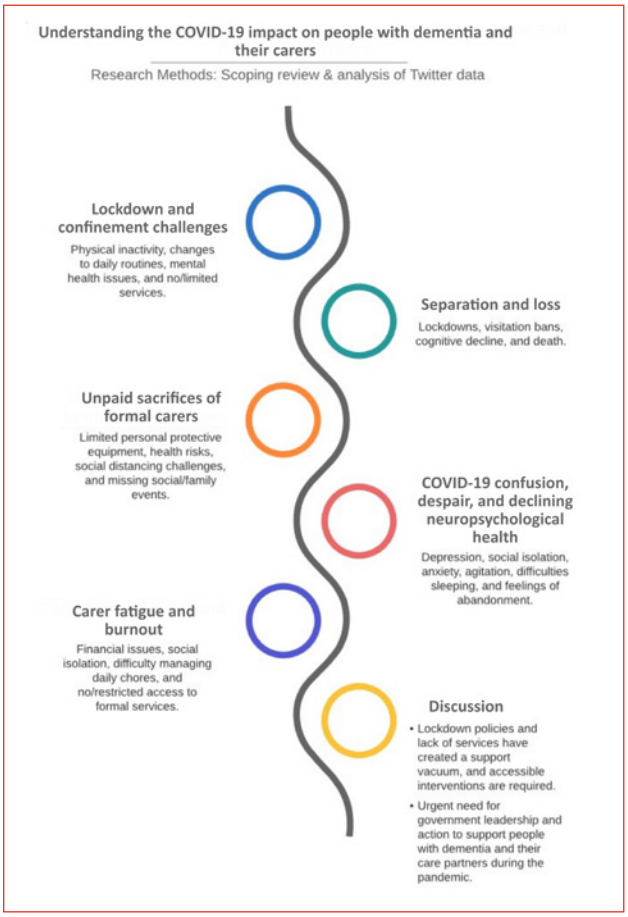


Figure 1. Scoping review and analysis of Twitter data.

References

1. Wang QQ, Davis PB, Gurney ME, Xu R. COVID-19 and dementia: Analyses of risk, disparity, and outcomes from electronic health records in the US. Alzheimer's Dement 2021. https://doi.org/10.1002/alz.12296.
2. Suárez-gonzález A, Livingston G, Cahill S, Hennelly N, Dawson WD, Weidner W, et al. Impact and mortality of COVID-19 on people living with dementia : cross-country report [Internet]. 2020 [cited 2021 Jul 9]. 1–31 p. https://ltccovid.org/2020/07/01/detrimental-effects-of-confinement-and-isolation-on-the-cognitive-and-psychological-health-of-people-.
3. Alzheimer's Society. Worst hit: dementia during coronavirus 2020:1–49. https://www.alzheimers.org.uk/sites/default/files/2020-09/Worst-hit-Dementia-during-coronavirus-report.pdf.
4. Bacsu JD, O'Connell ME, Cammer A, Azizi M, Grewal K, Poole L, et al. Using twitter to understand the COVID-19 experiences of people with dementia: Infodemiology study. J Med Internet Res [Internet]. 2021 Feb 1 [cited 2021 Jul 9];23(2). https://pubmed.ncbi.nlm.nih.gov/33468449/.
5. Bacsu JDR, O'Connell ME, Webster C, Poole L, Wighton MB, Sivananthan S. A scoping review of COVID-19 experiences of people living with dementia. Can J Public Heal [Internet]. 2021 Jun 1 [cited 2021 Jul 9];112(3):400–11. https://pubmed.ncbi.nlm.nih.gov/33825134/.

Expert essay

COVID-19 and dementia in Italy: a critical appraisal

Nicola Vanacore, Marco Canevelli

National Center for Disease Prevention and Health Promotion, Istituto Superiore di Sanita, Rome, ITALY

As of June 23, 2021, a total of 4,253,460 COVID-19 cases and 127,291 COVID-19 related deaths were recorded in Italy, placing the country in eighth place among the nations hardest hit by the pandemic (1) and among those with the highest case-fatality rate.

The COVID-19 pandemic has had, and continues to have, a profound impact on the health and well-being of people with dementia living in Italy. Based on the data extrapolated from the medical reports of approximately 7,200 individuals who died with COVID-19 in national hospitals between February 2020 and April 2021, 31.8% of the women and 17.5% of the men had a history of dementia (2). Several studies conducted in the country have suggested that these high mortality rates in people with dementia may be linked to:

1. The tendency of COVID-19 to present with atypical and misleading manifestations, such as delirium and behavioural disruptions, in older adults with cognitive deficits. This often results in delayed diagnosis and treatments (3).
2. The reduced access to intensive care and supportive therapies (4).
3. The number of people residing in long-term care facilities where the transmission of SARS-CoV-2 was more protracted and where significant organisational issues and resource shortages occurred (5).

Other studies conducted in Italy have also shown that a large percentage of people with dementia who did not contract the infection experienced a considerable decline in their cognitive, functional, and behavioural disturbances (6,7). This clinical deterioration was likely the result of changes imposed by the epidemic that affected their daily routines, placed them in prolonged isolation, and interrupted dedicated services, such as day care centres.

Underreporting of people with dementia dying with COVID-19 in Italy

Excess mortality, defined as the difference between all-cause mortality in observed and expected deaths, is considered a more accurate indicator of the COVID-19 death toll. The excess includes deaths correctly attributed to COVID-19 as well as those that went unreported or were incorrectly ascribed to other causes (8).

In 2020, the total number of deaths in Italy from all causes (n=746,146) was the highest recorded since the Second World War. Overall, 100,526 more deaths were registered comparatively to the 2015–2019 average, resulting in a 15.6% excess (9). Examining the age groups, the increase in deaths among those over the age of 80 accounted for 76.3% of the overall excess mortality (9). Unfortunately, complete analysis is not yet available for the 2020 year on the specific causes of death.

According to an Italian National Institute of Statistics report based on death certificates, 49,000 excess deaths were registered from March to April 2020, compared to the average for the same months in the previous five years. Considering the initial/underlying cause of the death, 60% of the deaths were attributable to COVID-19 (n=29,210), 10% to pneumonia, and 30% to other causes (10). Deaths from dementia and Alzheimer's disease increased by 49% (n=2,736 excess deaths) relative to the reference period (10). This data suggests that many people with dementia may have died during the first wave of the pandemic with undiagnosed COVID-19 or as a result of the fragmentation of care that prevented proper management of other concomitant medical conditions. Italian excess mortality diverged when verifying the location where death occurred, namely 155% in long-term care facilities, 46% in hospitals, and 27% at home (10).

It is conceivable that these figures may even be underestimated. It is a well-established fact that dementia is frequently underreported on death certificates both as a root or contributing cause of death. In a study examining 5,311 death certificates, representing 16.7% of total deaths among people testing positive for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) as of May 28, 2020, COVID-19 was found to be the underlying cause in 88.3% of cases. Dementia and Alzheimer's disease were reported as underlying causes in only in 38 cases, or 0.7%, and as a comorbidity in 6.1% of certificates (11). The findings show that dementia is indicated on death certificates at a significantly lower rate than data obtained from medical records. These indicate that 15.8% of COVID-19-related deaths occurred in people with dementia during this same period. (4). In the second half of 2020, the discrepancy between death certificates and clinical data widened. More precisely, dementia was reported as a comorbidity in people deceased with COVID-19 in 11.9% of cases based on death certificates as opposed to 30% of cases based on medical records (12). Therefore, it appears likely that the number of people with dementia who have died with COVID-19 is significantly underestimated.

The impact of the COVID-19 pandemic on dementia services in Italy

The pandemic also wielded a major impact on the services dedicated to the diagnosis, treatment, and care of people living with dementia and cognitive disorders.

As observed in other countries, most outpatient services (known as Centres for Cognitive Disorders and Dementia, CCDDs) markedly reduced their activities. For instance, between March 2020 and April 2020, 66.7% and 77.4% of patients respectively missed their first and follow-up appointments at a tertiary CCDD in Rome due to the government's restrictive measures (13).

Concurrently, most day care services closed, making the daily management of people with dementia even more difficult as it was almost entirely entrusted to families and formal carers.

Italian long-term care facilities faced critical situations with the SARS-CoV-2 outbreak. A national survey, covering the period of March 25 to May 5, 2020, was conducted to collect information regarding the spread and impact of the SARS-CoV-2 infection in long-term care facilities, and on how suspected and/or confirmed cases were managed within this setting (5). A total of 1,356 facilities hosting 100,806 residents were surveyed. Overall, 9,154 residents died from unrelated causes from February 1, 2020, to the questionnaire's completion date. Among them, 7.4% had COVID-19 and 33.8% had flu-like symptoms, most of whom were not provided with SARS-CoV-2 testing. Lack of personnel, difficulty in transferring people to hospitals or other services, residents isolating with COVID-19, high number of occupied beds, and specific geographic locations such as northern and central Italian regions, were positively associated with the spread of COVID-19 in these facilities (5). About one-third also reported the occurrence of adverse events, defined as any harm or injury resulting from medical care or the failure to provide care. These included falls, injuries, behavioural disorders, delirium, adverse drug events, dehydration, and bowel obstructions (14). The facilities that reported adverse events also indicated a higher use of psychoactive drugs and physical restraints compared with those that did not report any event. The determinants associated with these adverse events were the high number of occupied beds, residents hospitalised with flu-like symptoms and the geographical locations (14). The identification of these variables highlighted a pattern in facilities that were faced with critical situations at the virus' outbreak.

In October 2020, the Italian Dementia National Plan Working Group released the 'Interim guidance for the appropriate support of people with dementia in the current COVID-19 pandemic scenario'(15). This document provides practical information and recommendations on how to improve individuals' care at home and in outpatient, semi-residential, and residential settings. Its contents have already been disseminated to all Italian dementia services and general practitioners.

References

1. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. WHO Coronavirus (COVID-19) Dashboard With Vaccination Data [Internet]. Who. 2021 [cited 2021 Jul 9]. p. 1–5. https://covid19.who.int/.
2. Istituto Superiore di Sanità. Characteristics of SARS-CoV-2 patients dying in Italy Report based on available data on January 27th, 2021 [Internet]. 2020 [cited 2021 Jul 9]. https://www.epicentro.iss.it/en/coronavirus/bollettino/Report-COVID-2019_21_may_2020.pdf.
3. Poloni TE, Carlos AF, Cairati M, Cutaia C, Medici V, Marelli E, et al. Prevalence and prognostic value of Delirium as the initial presentation of COVID-19 in the elderly with dementia: An Italian retrospective study. EClinicalMedicine [Internet]. 2020 Sep 1 [cited 2021 Jul 9];26. https://pubmed.ncbi.nlm.nih.gov/32838241/.
4. Canevelli M, Palmieri L, Raparelli V, Lo Noce C, Colaizzo E, Tiple D, et al. Prevalence and clinical correlates of dementia among COVID-19-related deaths in Italy. Alzheimer's Dement Diagnosis, Assess Dis Monit [Internet]. 2020 [cited 2021 Jul 9];12(1). https://pubmed.ncbi.nlm.nih.gov/33225041/.
5. Lombardo FL, Bacigalupo I, Salvi E, Lacorte E, Piscopo P, Mayer F, et al. The Italian national survey on Coronavirus disease 2019 epidemic spread in nursing homes. Int J Geriatr Psychiatry [Internet]. 2021 Jun 1 [cited 2021 Jul 9];36(6):873–82. https://pubmed.ncbi.nlm.nih.gov/33368636/.
6. Cagnin A, Di Lorenzo R, Marra C, Bonanni L, Cupidi C, Laganà V, et al. Behavioral and psychological effects of coronavirus disease-19 quarantine in patients with dementia. Front Psychiatry [Internet]. 2020 Sep 1 [cited 2021 Jul 9];11:1–15. https://pubmed.ncbi.nlm.nih.gov/33033486/.

7. Canevelli M, Valletta M, Toccaceli Blasi M, Remoli G, Sarti G, Nuti F, et al. Facing Dementia During the COVID-19 Outbreak [Internet]. Vol. 68, Journal of the American Geriatrics Society. J Am Geriatr Soc; 2020 [cited 2021 Jul 9]. p. 1673–6. https://pubmed.ncbi.nlm.nih.gov/32516441/.
8. World Health Organization. WORLD HEALTH STATISTICS – MONITORING HEALTH FOR THE SDGs. World Heal Organ [Internet]. 2016 [cited 2021 Jul 9];1.121. https://reliefweb.int/report/world/world-health-statistics-2021-monitoring-health-sdgs.
9. ISTAT. Impatto dell'epidemia Covid-19 sulla mortalità totale della popolazione residente. Primo Quadrimestre, ISTAT [Internet]. 2020 [cited 2021 Jul 9];1–23. https://www.istat.it/it/archivio/254507.
10. Istat – Istituto Nazionale di Statistica. Prima ondata della pandemia. Un'analisi della mortalità per causa e luogo del decesso | Marzo-Aprile 2020 [Internet]. Statistiche Report. 2021 [cited 2021 Jul 9]. https://www.istat.it/it/archivio/256854.
11. Grippo F, Navarra S, Orsi C, Manno V, Grande E, Crialesi R, et al. The Role of COVID-19 in the Death of SARS-CoV-2–Positive Patients: A Study Based on Death Certificates. J Clin Med [Internet]. 2020 Oct 27 [cited 2021 Jul 9];9(11):3459. https://pubmed.ncbi.nlm.nih.gov/33121176/.
12. Grippo F, Grande E, Maraschini A, Navarra S, Pappagallo M, Marchetti S, et al. Evolution of Pathology Patterns in Persons Who Died From COVID-19 in Italy: A National Study Based on Death Certificates. Front Med [Internet]. 2021 Mar 22 [cited 2021 Jul 9];8. https://pubmed.ncbi.nlm.nih.gov/33829025/.
13. Spalletta G, Porcari DE, Banaj N, Ciullo V, Palmer K. Effects of COVID-19 Infection Control Measures on Appointment Cancelation in an Italian Outpatient Memory Clinic. Front Psychiatry [Internet]. 2020 Nov 30 [cited 2021 Jul 9];11. https://pubmed.ncbi.nlm.nih.gov/33329152/.
14. Lombardo FL, Salvi E, Lacorte E, Piscopo P, Mayer F, Ancidoni A, et al. Adverse Events in Italian Nursing Homes During the COVID-19 Epidemic: A National Survey. Front Psychiatry [Internet]. 2020 Sep 30 [cited 2021 Jul 9];11. https://pubmed.ncbi.nlm.nih.gov/33132938/.
15. Ministero della salute. Tavolo per il monitoraggio del recepimento e implementazione del Piano Nazionale Demenze. 2017.

Expert essay

COVID-19 and dementia incidence

Raj N Kalaria,[1] Vincent C.T. Mok[2]

[1] Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UNITED KINGDOM
[2] Gerald Choa Neuroscience Centre, Lui Che Woo Institute of Innovative Medicine, Division of Neurology, Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, CHINA

Global trends suggest that dementia incidence rates are declining in some western communities by as much as 5% despite population growth. However, in low- and middle-income countries (LMICs), these rates appear to be increasing (1). The current pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), or COVID-19, has major global implications for dementia rates including Alzheimer's disease. Several factors are likely to change the dynamics of dementia incidence now and for years to come, with specific impact on long-term care. Older people with cognitive impairment or dementia are more susceptible to viral infection because of their age, co-existing morbidities, immunosenescence (ageing of the immune system), and reduced ability to adhere to preventive measures (2). While it may vary from country to country depending on economic status and social structure type, up to 70% of the retired older people with Alzheimer's disease or another form of dementia may reside in long-term care facilities. In some instances, throughout 2020, as many as three-quarters of SARS-CoV-2-related deaths reported occurred in care residences. (3). Once infected, older people with dementia died earlier than expected, whereas survivors succumbed to long-term consequences or long-haul COVID. This is complicated by the uncertainty and variation in cases of SARS-CoV-2 infected older people who may already be in the prodromal phase or have early cognitive impairment. COVID-19 protective measures that included confinement and isolation, restrictions on social interaction, limits on physical tasks or daily activities of living as well as a lack of emotional support normally provided by visiting staff and/or family members, all likely commingled to further deteriorate cognitive, behavioural, and physical conditions in residents of care facilities and made them more vulnerable. Incidences of family dynamics stress, under these same conditions, were also a contributing factor to weakened resilience. In poorer economies of many LMICs, the peculiar challenges of SARS-CoV-2 for the elderly are preceded by existing fragile healthcare systems, ongoing poverty and poor healthcare financing. Infection may have further predisposed an elderly adult to worsening neuropsychiatric symptoms such as anxiety, agitation and depression (4).

SARS-CoV-2, as well as other members of the human coronaviruses family, are neurotropic and act as pathogens in the central nervous system. The neurological symptoms associated with SARS-CoV-2 infection include confusion (brain fog), headache, ageusia, anosmia, dizziness, epilepsy, and acute cerebrovascular disease. Post-mortem studies confirm the presence of both SARS-CoV-2 antigen and ribonucleic acid (RNA) in the brain tissue of COVID-19 individuals, suggesting direct invasion of the virus into the central nervous system. While the virus may hasten death or dementia, it may also cause neurological injury or accelerate brain ageing mechanisms to cause new dementia variants within the spectrum of long-term complications of COVID-19 (5). This is analogous to the notion that HIV survivors on combination antiretroviral therapy (ART) may unmask dementia syndromes including Alzheimer's type of pathologies (6). Up to 30% of SARS-CoV-2 infected individuals may suffer strokes and a percentage of those who survive may develop delayed post-stroke dementia (7). Given all these factors, it is difficult to predict exactly how dementia diagnosis or prevalence will change but it is probable that dementia and Alzheimer's disease diagnosis will undergo a major change, particularly because of expected variant presentations. Meanwhile, to mitigate some of these challenges, healthcare services have continued to provide consultations and clinical care via telemedicine and even established home-based care for ambulatory geriatric patients to prevent the risk of infection by attending regular hospital visits.

References

1. Nichols E, Szoeke CEI, Vollset SE, Abbasi N, Abd-Allah F, Abdela J, et al. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol [Internet]. 2019 Jan 1 [cited 2021 Jul 9];18(1):88–106. https://pubmed.ncbi.nlm.nih.gov/30497964/
2. Mok VCT, Pendlebury S, Wong A, Alladi S, Au L, Bath PM, et al. Tackling challenges in care of Alzheimer's disease and other dementias amid the COVID-19 pandemic, now and in the future [Internet]. Vol. 16, Alzheimer's and Dementia. Alzheimers Dement; 2020 [cited 2021 Jul 9]. p. 1571–81. https://pubmed.ncbi.nlm.nih.gov/32789951/
3. Singh H, Popli T. Stopping the sars-cov-2 surge in the usa-cdc recommendations and ground realities [Internet]. Vol. 88, Advances in Respiratory Medicine. Adv Respir Med; 2020 [cited 2021 Jul 9]. p. 173–5. https://pubmed.ncbi.nlm.nih.gov/32706099/
4. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Vol. 396, The Lancet. Lancet Publishing Group; 2020. p. 413–46.
5. de Erausquin GA, Snyder H, Carrillo M, Hosseini AA, Brugha TS, Seshadri S. The chronic neuropsychiatric sequelae of COVID-19: The need for a prospective study of viral impact on brain functioning. Alzheimer's Dement [Internet]. 2021 Jun 1 [cited 2021 Jul 9];17(6):1056–65. https://pubmed.ncbi.nlm.nih.gov/33399270/
6. Fulop T, Witkowski JM, Larbi A, Khalil A, Herbein G, Frost EH. Does HIV infection contribute to increased beta-amyloid synthesis and plaque formation leading to neurodegeneration and Alzheimer's disease? J Neurovirol [Internet]. 2019 Oct 1 [cited 2021 Jul 9];25(5):634–47. https://pubmed.ncbi.nlm.nih.gov/30868421/
7. Allan LM, Rowan EN, Firbank MJ, Thomas AJ, Parry SW, Polvikoski TM, et al. Long term incidence of dementia, predictors of mortality and pathological diagnosis in older stroke survivors. In: Brain [Internet]. Brain; 2011 [cited 2021 Jul 9]. p. 3713–24. https://pubmed.ncbi.nlm.nih.gov/22171356/

Conclusions

The impact of the COVID-19 pandemic is far-reaching, and we have yet to cross the finish line. Most countries enforced lockdown measures to contain the spread of the virus which greatly restricted people's movements and cut off much access to healthcare services for people with dementia symptoms, or follow-up appointments for those already diagnosed. Not only that, but it resulted in feelings of isolation, separation and loss with ensuing repercussions manifesting as depression, agitation, anxiety, troubled sleep, and cognitive decline. It also placed the onus of responsibility on informal carers who faced their own challenges with increased workloads, leading to carer fatigue and burnout as services that provided needed respite were closed.

As an example, the impact of COVID-19 in Italy has been extensive with high death rates. Greatly affecting the older population in long-term care facilities, many experienced additional deteriorations of cognitive and functional ability. This too can be traced to the reduction or cessation of medical and support services. The full measure of COVID-19's effect is not fully known as data from death certificates and medical records varies substantially in reporting dementia as a contributing factor.

The fact is, older people with cognitive impairment or dementia who reside in long-term care facilities are more susceptible to infection, leading to higher rates of death in this age group and setting. The isolation imposed by lockdown measures exacerbated conditions in low- and middle-income countries where fragile healthcare systems already exist. In the interim, efforts to set up telemedicine and home-based care for geriatric individuals are aimed at providing reliable medical care.

Chapter 22
Multiple comorbidities

José A. Morais

Key points

- Differentiating whether a dementia syndrome is due to Alzheimer's disease, cerebrovascular disease or mixed origin may be challenging as they present similar risk factors and cognitive profiles.
- More than 80% of the global burden for stroke is attributable to modifiable risk factors.
- Better understanding of the determinants of vascular contributions to cognitive disorders is required.
- Risk of malnutrition and subsequent vitamin deficiencies are strongly correlated with cognitive decline and nutritional status should be routinely explored.
- In the case of ventriculomegaly, it is important to evaluate the presence and severity of the key symptoms and signs of idiopathic normal pressure hydrocephalus (gait changes, cognitive decline and urine incontinence).

General background

Most people over the age of 75 have an assortment of medical conditions that may explain, to a certain extent, memory and other cognitive complaints and how they impact activities of daily life. The clinician performing the diagnostic assessment must prioritise these different medical conditions after evaluating the information provided by the individual's medical history, physical examination, and laboratory tests including brain imaging.

The following essays highlight some of the most common conditions influencing the deliberation of a dementia diagnosis, its causes and management. This may include differentiating between dementia caused by Alzheimer's disease and a dementia of vascular origin. Topics range from stroke to nutritional deficits, as well as the surprisingly common anomaly called ventriculomegaly, or enlarged cerebral ventricles, diagnosed upon analysis of brain scans.

Expert essay

The differential diagnosis between Alzheimer's disease and vascular dementia, including the concept of mixed dementia

Lisa W.C. Au, Vincent C.T. Mok

Division of Neurology, Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, CHINA

Challenges inherent to the differentiation

Differentiating whether a dementia syndrome is due to Alzheimer's disease, cerebrovascular disease or a contribution from both (mixed Alzheimer's disease and CVD) can be challenging given that some of the associated risk factors such as age, hypertension and diabetes as well as their cognitive profiles tend to overlap. Yet, determining the contribution of Alzheimer's disease and/or cerebrovascular disease in accounting for the dementia syndrome is important as it will affect its prognosis or treatment of the syndrome. Further, as age is one of the strongest risk factors for both diseases, both co-occurring together is especially common among older people. Autopsy studies show that cerebrovascular disease pathology (for example, lacune, microinfarct, white matter changes, enlarged perivascular space, micro- or macro-haemorrhage, large infarct, atherosclerosis, arteriolosclerosis, cerebral amyloid angiopathy) co-occurs with Alzheimer's disease pathology (namely, amyloid beta [Aβ] and phosphorylated tau [p-tau]) in about 40–80% of dementia cases of older people. What's more, it has additive effects with Alzheimer's disease pathology in lowering cognitive function and increases the odds of dementia especially among those with less burden of Alzheimer's disease pathology (1,2). Given this close association between Alzheimer's disease and CVD, the aetiological contribution to a dementia syndrome for an individual may fall somewhere along a spectrum, with pure Alzheimer's disease at one end of the spectrum and pure cerebrovascular disease at the other end (Figure 1). Other brain pathologies (for example, Lewy bodies) can also mix with Alzheimer's disease and/or cerebrovascular disease.

Mixed dementia involving non-Alzheimer's disease/cerebrovascular disease pathology is not as common as mixed Alzheimer's disease and CVD and will not be discussed further in this essay.

In the context of progressive cognitive decline

Although Alzheimer's disease is characterised by a slowly progressive cognitive decline associated with predominant memory impairment at the initial stage, age-related sporadic cerebral small vessel disease may also present with similar clinical manifestation and may be misdiagnosed as Alzheimer's disease (3). Cerebral small vessel disease is the most common type of cerebrovascular disease associated with cognitive impairment and dementia. A typical cognitive profile of small vessel disease includes prominent executive dysfunction, slow processing speed and memory impairment. Note that the memory impairment in small vessel disease is due to problems retrieving previously encoded information and can be improved with cueing or recognition. This differs from Alzheimer's disease where the problem lies with encoding and storage of information. A neuropsychological assessment battery that evaluates executive function, processing speed and recognition memory may help to clinically differentiate small vessel disease from Alzheimer's disease (4). Other patterns of temporal evolution include acute decline or stepwise deterioration related to stroke event(s) (5). Clinical features that may suggest SVD include parkinsonism, particularly affecting the lower body, upper motor neuron signs (for example, hemiparesis with brisk reflex and extensor plantar response) or pseudobulbar palsy (6). These features may or may not occur in association with the symptoms of a stroke (6). Cerebral small vessel disease can exist on its own while also commonly found to co-occur with Alzheimer's disease. Clinical studies show that among individuals diagnosed with Alzheimer's disease, prevalence of early confluent to confluent white matter hyperintensity (WMH) (refer to Chapter 13) was found to increase from 20% in those under 60 years of age to almost 50% in those over 80 years of age (7). Concurrent presence of small vessel disease in Alzheimer's disease is associated with a more rapid conversion from mild cognitive impairment to dementia (6). Given that direct visualisation of the brain small vessel

with conventional imaging techniques is difficult, in vivo assessment of small vessel disease depends on detecting the impacts of small vessel disease upon the brain parenchyma, which is best seen on MRI. Conventional MRI biomarkers of small vessel disease include WMH, lacunes, microbleeds and enlarged perivascular space (6).

Overall, since SVD may mimic the clinical presentation of Alzheimer's disease, those presenting with progressive cognitive decline characterised by memory complaints may be misdiagnosed as having Alzheimer's disease if a structural brain imaging such as an MRI is not performed. Noteworthy is that if the MRI reveals features of SVD (for example, confluent WMH and/or multiple lacunes), the progressive cognitive syndrome may be due to either pure SVD or to mixed Alzheimer's disease and SVD. In this scenario, medial temporal lobe atrophy (MTA), which is considered an imaging biomarker of Alzheimer's disease, (Chapter 13) may not be a helpful pointer of Alzheimer's disease because it is also associated with small vessel disease. Additional investigations that could detect specific Alzheimer's disease pathology (that is, Aβ and p-tau) may become important. At present, these investigations may include amyloid and tau positron emission tomography (PET) or cerebrospinal fluid (CSF) analysis for Aβ42 (or the Aβ42/Aβ40 ratio) and p-tau (for example, p-tau 181, p-tau 217), which are accessible in more specialised centres. Recent development of blood-based platforms will likely enable easier detection of molecular biomarkers of Alzheimer's disease in daily clinical practice (8).

In the context of stroke

For people presenting with acute cognitive decline immediately after a stroke, it is likely that a vascular component is responsible for the cognitive decline. However, this does not mean that concurrent Alzheimer's disease pathology can be excluded. In fact, concurrent Alzheimer's disease pathology is not unusual in the context of a stroke and its presence increases the odds of developing dementia after a cerebrovascular event (5). A study using in vivo amyloid PET shows that about 30% of people with new onset dementia after a stroke or transient ischemic attack (TIA) have concurrent Alzheimer's disease pathology and this prevalence is about four times higher than that found in those who do not develop dementia after stroke/TIA (9). For those individuals who develop dementia after an acute cerebrovascular accident, they are more likely to have concurrent Alzheimer's disease pathology contributing to the dementia syndrome if the acute lesion is not prone to induce cognitive impairment (for example, TIA with no evidence of ischaemic brain tissue on imaging or if the lesion is not located at a strategic location) and imaging do not reveal severe chronic cerebrovascular disease burden (for example, multiple old infarcts or confluent WMH) (5). A high index of scepticism for concurrent Alzheimer's disease is needed in such clinical scenarios. Strategic locations for inducing post-stroke cognitive impairment include left frontotemporal lobes, left thalamus and right parietal lobe (10). Moreover, for those with concurrent Alzheimer's disease, their rate of cognitive decline is much faster than those without it (5). However, a slowly progressive cognitive decline in stroke survivors does not necessarily imply the presence of concurrent Alzheimer's disease pathology. In fact, in the context of a stroke, the progressive decline in cognition is commonly associated with severe SVD, rather than with Alzheimer's disease (5). In general, to ascertain the presence or contribution of Alzheimer's disease in the context of a stroke, additional investigations (namely PET, CSF and/or blood tests) as previously stated will be required.

Conclusion

In summary, although certain clinical pointers may help to differentiate between Alzheimer's disease and CVD, clinical features overlap making the differentiation challenging. Accurate differentiation between Alzheimer's disease and CVD or mixed diseases will depend on investigations to detect respective biomarkers. An MRI is most helpful to estimate the presence and relevance of CVD. To date, use of PET or CSF analysis for the detection of Alzheimer's disease biomarkers is mostly restricted to specialised centres. Recent development in blood-based technologies will likely enable easier differentiation between Alzheimer's disease and cerebrovascular disease in clinical practice.

References

1. Toledo JB, Arnold SE, Raible K, Brettschneider J, Xie SX, Grossman M, et al. Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. Brain. 2013;136(9):2697–706.
2. Schneider JA, Arvanitakis Z, Bang W, DA. B. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology. 2007;69:2197–204.
3. Pantoni L, Garcia JH, Brown GG. Vascular pathology in three cases of progressive cognitive deterioration. J Neurol Sci. 1996;135(2):131–9.
4. Tierney MC, Black SE, Szalai JP, Snow WG, Fisher RH, Nadon G, et al. Recognition memory and verbal fluency differentiate probable alzheimer disease from subcortical ischemic vascular dementia. Arch Neurol. 2001;58(10):1654–9.
5. Mok VCT, Lam BYK, Wong A, Ko H, Markus HS, Wong LKS. Early-onset and delayed-onset poststroke dementia-revisiting the mechanisms. Vol. 13, Nature Reviews Neurology. 2017.
6. Lau AYL, Ming BY, Ko H, Lam BYK, Shi L, Ma KKY, et al. Pandemic of the aging society-sporadic cerebral small vessel disease. Chin Med J (Engl). 2021;134(2):143–50.
7. Lam BYK, Yiu B, Ampil E, Chen CLH, Dikot Y, Dominguez JC, et al. High burden of cerebral white matter lesion in 9 Asian cities. Vol. 11, Scientific Reports. Scientific reports; 2021.
8. Zetterberg H, Blennow K. Moving fluid biomarkers for Alzheimer's disease from research tools to routine clinical diagnostics. Mol Neurodegener. 2021;16(1):10.
9. Yang J, Wong A, Wang Z, Liu W, Au L, Xiong Y, et al. Risk factors for incident dementia after stroke and transient ischemic attack. Alzheimer's Dement. 2015;11(1).
10. Weaver NA, Kuijf HJ, Aben HP, Abrigo J, Bae HJ, Barbay M, et al. Strategic infarct locations for post-stroke cognitive impairment: a pooled analysis of individual patient data from 12 acute ischaemic stroke cohorts. Lancet Neurol. 2021 Apr;20(6):448–59.

Expert essay

Risk factors for cerebrovascular disease

Laksanun Cheewakriengkrai

Phramongkutklao Hospital, Bangkok, Thailand

According to the top 10 causes of death in the world reported by the WHO, stroke ranks as number two, after ischemic heart disease in 2020. The number of deaths due to stroke increased from approximately 5.5 million in 2000 to 6.2 million in 2019, which is roughly 11% of the total deaths (1). Overall, the age-standardised total stroke prevalence rates are the highest in Oceania, South-east Asia, North Africa and the Middle East, and East Asia. Stroke or cerebrovascular disease is an acute disease that can occur within minutes to hours. The presenting symptoms vary from the common, such as weakness, hemisensory loss, and facial weakness to uncommon ones, such as apathy, abnormal movement, acute dementia, and more.

Strokes can be classified into two main categories: haemorrhagic and ischemic strokes. The majority of strokes, approximately 80%, involve ischemic stroke, which affects a variety of large and small vessels and is caused by multiple aetiologies, such as atherosclerosis, cardioembolic, lacunar or other specific causes. Of course, prevention is better than treatment. This Chapter will review the risk factors for cerebrovascular disease, focusing on the well-known risk factors (Figure 1).

Non-modifiable risk factors

1. **Age:** The prevalence of stroke increases with age, with the percentage of population affected doubling for each decade after the age of 40 (2). As countries around the world become ageing societies, the numbers of all stroke patients are rising in both men and women. Ageing alters both structure and function of micro- and macro-circulations. Age-related microcirculatory changes are presumably mediated by endothelial dysfunction, impaired cerebral autoregulation, and neurovascular coupling. Silent cerebrovascular diseases represent structural abnormalities that increase with advancing age and forecast increased risk of future symptomatic strokes (3).
2. **Gender:** The relationship between stroke and gender depends on age. Females have a higher lifetime risk of stroke than males. In the Framingham study, the lifetime risk of stroke among those 55 to 75 years of age was 1 in 5 for females and ~1 in 6 for males (2). Age-specific incidence rates are substantially lower in females than in males in the younger and middle-aged groups, but equal to higher in the oldest age groups.
3. **Ethnicity:** There are ethnicity disparities in stroke. Among the US population, the age-adjusted incidence of first ischemic stroke is higher in Black and Hispanic individuals compared to White individuals (3). In other parts of the world, for example in Southeast Asia, some countries in the region have higher age-standardised prevalence and mortality rates of total stroke (and ischemic stroke) than the US and most European countries (3).
4. **Genetics:** Those with a positive family or documented parental history of stroke before 65 years of age have an increased risk of stroke in offspring. Genetic influences on stroke risk can be considered on the basis of the influence on individual risk factors, the genetics of common stroke types, and uncommon or rare familial causes of stroke. Identification of the underlying gene for these disorders is important for diagnosis, counselling, and patient management (4).

Modifiable risk factors

1. **Hypertension** is a well-known and a strong risk factor for all strokes. Diagnosis of high blood pressure is intra-individual, based on measurement categories or differences in blood pressures at different time points. In accordance with most major guidelines, it is recommended that hypertension be diagnosed when a person's systolic blood pressure (SBP) is ≥140 mm Hg and/or their diastolic blood pressure (DBP) is ≥90 mm Hg (5). Since elevated blood pressure is related to all causes of death, cardiovascular events, heart disease, and stroke in both ischemic and haemorrhagic (6), early treatment and lifestyle change are recommended for all patients. The American Heart Association (AHA)/American Stroke Association (ASA) 2021 guideline for secondary stroke prevention suggested a target blood pressure of 130/80 mm Hg or lower for people with a high risk of stroke or previous stroke/TIA (7).

2. **Diabetic mellitus** can cause pathological changes in both small and large vessels leading to many serious complications, one of which is stroke. The diabetic duration correlated well with ischemic stroke risk, which increases 3% each year and triples for those with diabetes for ≥10 years (8). Furthermore, hyperglycaemia during the acute stroke phase is associated with poor outcomes and showed significantly poorer performance in global cognition and in all domains compared with individuals with normal fasting glucose level in 3–6 months after stroke (9).
3. **Dyslipidaemia:** The relationship between stroke and dyslipidaemia is tangible. High cholesterol and high low-density lipoproteins (LDL) increase the risk of ischemic stroke whereas high high-density lipoproteins (HDL) were known as a protective cardiovascular factor. Evidence for the direct influence of triglyceride to stroke is still being debated. Recent guidelines recommend more aggressive cholesterol lowering than in the past because it shows the benefit on coronary atherosclerosis plaque regression and significant reduction of cardiovascular death, myocardial infarction and ischemic stroke. However, very low cholesterol and LDL (<30mg/dl) has a potential side effect of intraparenchymal haemorrhage (10). For some ischemic stroke patients with previous haemorrhage, small vessel disease, or cerebral amyloid angiopathy, treatment at very low level of LDL should be made with caution.
4. **Smoking:** The risk of stroke correlates with the current smoking status, with higher numbers of cigarettes smoked per day showing a higher risk of stroke. Ischemic stroke seems to be more affected than haemorrhagic stroke (11). Smoking cessation rapidly reduces the risk of stroke, which nearly disappears 2–4 years after cessation (12).
5. **Physical inactivity** is one of the key risk factors in the INTERSTROKE study that accounted for more than 80% of the population attributable risk (PAR) for stroke (11). The relationship between physical activity and stroke reduction might be the effect of decreased blood pressure, blood level and body weight. Healthy adults should perform at least moderate to vigorous intensity aerobic physical activity at least 40 minutes/day for 3 to 4 days/week (4,12).
6. **Diet and nutrition:** It is likely that Mediterranean, DASH-style diets, or other diets that are low in sodium, contain plant-derived nutrients, have decreased caloric intake related to saturated and trans-fat, limit sweet intake and are rich in fruits and vegetables can reduce the stroke risk (4). For the nutrition supplement, folic or B vitamin (B6, B12) may be considered for prevention of ischemic stroke in patients with hyperhomocysteinemia, but its clinical outcome for reduced CVD risks or recurrent stroke was not well established (4).
7. Other risk factors
    a. **Obesity:** The waist-to-hip ratio (>0.91 in men and >0.86 in women) was attributed as a risk factor of stroke more than the overall increase in weight, as indicated by the body mass index. While there does not appear to be a direct correlation between weight loss and the risk of stroke, there may be an indirect effect as weight reduction helps to improve control of blood pressure, glucose level and myocardial infarction, which are the primary risk factors of stroke (11).
    b. **Metabolic syndrome** is a group of composite conditions that, based on the harmonious definition, includes high blood pressure ≥130/≥85 mm Hg or on medication, fasting glucose ≥100 mg/dL (>5.5 mmol/L) or on medication, abdominal obesity as determined by waist circumference >102 cm for men and >88 cm for women, abnormal HDL cholesterol <40 mg/dL (< 1.03 mmol/L) for men and <50 mg/dL (<1.30 mmol/L) for women and triglyceride levels ≥150 mg/dL (≥ 1.7 mmol/L). The combination of these risk factors correlated with increased stroke risk. Management of individual components of the metabolic syndrome is recommended, including lifestyle measures (such as exercise, appropriate weight loss and proper diet) and pharmacotherapy (for example, medications for BP lowering, lipid lowering, glycaemic control, and antiplatelet therapy).
    c. **Alcohol intake:** The effect of alcohol may depend on the level of consumption. Light-to-moderate alcohol consumption (≤2 drinks per day in men and ≤1 drink per day in women) may have a protective effect against stroke, due to the higher levels of HDL cholesterol, reduced platelet aggregation, lower fibrinogen concentrations, and increased insulin sensitivity and glucose metabolism. However, heavy alcohol consumption is associated with an increased risk of all types of strokes, especially, haemorrhagic intracerebral haemorrhage (11), as well as with hypertension, hypercoagulability, reduced cerebral blood flow, and an increased risk of AF (4).
    d. **Sleep-related breathing disorders:** obstructive sleep apnoea is a silent problem leading to multiple diseases such as hypertension, coronary artery disease, arrhythmias, ischemic stroke, metabolic disorders, cognitive impairment and more. Screening for sleep apnoea through a detailed history, including structured questionnaires, physical examination, and, if

indicated, polysomnography may be considered in people with a history of excessive daytime sleepiness, high body weight, narrowed airway and a family history of sleep apnoea.

e. **Air pollution:** Even though air pollution was not in the top ten potentially modifiable risk factors associated with acute stroke in the 32 countries, airborne particulate matters under 10 μm (PM10), 2.5 μm (PM2.5) and other toxic particulates have been connected to ischemic stroke. In nationwide studies, Korea and China found that both short-term and long-term exposure of ambient PM were associated with ardioembolic stroke and also increased stroke mortality (13,14).

8. Atrial fibrillation and extracranial carotid artery stenosis

a. **Atrial fibrillation:** An estimate of an individual's risks for cardioembolic stroke after established diagnosis of atrial fibrillation (persistent or paroxysmal) is important. In most clinical practice, we use CHA2DS2-VASc score (15) to estimate the risk with 0 points corresponding to low risk (0.5%–1.7%/y), 1 point reflecting moderate risk (1.2%–2.2%/y), and ≥2 points indicating high risk (1.9%y–7.6%y) (16). AHA/ASA guidelines recommend long-term oral anticoagulant therapy with warfarin at a target INR of 2.0 to 3.0 for people with valvular AF at high risk for stroke and those with previous stroke or TIA. Direct oral anticoagulant (DOACs) can be used in nonvalvular AF patients to prevent or reduce the risk of stroke (4,7).

b. **Extracranial carotid artery stenosis:** General screening for carotid artery stenosis in the general population is not recommended as not every carotid stenosis carries the same risk for future stroke. The best medical treatment with antiplatelet, screening for other treatable risk factors of stroke and lifestyle changes are suggested. Surgical intervention is still under debate for primary prevention (17). However, carotid endarterectomy (CEA) is strongly recommended in people with a TIA or nondisabling ischemic stroke within the past 6 months and ipsilateral severe (70%–99%) carotid artery stenosis (7).

In conclusion, it is evident that the risk of cerebrovascular disease is dependent on a multitude of risk factors. Yet, more than 80% of the global burden for stroke is attributable to modifiable risk factors. Therefore, if the general population can modify their lifestyle, diet and/or other behaviours, we should be able to better mitigate the associated risk factors, like atherosclerosis vascular risk factors, and reduce the occurrence of stroke and its associated risk of dementia.

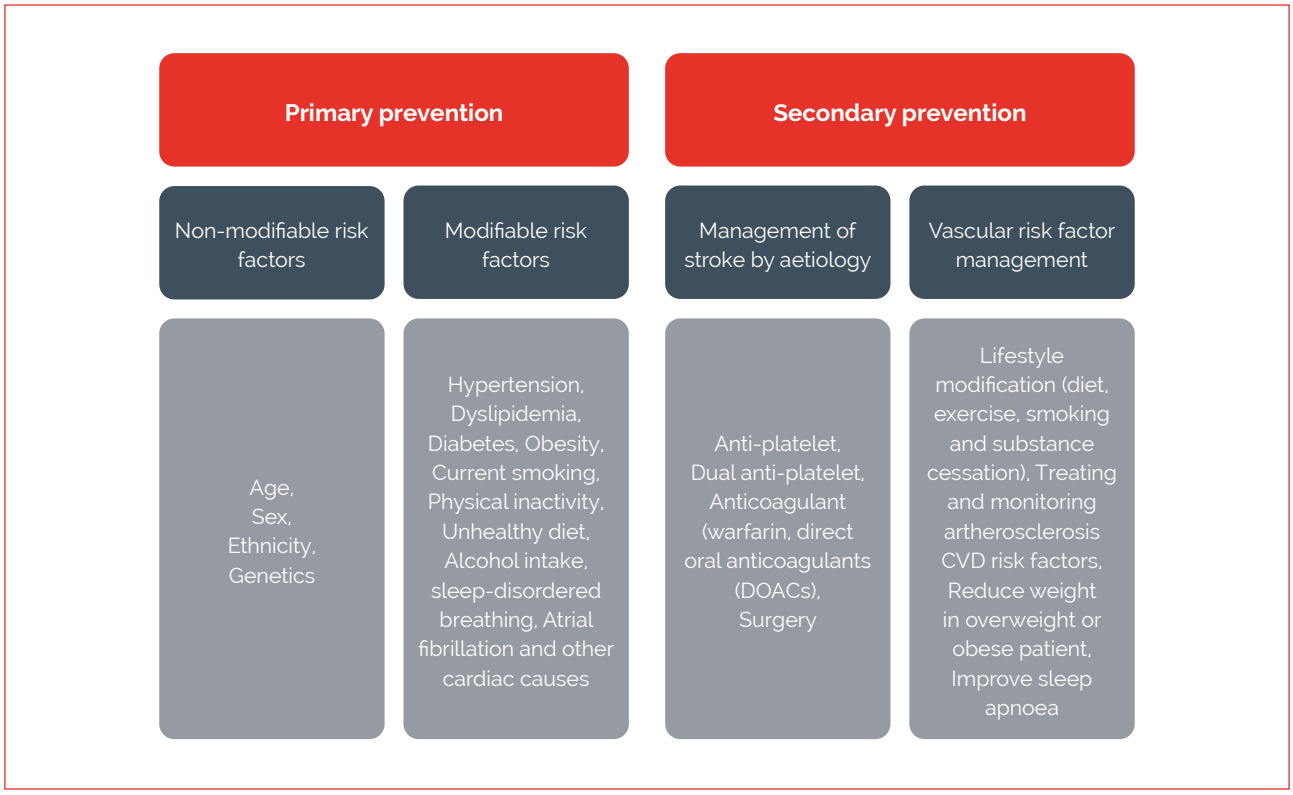


Figure 1. Summary of well-known risk factors for ischemic stroke in terms of both primary and secondary prevention.

References

1. World Health Organization. The top 10 causes of death [Internet]. WHO's Global Health Estimates. 2020 [cited 2021 Jul 12]. who.int
2. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart Disease and Stroke Statistics-2021 Update A Report from the American Heart Association. Circulation. 2021;143:E254–743.
3. Yousufuddin M, Young N. Aging and ischemic stroke. Aging (Albany NY). 2019;11(9):2542–4.
4. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: A statement for healthcare professionals from the American heart association/American stroke association. Stroke. 2014;45(12):3754–832.
5. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension global hypertension practice guidelines. J Hypertens. 2020;38(6):982–1004.
6. Lida M, Ueda K, Okayama A, Kodama K, Sawai K, Shibata S, et al. Impact of elevated blood pressure on mortality from all causes, cardiovascular diseases, heart disease and stroke among Japanese: 14 year follow-up of randomly selected population from Japanese – Nippon data 80. J Hum Hypertens. 2003;17(12):851–7.
7. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the [A]merican Heart Association/American Stroke Association. StrokeStr0000000000000. 2021;375.
8. Banerjee C, Moon YP, Paik MC, Rundek T, Mora-Mclaughlin C, Vieira JR, et al. Duration of diabetes and risk of ischemic stroke: The Northern Manhattan Study. Stroke. 2012;43(5):1212–7.
9. Lo JW, Crawford JD, Samaras K, Desmond DW, Köhler S, Staals J, et al. Association of Prediabetes and Type 2 Diabetes with Cognitive Function after Stroke: A STROKOG Collaboration Study. Stroke. 2020;2020(51):1640–6.
10. Karagiannis AD, Mehta A, Dhindsa DS, Virani SS, Orringer CE, Blumenthal RS, et al. How low is safe? The frontier of very low (<30 mg/dL) LDL cholesterol. Eur Heart J [Internet]. 2021 Jun 7 [cited 2021 Jul 12];42(22):2154–69. https://pubmed.ncbi.nlm.nih.gov/33463677
11. O'Donnell MJ, Denis X, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): A case-control study. Lancet. 2010;376(9735):112–23.
12. Boehme AK, Esenwa C, Factors EMSSR. Genetics, and Prevention. Circ Res. 2017;120(3):472–95.
13. Chung JW, Bang OY, Ahn K, Park SS, Park TH, Kim JG, et al. Air pollution is associated with ischemic stroke via cardiogenic embolism. Stroke. 2017;48(1):17–23.
14. Chen G, Wang A, Li S, Zhao X, Wang Y, Li H, et al. Long-term exposure to air pollution and survival after ischemic stroke: The China national stroke registry cohort. Stroke. 2019;50(3):563–70.
15. Lip GY, Nieuwlaat R, Pisters R, Lane DA, HJ. C. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263–72.
16. Hart RG, Pearce LA, Halperin JL, Hylek EM, Albers GW, Anderson DC, et al. Comparison of 12 risk stratification schemes to predict stroke in patients with nonvalvular atrial fibrillation. Stroke [Internet]. 2008 Jun 1 [cited 2021 Jul 12];39(6):1901–10. https://pubmed.ncbi.nlm.nih.gov/18420954
17. Howard DPJ, Gaziano L, Rothwell PM. Risk of stroke in relation to degree of asymptomatic carotid stenosis: a population-based cohort study, systematic review, and meta-analysis. Lancet Neurol. 2021;20(3):193–202.

Expert essay

Post-stroke cognitive impairment: in search of a profile that may inform treatment

Kok Pin Ng,[1] Chathuri Yatawara,[1] Vincent C.T. Mok,[2] Perminder S. Sachdev,[3] Nagaendran Kandiah[1]

[1] Department of Neurology, National Neuroscience Institute, Singapore, SINGAPORE
[2] Division of Neurology, Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, CHINA
[3] Centre for Healthy Brain Ageing (CHeBA), School of Psychiatry, University of New South Wales, Sydney 2052, AUSTRALIA

Cerebrovascular disease, including clinically overt stroke and silent cerebrovascular disease, is an important contributor to cognitive dysfunction (1). Among stroke survivors, 44% will go on to develop some form of cognitive impairment with an estimated 10%–20% going on to develop dementia (2–4). The incidence of delayed onset post-stroke dementia ≥5 years after stroke is up to 9 times greater than the age-matched population (5). Several studies have demonstrated that even among people who suffer mild strokes (modified Rankin <3), up to 41% go on to develop mild cognitive impairment (6). Clinical outcomes are also poorer for stroke survivors who develop post-stroke cognitive impairment, including poorer physical outcomes, higher institutionalisation and higher mortality than non-PSCI stroke survivors (7,8). However, the focus of post-stroke care has traditionally been on physical disability, while screening for post-stroke cognitive impairment, which may develop in the acute stage or delayed until years after stroke, is often overlooked. Therefore, it is paramount to emphasise the importance of cognitive assessment of stroke survivors by stroke-clinicians. Reviews of studies have found significant heterogeneity related to the study setting (populations which include patients with minor strokes versus hospital-based), inclusion or exclusion of pre-stroke dementia, differences in diagnostic criteria and geographic regions (2,9). Hence, efforts to harmonise the methodologies of future studies are greatly needed to have a better understanding of post-stroke cognitive impairment, including cognitive and neuropathological markers, risk factors and mechanisms. This knowledge will better inform prognosis and guide evidence-based interventions using precision-medicine practices.

Risk factors, neuropathology, and mechanisms of post-stroke cognitive impairment

The risk profiles can be broadly categorised into demographics, cardiovascular risk factors, pre-stroke pathologies and acute stroke characteristics. Demographic factors such as increasing age and low education are consistently demonstrated to increase the risk (2,10). On the other hand, evidence of hypertension, diabetes mellitus, hyperlipidaemia, smoking, and atrial fibrillation as specific cardiovascular risk factors of post-stroke cognitive impairment, beyond being risk factors for ischemic strokes, are less consistent. A systemic review in 2009 found that diabetes and atrial fibrillation are significant predictors (2), while a recent study which harmonised data from 13 studies found that diabetes is strongly associated with post-stroke cognitive impairment while hypertension, smoking, and atrial fibrillation have weaker domain-specific associations (4).

The neuropathology of cerebrovascular disease which can be visualised on structural MRI is heterogenous and includes a combination of acute stroke lesions such as large territorial infarcts, multiple infarcts, strategic infarcts and brain haemorrhage, and chronic cerebrovascular disease lesions such as white matter hyperintensities (WMH), lacunes and microbleed (3). Given the key role of dementia-prone acute stroke lesions in causing post-stroke cognitive impairment, a recent study pooled data from 12 acute ischaemic stroke cohorts and reported a map of strategic infarcts associated with post-stroke cognitive impairment. Specifically, infarcts

in the left frontotemporal lobes, left thalamus, and right parietal lobe were strongly associated with PSCI (11). However, not all dementia-prone acute stroke lesions lead to post-stroke cognitive impairment, and brain resilience, which is defined as the overall capacity of the brain to recover from injury and to maintain its usual function, has been proposed to have a complex interplay with acute stroke lesions in influencing the risk (3).

Emerging evidence suggests that the risk is also driven by pre-existing brain atrophy and extent of chronic cerebrovascular disease in stroke survivors. Global cortical atrophy, which reduces brain reserve, has been shown to increase the risk of post-stroke cognitive impairment (12) and increase the range of cognitive domains impaired after stroke (13). Such global cortical atrophy may suggest concurrent Alzheimer's disease. The Stroke Registry Investigating Cognitive Decline (STRiDE) study showed that amyloid deposition is more frequently present in those with early-onset dementia (29.7%) after stroke than in those without (7.7%) (14). The presence and severity of white matter hypertensities, an imaging feature of cerebral small vessel disease, have also been shown to substantially increase the risk of dementia, functional impairment, stroke recurrence and mortality after ischaemic stroke in a recent systemic review of 71,298 ischemic stroke patients (15). Furthermore, findings from the STRiDE study showed that severe small vessel disease, as reflected by confluent white matter hyperintensities and/or multiple lacunes, are independent predictors of delayed onset dementia after stroke (16). Microbleeds, another silent cerebrovascular lesion which characterises tissue damage due to small vessel cerebrovascular disease or accumulation of amyloid in the vessels, are shown to be associated with increased risk of developing post-stroke cognitive impairment, with one recent study showing that risk increased by four times (17). The risk of post-stroke dementia also varies depending on the presence of chronic cerebrovascular pathologies and type of acute infarcts. In this regard, we recently found that the risk of post-stroke dementia was largest for stroke survivors with acute large subcortical infarcts (>15 mm) and concomitant periventricular white matter hyperintensities compared with patients with large subcortical infarcts and punctate/absent periventricular white matter hyperintensities (18). Therefore, profiling chronic cerebrovascular disease lesions in addition to acute stroke lesions in stroke survivors plays a critical role in informing the prognosis of post-stroke cognitive impairment and post-stroke dementia.

Future directions

Several clinical and neuroimaging factors have been identified as predictive of post-stroke cognitive impairment among stroke survivors. Therefore, to facilitate the screening of individuals at risk of delayed post-stroke cognitive impairment, risk scores that incorporate clinical and neuroimaging markers commonly adopted in clinics such as CHANGE have been developed to specifically identify stroke survivors at risk (19). However, it is important to note that the factors may differ in predicting acute or delayed onset, and therefore, a 'one approach fits all' characterisation of risk factors for all post-stroke cognitive impairment may not be justifiable. In addition to structural MRI, evaluation of white matter tract integrity using diffusion tensor imaging and imaging of blood brain barrier integrity will also be useful. Profiling each factor at the appropriate time point post-stroke to reliably predict the risk of post-stroke cognitive impairment will allow a precision medicine approach so that a personalised intervention can be applied at the right time to improve cognitive outcome. However, the large clinical and neuroimaging heterogeneity of risk factors and mechanisms highlights the difficulty of developing a consensus on the most reliable factors to inform clinicians who treat stroke survivors. Furthermore, many existing studies did not account for factors such as premorbid cognitive ability or resilience/reserve.

To address these inconsistencies, there have been international efforts to form consortiums with the aim to develop a standardised approach when pooling data from cohorts (11,20). One such effort is the Stroke and Cognition Consortium (STROKOG), which harmonises data from participants from different continents, so as to facilitate a better understanding of the determinants of vascular contributions to cognitive disorders and help improve the diagnosis and treatment of vascular cognitive disorders (20). Future research may also benefit from pooling of the international consortia to form larger datasets with harmonised study methodologies. The pooling of data across the world will further support the use of machine learning and artificial intelligence to better characterise the risk profiles of post-stroke cognitive impairment to help find patterns and trends which will support the development of individualised predictive models to inform a personalised multi-domain intervention.

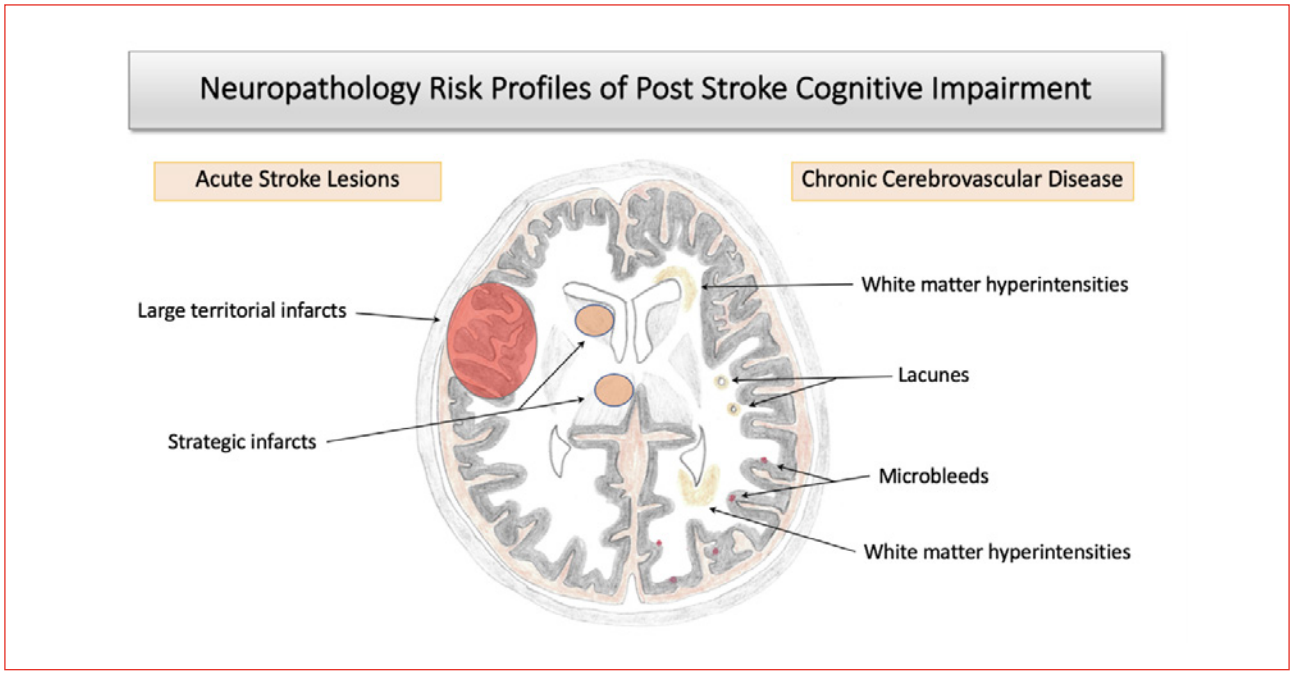


Figure 1. Illustration of brain vascular lesions of various size and location.

References

1. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: A statement for healthcare professionals from the American Heart Association/American Stroke Association. Vol. 42, Stroke. 2011. p. 2672–713.
2. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet Neurol. 2009;8(11).
3. Mok VCT, Lam BYK, Wong A, Ko H, Markus HS, Wong LKS. Early-onset and delayed-onset poststroke dementia-revisiting the mechanisms. Vol. 13, Nature Reviews Neurology. 2017.
4. Lo JW, Crawford JD, Desmond DW, Godefroy O, Jokinen H, Mahinrad S, et al. Profile of and risk factors for poststroke cognitive impairment in diverse ethnoregional groups. Neurology. 2019;93(24).
5. Kokmen E, Whisnant JP, O'Fallon WM, Chu CP, Beard CM. Dementia after ischemic stroke: A population-based study in Rochester, Minnesota (1960-1984). Neurology. 1996;46(1).
6. Jacova C, Pearce LA, Costello R, McClure LA, Holliday SL, Hart RG, et al. Cognitive impairment in lacunar strokes: The SPS3 trial. Ann Neurol. 2012;72(3).
7. Brodaty H, Altendorf A, Withall A, Sachdev PS. Mortality and institutionalization in early survivors of stroke: The effects of cognition, vascular mild cognitive impairment, and vascular dementia. J Stroke Cerebrovasc Dis. 2010;19(6).
8. Patel MD, Coshall C, Rudd AG, Wolfe CDA. Cognitive impairment after stroke: Clinical determinants and its associations with long-term stroke outcomes. J Am Geriatr Soc. 2002;50(4).
9. Sun JH, Tan L, Yu JT. Post-stroke cognitive impairment: Epidemiology, mechanisms and management. Vol. 2, Annals of Translational Medicine. 2014.
10. Gottesman RF, Hillis AE. Predictors and assessment of cognitive dysfunction resulting from ischaemic stroke. Vol. 9, The Lancet Neurology. 2010.
11. Weaver NA, Kuijf HJ, Aben HP, Abrigo J, Bae HJ, Barbay M, et al. Strategic infarct locations for post-stroke cognitive impairment: a pooled analysis of individual patient data from 12 acute ischaemic stroke cohorts. Lancet Neurol. 2021 Apr;20(6):448–59.
12. Chen X, Duan L, Han Y, Tian L, Dai Q, Wang S, et al. Predictors for vascular cognitive impairment in stroke patients. BMC Neurol. 2016;16(1).
13. Yatawara C, Ng KP, Chander R, Kandiah N. Associations between lesions and domain-specific cognitive decline in poststroke dementia. Neurology. 2018;91(1):e45–54.
14. Yang J, Wong A, Wang Z, Liu W, Au L, Xiong Y, et al. Risk factors for incident dementia after stroke and transient ischemic attack. Alzheimer's Dement. 2015;11(1).
15. Georgakis MK, Duering M, Wardlaw JM, Dichgans M. WMH and long-term outcomes in ischemic stroke: A systematic review and meta-analysis. Neurology. 2019;92(12).
16. Mok VCT, Lam BYK, Wang Z, Liu W, Au L, Leung EYL, et al. Delayed-onset dementia after stroke or transient ischemic attack. Alzheimer's Dement. 2016;12(11).
17. Yatawara C, Guevarra AC, Ng KP, Chander R, Lam BYK, Wong A, et al. The role of cerebral microbleeds in the incidence of post-stroke dementia. J Neurol Sci. 2020;412.
18. Yatawara C, Guevarra A, Ng KP, Chander R, Kandiah N. Interactions between Acute Infarcts and Cerebrovascular Pathology Predict Poststroke Dementia. Alzheimer Dis Assoc Disord. 2020;34(3):206–11.
19. Chander RJ, Lam BYK, Lin X, Ng AYT, Wong APL, Mok VCT, et al. Development and validation of a risk score (CHANGE) for cognitive impairment after ischemic stroke. Sci Rep. 2017;7(1).
20. Sachdev PS, Lo JW, Crawford JD, Mellon L, Hickey A, Williams D, et al. STROKOG (stroke and cognition consortium): An international consortium to examine the epidemiology, diagnosis, and treatment of neurocognitive disorders in relation to cerebrovascular disease. Alzheimer's Dement Diagnosis, Assess Dis Monit. 2017;7:11–23.

Expert essay

Nutritional deficits in the differential diagnosis of dementia

Christelle N. Ouaijan,[1] Georges E. Karam[2]

[1] Department of Clinical Nutrition, St George Hospital University Medical Center, Beirut, LEBANON
[2] Department of Psychiatry and Clinical Psychology, St Georges Hospital University Medical Center/Balamand University, Beirut, LEBANON

Both malnutrition and low levels of specific nutrients are associated with cognitive impairment and dementia in older adults. Malnutrition has been shown to contribute to the rapid decline in dementia. Most prevalent and significant deficiencies are vitamins B1, B9, B12 and D. Each of these has a specific proposed mechanism. Older people should be regularly screened for malnutrition and vitamin deficiencies. Prophylactic vitamin supplementation is not recommended and should be reserved only in cases of proven deficiencies. A well-balanced nutritional therapy based on the Mediterranean diet guidelines and oral nutrition supplements should be endorsed to all older people.

Introduction

The burden of malnutrition is heightened in older people with the process of ageing and has been correlated to cognitive decline and the risk of dementia. In addition to muscle loss and frailty, malnourished older people develop deficiencies in vitamins and minerals with a known metabolism linked to cognitive function. Therefore, clinicians should be aware of these nutritional deficits in both the assessment process and the treatment plan of older people at any stage of dementia (1).

Malnutrition in older adults and risk of dementia

Weight loss is the first identified criterion of malnutrition, and it has been directly linked with the severity of dementia in data across several countries. Prevalence of malnutrition has been reported to be up to 50% in people with Alzheimer's disease, especially in low- and middle-income countries. Dementia severity was also independently associated with muscle wasting in isolation of other risk factors and malnutrition was presented to be a strong predictor of disease progression and cognitive decline (2). This correlation can be explained by the different problems encountered during the stages of dementia and directly affecting food intake such as olfactory dysfunction, dyspraxia, agnosia and dysphagia (3).

Metabolism of vitamins and cognitive function

Consequently, the decrease in food intake and appetite loss observed during ageing and dementia is directly associated to deficiencies in micronutrients. The metabolism of these micronutrients, mainly B vitamins, has long been recognised to be linked to cognitive metabolism, and therefore to increased risk of dementia (4). The first vitamin of note is B12 or cobalamin, a very common one in older people due to decreased absorption. Its deficiency is well-established in association with elevated plasma levels of homocysteine, a risk factor of Alzheimer's disease (4). However, cross-sectional studies have been contradictory and a better correlation was established when serum levels of folate (vitamin B9) were taken into consideration (1). Since both vitamins are needed for the conversion of homocysteine to methionine, they share the metabolism of decreasing hyperhomocysteinemia. So far, trials on supplementation have been disappointing in preventing or delaying cognitive decline, but on the other hand, increased intake of folate and to a lesser extent B12 from food sources in observational studies have been linked to improving cognitive function and decreasing risk of Alzheimer's disease (5).

Another B vitamin that is linked to neurological problems is B1 or thiamine (6). Korsakoff syndrome, its well-known deficiency, shares some metabolic features in the brain with Alzheimer's disease. These features are directly linked in both cases with diminished glucose metabolism in the brain, a pathway dependent on thiamine. Reduced glucose metabolism has even been observed long before the person demonstrates significant clinical signs of dementia (6). Conversely, possible causes of deficiency have not yet been well-established. Besides alcoholism, thiamine deficiency from decreased intake is not very common due to flour fortification, but it is observed in older people in low-income countries where this fortification procedure is not mandated, and older people tend to consume fewer alternative protein sources of B1. To date, trials of thiamine supplementation have only been conducted in a small sample size generating non-conclusive results (6).

Besides B vitamins, vitamin D deficiency, which is very common in older people due to reduced sun exposure, among other factors, has implications for dementia onset and progression (7). With suggested mechanisms of amyloidosis in several areas of the brain and neurogenesis in the hypothalamus, cross-sectional and longitudinal studies have exhibited associations between low vitamin D levels and cognitive impairment (7). Since vitamin D supplementation is now commonly prescribed to treat deficiencies, intervention studies are starting to be conducted regarding its role in prevention and treatment of cognitive impairment (7).

Screening of nutrition status in diagnosing dementia

All these described metabolic pathways and mostly observational studies can be translated into practical implications in the diagnosis of dementia as well as its prevention and treatment in older adults. Screening for malnutrition should be done frequently in older adults at both community and hospital levels. Mini Nutritional Assessment® is a validated assessment tool for use in this population and is easy to use. It has well defined categories of risk for malnutrition and is comprised of questions related to food intake. These questions, if properly investigated, can determine if an older person is skipping meals or food groups, and consequently, is at risk for certain vitamin deficiencies (8). The next step would be to investigate these deficiencies through a biochemical assessment while focusing mainly on vitamin B12, folate and vitamin D. This in-depth nutrition assessment will add perspective to the differential diagnosis of dementia and guide the steps in its management (8).

Practical recommendations

Until now, recommendations on these specific vitamins' supplementation have only been proven efficient in delaying cognitive decline in case of deficiencies (4). Prophylactic supplementation should not be part of practice, but intake of these vitamins can be secured from a well-balanced diet. The Mediterranean dietary pattern based on consuming more fruits, vegetables and legumes, is particularly rich in these vitamin (except B12 that depends on animal sources of intake) in addition to other antioxidants and should be endorsed to older adults in order to prevent and even delay cognitive decline in the early stages of dementia (9).

In the case of malnutrition and decreased food intake, caloric and protein requirements cannot be met easily with a healthy diet alone. Oral Nutrition Supplements (ONS) may be added to the daily intake of an older adult with malnutrition or even who is at risk of malnutrition, and this, to enhance nutritional requirements. These ready-to-sip liquids in assorted flavours are easily consumed and incorporated into a daily routine. Their use is associated with increased weight, better quality of life and decreased mortality (10). An additional advantage of these oral nutrition supplements is their enrichment in the above-mentioned vitamins and omega-3, among other nutrients.

Risk of malnutrition and subsequent vitamin deficiencies are strongly correlated with cognitive decline. These established observations in many studies are now considered in the diagnosis of dementia by adding a well-defined screening of nutrition status. As for the prevention and treatment of dementia, healthy dietary patterns and fortified oral nutrition supplements are recommended for implementation in the management in cases of malnutrition. Larger intervention trials for specific vitamin supplementation are needed to establish more evidence-based recommendations on dosage and timing.

References

1. Faxén-Irving G, Basun H, Cederholm T. Nutritional and cognitive relationships and long-term mortality in patients with various dementia disorders. Age Ageing. 2005 Mar;34(2):136–41.
2. Albanese E, Taylor C, Siervo M, Stewart R, Prince MJ, Acosta D. Dementia severity and weight loss: A comparison across eight cohorts. the 10/66 study. Alzheimer's Dement. 2013 Nov;9(6):649–56.
3. Volkert D, Chourdakis M, Faxen-Irving G, Frühwald T, Landi F, Suominen MH, et al. ESPEN guidelines on nutrition in dementia. Clin Nutr. 2015 Dec;34(6):1052–73.
4. Mielech A, Puścion-Jakubik A, Markiewicz-żukowska R, Socha K. Vitamins in alzheimer's disease – review of the latest reports. Nutrients. 2020;12(11):1–15.
5. Carney E, Canada T. Dietary folate and vitamin B12 intake and cognitive decline among community-dwelling older persons: Commentary. Nutr Clin Pract. 2006 Apr;21(2):188–9.
6. Gibson GE, Hirsch JA, Fonzetti P, Jordan BD, Cirio RT, Elder J. Vitamin B1 (thiamine) and dementia. Ann N Y Acad Sci. 2016 Mar;1367(1):21–30.
7. Littlejohns TJ, Kos K, Henley WE, Kuźma E, Llewellyn DJ. Vitamin D and Dementia. J Prev Alzheimer's Dis. 2016;3(1):43–52.
8. Corish CA, Bardon LA. Malnutrition in older adults: Screening and determinants. Proc Nutr Soc. 2019 Aug;78(3):372–9.
9. Safouris A, Tsivgoulis G, Sergentanis T, Psaltopoulou T. Mediterranean Diet and Risk of Dementia. Curr Alzheimer Res. 2015;12(8):736–44.
10. Milne AC, Potter J, Vivanti A, Avenell A. Protein and energy supplementation in elderly people at risk from malnutrition. Cochrane Database Syst Rev. 2009 Apr;15(2):2.

Expert essay

How to evaluate the individual with ventriculomegaly on brain imaging

Xiaofeng Li,[1] Serge Gauthier[2,3]

[1] Department of Neurology, The second affiliated hospital of Chongqing Medical University, Chongqing, CHINA
[2] McGill Centre for Studies in Aging, Faculty of Medicine, McGill University, CANADA
[3] Departments of Psychiatry and Neurology & Neurosurgery, CANADA

As computer tomography (CT) and magnetic resonance imaging (MRI) are now widely available, brain scanning is easily integrated into the workup of those people presenting with cognitive complaints. In clinical practice, enlarged lateral ventricles are common. The Evans' index has been the most extensively used radiological marker of abnormal ventricular enlargement. It is defined as the ratio between the maximum diameter of the frontal horns of the lateral ventricles and the maximum inner diameter of the skull in the same section (Figure 1). Evans' index equal or over 0.30 is regarded as enlargement of lateral ventricles or ventriculomegaly. What is the clinical significance? What shall the clinician do if they encounter the appearance of enlarged ventricles on brain imaging? Some relevant information is provided below for reference.

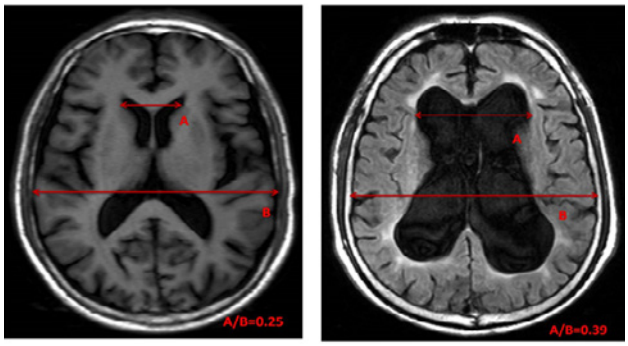


Figure 1. Left: Evens index = A/B < 0.3; Right: Evens index = A/B > 0.3.

Enlarged lateral ventricles can be caused by excessive cerebrospinal fluid (CSF), brain atrophy or both. Hydrocephalus is defined as excessive CSF in the ventricular system. CSF is produced through choroid plexus excretion, flow beginning from lateral ventricles to the third ventricle, the aqueduct of Sylvius and the fourth ventricle, enters the subarachnoid space through the median aperture and lateral apertures, finally absorbed into the venous sinuses of dura matter through arachnoid granulations following a fixed direction. Hydrocephalus can be divided into non-communicating/obstructive hydrocephalus and communicating hydrocephalus according to the presence of the obstruction in the CSF flow pathway or not. The former can lead into acute intracranial hypertension with headache, vomiting, and/or disturbances of consciousness. Therefore, obstructive hydrocephalus is seldom ignored and misdiagnosed. The latter with some known causes such as subarachnoid haemorrhage, meningitis and head trauma is called secondary hydrocephalus. Communicating hydrocephalus without known causes, often with normal intracranial pressure, is called idiopathic normal pressure hydrocephalus (iNPH). iNPH is a condition characterised by gait disturbance, cognitive impairment, and urinary incontinence. However, its onset is slow, and the condition may go undetected until a triadic syndrome is fully established (1). Enlarged ventricles may be caused by brain atrophy, of which the most common cause is Alzheimer's disease. Both hydrocephalus and brain atrophy can coexist, which makes an accurate diagnosis even more difficult.

Enlarged ventricles caused by obstructive or secondary communicating hydrocephalus can be treated with shunt surgery, with a good outcome result in many people, hence the importance of further workup. Response to shunting is less predictable in iNPH. That is why this essay will further explore its clinical manifestations and investigation.

The individual with enlarged ventricles but with no symptoms or signs should be followed up regularly (2).

Gait disturbances may be the first symptom: the person cannot walk as fast as before or keep up with fellow pedestrians. Some individuals may just complain of unsteadiness or dizziness. Upon examination, there may be more variable and shorter strides as well as a lower cadence. The feet cannot be raised to a normal height. A decreased stride length, decreased foot-to-floor clearance and a broad-based gait are typical features of gait abnormality in iNPH (3). Over time, the gait disturbance in iNPH develops three characteristics: small-step gait, magnet gait, and broad-based gait. Freezing gait may become obvious when individuals are walking in a narrow space, or when they change direction. Due to this gait pattern, people

with iNPH are often misdiagnosed with Parkinson's disease; however, they do not present with increased muscle tone as with most Parkinson patients. Gait can be evaluated by the 3-meter Timed Up and Go test (TUG), 10-metre walking test, dual task walking test and Gait Status Scale. TUG is the most frequently used (4): the suggested procedure is to have the individual stand up from a seated position and walk a distance of 3 metres as quickly and as safely as possible. After reaching a line indicating the 3-metre distance, the person turns 180 degrees, walks back to the chair, and sits down as quickly as possible. The time it takes from standing to sitting is recorded, a mean value of 16.5 seconds being the cut-off. TUG is also very useful in predicting responsiveness to the shunt operation. The time difference recorded on the TUG is calculated as (TUG time before spinal tap test – TUG time after spinal tap test or shunt surgery): the improvement of 5 seconds on the TUG at the spinal tap test is a highly accurate predictive factor for improvement of 10 seconds on the TUG 12 months after shunt surgery (5).

Cognitive impairment may be described as not being able to think as quickly as before, or the fact that figuring out a problem takes longer. Some people may describe their brain as being 'rusty' or something similar. iNPH is thus associated more with executive frontal lobe and attention deficits than with memory impairment. Psychomotor speed has declined, and attention and eventually working memory are impaired. The neuropsychological assessment can include short screening scales such as the Mini Mental State Examination (MMSE), or the Montreal Cognitive Assessment (MoCA; more sensitive than the MMSE for executive impairment). More specialised tests include the Frontal Assessment Battery (FAB), a short test designed to assess conceptualisation and abstract reasoning, mental flexibility, motor programming and executive control of action, resistance to interference, self-regulation and inhibitory control, as well as environmental autonomy. The Trail Making Test Part A (TMT-A) aims at evaluating psychomotor speed by connecting randomly located numbers in numerical order as quickly and accurately as possible. The TMT-B test which connects numbers and letters in an alternating sequence is partly included in the MoCA. Other more complex neuropsychological tests include the Stroop test, the Ray auditory verbal learning test (RAVLT), the Digit span, the Rey-Osterrieth complex figure test, the WAIS-III and the Grooved Pegboard Test.

Urge micturition or incontinence associated with an overactive bladder is characteristic of dysuria in people with iNPH. Due to common prostate hyperplasia, this symptom may be misinterpreted. The International Consultation on Incontinence Questionnaire is suggested for evaluation of urinary incontinence (6).

In the case of ventriculomegaly, particularly if supported by an abnormal Evans' index, it is important to evaluate the presence and severity of the key symptoms and signs (gait changes, cognitive decline and urine incontinence) of the iNPH triad, as the decision to undergo a shunt procedure requires a referral to a neurosurgical service for further assessment. This may include additional brain imaging and a CSF spinal tap test (7). This referral should be made by also factoring in the presence of advanced dementia and what is in the person's best interests.

References

1. Hebb AO, Cusimano MD. Idiopathic normal pressure hydrocephalus: A systematic review of diagnosis and outcome. Neurosurgery. 2001;49(5):1166–86.
2. Kimihira L, Iseki C, Takahashi Y, Sato H, Kato H, Kazui H, et al. A multi-center, prospective study on the progression rate of asymptomatic ventriculomegaly with features of idiopathic normal pressure hydrocephalus on magnetic resonance imaging to idiopathic normal pressure hydrocephalus. J Neurol Sci. 2020;419(11716):6.
3. Stolze H, Kuhtz-Buschbeck JP, Drücke H, Jöhnk K, Diercks C, Palmié S, et al. Gait analysis in idiopathic normal pressure hydrocephalus – which parameters respond to the CSF tap test? Clin Neurophysiol. 2000;111(9):1678–86.
4. Mendes GAS, de Oliveira MF, Pinto FCG. The Timed Up and Go Test as a Diagnostic Criterion in Normal Pressure Hydrocephalus. World Neurosurg. 2017;105:456–61.
5. Yamada S, Ishikawa M, Miyajima M, Nakajima M, Atsuchi M, Kimura T, et al. Timed up and go test at tap test and shunt surgery in idiopathic normal pressure hydrocephalus. Neurol Clin Pract. 2017;7(2):98–108.
6. Uren AD, Cotterill N, Pardoe M, Abrams P. The International Consultation on Incontinence Questionnaires (ICIQ): An update on status and direction. Neurourol Urodyn. 2020;39(6):1889–96.
7. Nakajima M, Yamada S, Miyajima M, Ishii K, Kuriyama N, Kazui H, et al. Guidelines for management of idiopathic normal pressure hydrocephalus (Third edition): Endorsed by the Japanese society of normal pressure hydrocephalus. Neurol Med Chir (Tokyo). 2021;61(2):63–97.

Conclusions

The essays contained in this Chapter demonstrate the importance of identifying vascular risk factors that contribute to the development of cognitive impairment and, subsequently, how this illness is managed. The distinctive perspectives converging on the same topic highlight the complexity of recognising symptoms and rendering an accurate diagnosis. These contributing risk factors are two-fold. They include non-modifiable ones, those out of your control, such as age, gender, ethnicity or genetics as well as modifiable ones, signalling the lifestyle choices you make and control, including smoking, level of physical activity, alcohol consumption or hypertension. For example, modifiable risk factors greatly contribute to the onset of stroke, which engenders possible long-term cognitive degeneration.

Malnutrition, or even a decrease in caloric intake, is another prevalent risk factor, leading to a deficiency in essential nutrients associated with cognitive impairment and dementia in older adults. This condition can be enhanced by taking fortified nutritional supplements that complement food intake and provide vitamin supplementation.

Finally, identifying iNPH at the earliest opportunity, for example when gait disturbance appear, may ward off further complications before cognitive deficits occur. As many of these factors are present at middle age, a preventive approach should be adopted. For example, in community-dwelling individuals of a mean age of 53 years, walking more than 7,500 steps a day, which is considered light physical activity and accessible to most older adults, was associated with higher total brain volume, equivalent to approximately 1.4 to 2.2 years less brain ageing (1).

Additional references

1. Spartano NL, Demissie S, Himali JJ, Dukes KA, Murabito JM, Vasan RS, et al. Accelerometer-determined physical activity and cognitive function in middle-aged and older adults from two generations of the Framingham Heart Study. Alzheimer's Dement Transl Res Clin Interv [Internet]. 2019 Oct 15;5:618–26. https://europepmc.org/articles/PMC6807299.

Chapter 23
Young-onset dementias

Pedro Rosa-Neto

Key points

- Patients with young-onset dementia, including Down syndrome, require careful evaluation to rule out treatable causes of dementia.
- Biomarkers play a major role ruling out Alzheimer's disease in young-onset dementia.

General background

Young-onset (also referred to as early-onset) refers to people under the age of 65 who are diagnosed with dementia. Although the cut-off at age 65 is arbitrary, it has been established that the cause of dementia can vary greatly among younger people. Determining its underlying cause in a definitive way is critical as it may affect how their condition is managed. Among the several diseases that cause dementia in young people, some are degenerative such as Alzheimer's disease, but others may be related to brain circulation, cancer, infections or even genetic conditions. Therefore, the diagnosis and management of these individuals should be conducted in tertiary centres staffed with multidisciplinary teams (1–4). Many of these issues are explored more fully in the expert essays contained within this Chapter. They detail some of the complexities unique to this diagnosis and detail the journey taken by young individuals. A thorough medical investigation of these cases is vital as many of them may require specialised therapies to address the underlying cause of their dementia.

Survey results

The survey reveals a consensus of referring young-onset dementia patients to specialised centres (Chart 1). However, results also indicate that 11% of the 1,111 clinicians do not refer to specialised centres. This is largely due to a lack of available specialists or the high cost of these assessments. Approximately 17% of the respondents refer to a specialist at either the patient's or the family's request.

Specifically, regarding patients with previous intellectual disabilities (i.e. neurodevelopmental disorders or genetic conditions) only 21% of respondents refer to a clinician with experience in this specific issue, while 38% refer to a neuropsychologist.

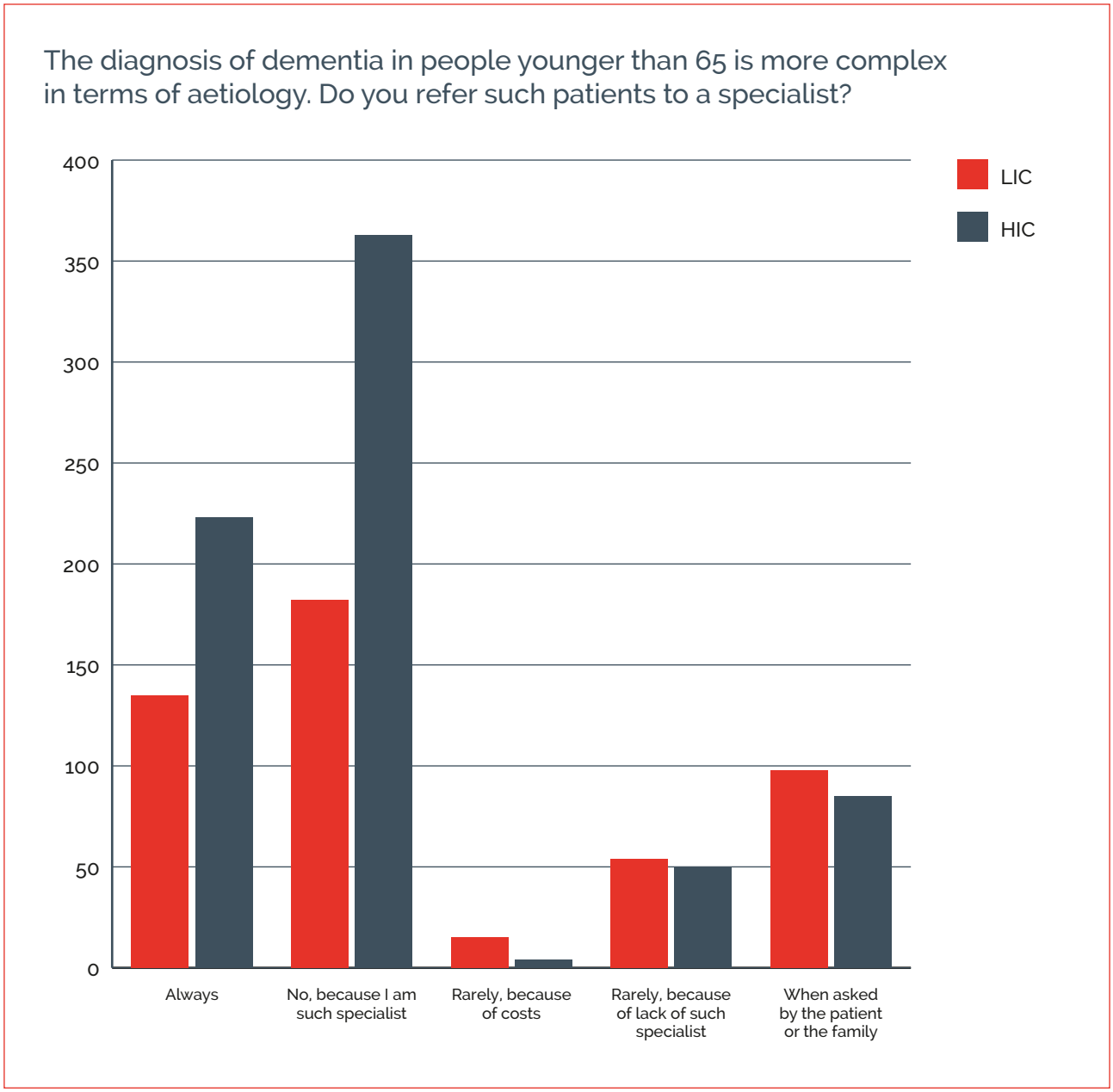


Chart 1. Clinician responses.

Causes of young-onset dementia

Although Alzheimer's disease, frontotemporal and Lewy body dementias account for the symptoms in almost half of young-onset dementia cases, the prevalence of rarer dementia causes (rare vascular causes, infectious, inflammatory, autoimmune, genetic abnormalities or metabolic) increases in individuals under the age of 65. As many of these causes are treatable, the first assessment by a general practitioner should be followed up by a referral to either a memory centre or general neurology for further clinical investigation. Rare disorders are frequently associated with neurologic and systemic manifestations (Table 1). A summary of the causes of dementia in young people is illustrated in the section below (2,5–7).

The cause of dementia presents as even more atypical for those individuals younger than 35 years of age.

Alzheimer's disease – Certain clinical scenarios are associated with young-onset Alzheimer's disease. The APOE4 genotype is a common generic risk factor associated with Alzheimer's dementia symptoms before the age of 65. Down syndrome is another frequent genetically-driven cause of Alzheimer's disease seen in the third and fourth decades of life. Carriers of autosomal dominant Alzheimer's disease may present dementia symptoms as early as in their third decade; however, these families are rare. Sporadic Alzheimer's disease may resemble the amnestic typical clinical presentation of specific dementias. As well, nearly 10% of these individuals may have de novo mutations in PS1, PS2 and APP genes.

These non-amnestic atypical variants of Alzheimer's disease have only been fully incorporated in the operational definition of Alzheimer's disease in 2010–2011. Recent biomarker research has also shown that tau pathology and neurodegeneration rather than amyloid pathology correlate with Alzheimer's dementia symptoms (Figure 1). These patterns of tau distribution observed in the PET scans constitute signatures of these specific Alzheimer's disease subtypes (8–11).

Table 1. Systemic and neurological abnormalities associated with young-onset dementias

Neurological or systemic abnormalities	Rare causes for early-onset dementias
Abnormal gait and station	Normal pressure hydrocephalus, Parkinson's dementia, progressive supranuclear palsy, vascular dementia, neurosyphilis, Type 1 myotonic dystrophy, autosomal dominant Alzheimer's disease (spastic paraparesis), chronic traumatic encephalopathy
Anaemia	Vitamin B12 deficiency, neuroacanthocytosis, Wilson disease, alcohol abuse
Ataxia	Spinocerebellar atrophy, paraneoplastic encephalopathy, prion disease, dentatorubral-pallidoluysian atrophy, multiple system atrophy, leukoencephalopathies, mitochondrial diseases
Cardiac disease	Late-onset Fabry disease, Type 1/2 myotonic dystrophy, Down Syndrome
Gastrointestinal dysfunction	Whipple disease
Liver dysfunction	Wilson disease, Gaucher disease, mitochondrial diseases
Migraine and stroke	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, mitochondrial diseases, chronic traumatic encephalopathy
Paget disease of bone	Frontotemporal dementias
Renal impairment	Late-onset Fabry disease, mitochondrial disease
Respiratory disease	Frontotemporal with motor neuron diseases, mitochondrial disease, anti-NMDAR encephalitis, Type 1 myotonic dystrophy
Skin lesions	Systemic vasculitis, late-onset Fabry disease
Sleep disturbance	Neurodegenerative dementias, prion disease
Splenomegaly	Niemann-Pick type C, Gaucher disease
Tendon xanthomas	Cerebrotendinous xanthomatosis
Urinary incontinence	Normal pressure hydrocephalus

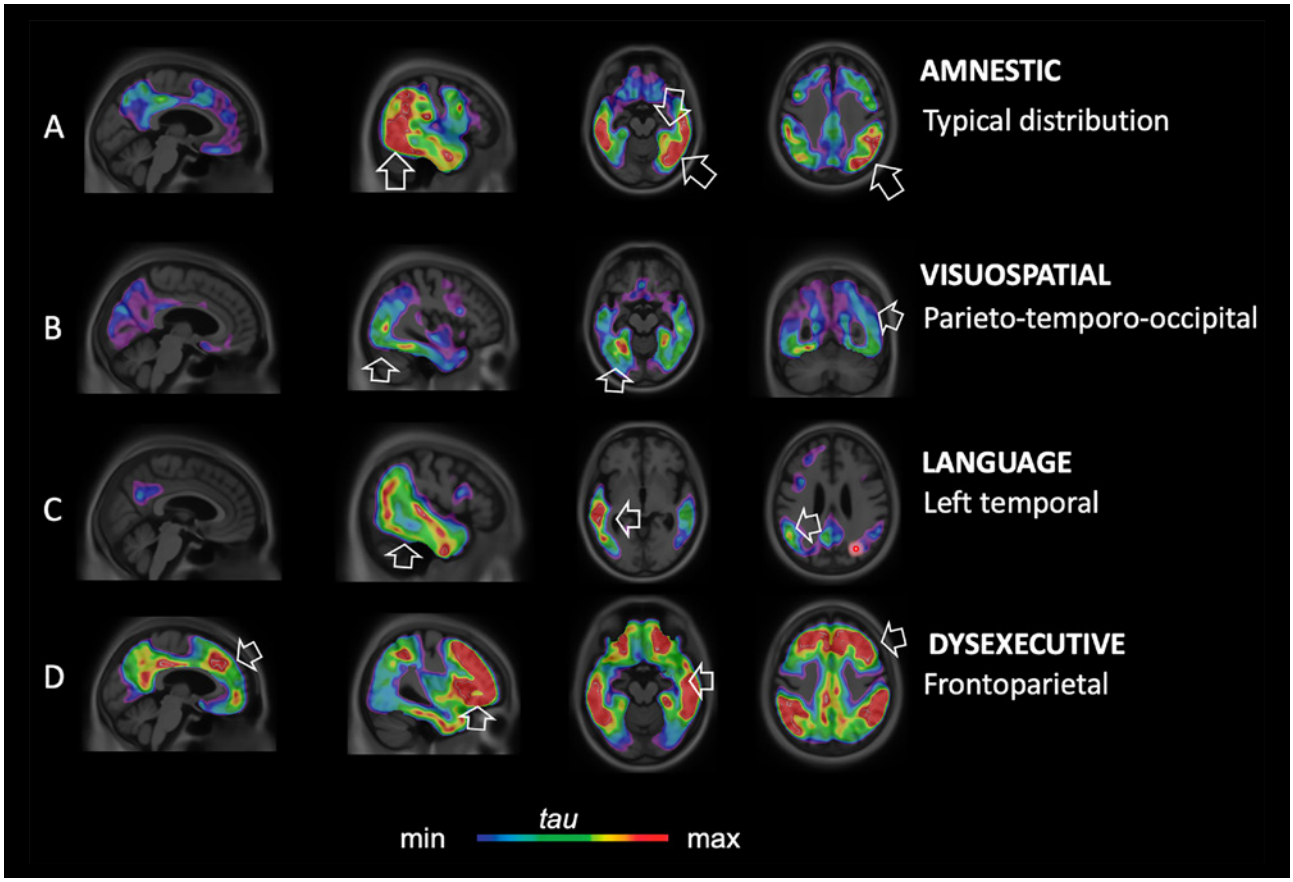


Figure 1. These images represent the distribution of neurofibrillary tangles (rainbow colour) overlaid in a structural MRI (grey tone). The amnestic type of Alzheimer's disease (A) shows tau deposition in the trans and entorhinal areas, limbic cortices, associative neocortex and in the most advanced cases in the primary sensory areas. Note that in visuospatial (B), language (c) and dysexecutive variants of Alzheimer's disease (D) neurofibrillary tangles accumulate in the parieto-temporal-occipital, left temporoparietal and frontoparietal regions, respectively (12, 13).

Other degenerative causes of young-onset dementia

Frontotemporal dementia – A behavioural variant, semantic dementia and progressive non-fluent aphasia are inescapable clinical manifestations of frontal and temporal lobes degeneration. While the behavioural variant features a progressive decline in social cognition and executive function, the semantic and non-fluent primary progressive aphasias are characterised by a degeneration that affects both language centres responsible for semantic and phoneme production (14).

Lewy body dementias – Young-onset Lewy body dementias, including Parkinson's disease dementia and dementia with Lewy bodies, may be associated with alpha-synuclein gene copy number variations, glucocerebrosidase gamma-synuclein gene mutations (15).

A wide range of disease processes underlie **vascular dementia** in young individuals. Inherited vascular dementias causes microangiopathy, lacunar infarcts predominantly in the anterior quadrant of the brain and causes frequent migraines, neuropsychiatric symptoms (such as depression and irritability) and executive dysfunction. This points to dementia onset in the fifth decade of life. Mutations in the NOTCH3 gene on chromosome 19 leads to cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Mutations on the CTSA gene lead to cathepsin A–related arteriopathy with strokes and leukoencephalopathy (CARASAL).

Individuals with CARASAL may present with migraine, transient ischemic attacks, stroke with central facial palsy, cognitive dysfunction with impaired concentration, dementia, depression, movement disorder, vertigo, dysphagia, dysarthria, sicca syndrome, impaired REM sleep, and therapy-resistant hypertension, among others. Brain MRI typically shows a leukoencephalopathy that is disproportionately severe and extensive compared to the clinical disease (16–18).

Cerebral amyloid angiopathy is characterised by amyloid beta-peptide deposits within the brain's small- to medium-sized blood vessels and meninges. Dementia is a consequence of progressive brain infarcts and lobar haemorrhages induced by amyloid deposits on the blood vessels.

Among the **infectious causes** of young-onset dementia are HIV-associated neurocognitive disorder, neurosyphilis, herpes encephalitis, Whipple's disease, and progressive multifocal leukoencephalopathy.

Primary angiitis of the central nervous system (PACNS) is caused by an elusive immune-mediated attack on small and medium blood vessels resulting in vessel occlusion, thrombosis and tissue ischemia. Secondary angiitis of the central nervous system can be the result of systemic autoimmune vasculitis (namely Behçet syndrome and Lupus), or an infectious process (such as varicella zoster virus, neurosyphilis or Lyme disease). Brain angiitis leads to cognitive dysfunction. In these instances, these may be accompanied by headaches, seizures, stroke, and cerebral haemorrhage (19,20).

Paraneoplastic and autoimmune encephalitis are clinically characterised by rapidly progressive dementia with a fluctuating course and other neurological manifestations such as seizures. They are caused by Anti-Hu (ANNA-1) or anti-leucine-rich glioma inactivated 1 (LGI1) antibodies. Nonparaneoplastic autoimmune encephalopathies can present clinically as a rapidly progressive dementia such as Hashimoto encephalopathy. Slow and progressive cognitive decline has been described in individuals with systemic Lupus erythematosus and Sjögren, and Behçet syndromes. Rare forms of young-onset dementia are summarised in Table 2 (21,22).

Chronic traumatic encephalopathy designates the progressive cognitive decline characterised by executive impairment, associated with behavioural (irritability, personality changes, depression, and suicidality) motor (parkinsonism), speech and gait abnormalities following repeated traumatic brain injuries. These symptoms have been frequently observed in professional athletes exposed to repetitive head trauma, particularly professional boxers and football players. Members of the army or other professionals exposed to repetitive traumatic brain injuries might suffer from similar symptoms. The brain lesions found in the brain of these patients is neuronal and astrocytic accumulation of hyperphosphorylated tau aggregates. These abnormalities occur on the superficial cortical layers, within the depths of cortical sulci (8–11).

Substance abuse is a cause of dementia in young adults. Alcohol-related syndromes such as Korsakoff syndrome or disease are well-known as causes of dementia. People with Korsakoff syndrome have substantial anterograde memory impairment and confabulation. These symptoms are associated with lesions in the anterior thalamus rather and mamillary bodies. Marchiafava-Bignami relates to the demyelination and necrosis of the corpus callosum, due to alcohol abuse. Neuropathological studies have shown that substantial brain damage resulting from abusing such drugs as methamphetamine, cocaine-crack and heroin may inflict significant cognitive decline (12). Episodic memory and executive function deterioration as well as language abnormalities have been described in these cases.

Pseudodementia or cognitive abnormality imposed by a mental health condition is often confounded with dementia as it manifests with forgetfulness, difficulties in multitasking, excessive inattention, apathy, reduced energy, and distractibility. Depression and anxiety and other psychiatric conditions may potentially cause severe cognitive deficiency, though this may be potentially reversible with the appropriate therapy. Other reversible causes of dementia have been discussed in the Chapter (15,23–26).

The expert essays describe some of the complexities involved in the diagnosis journey of young individuals affected by dementia. The investigation of these patients is crucial as many may require specific therapies for the underlying cause of dementias.

Table 2. Rare genetic causes of young-onset dementia

Diseases	Protein abnormality	Chromosome
Mitochondrial disease	Energy metabolism	Mitochondrial DNA
Hereditary diffuse leukoencephalopathy with axonal spheroids	Colony-stimulating factor 1 receptor (CSF1R)	5
Adult-onset autosomal dominant leukodystrophy	LMNB1 duplication (intermediate filament)	5
Adult polyglucosan body disease	GBE1	3
Adult neuronal ceroid lipofuscinosis (Kufs disease)	DNAJC5	20
Cathepsin A–related arteriopathy with strokes and leukoencephalopathy (CARASAL)	CTSA gene -β-galactosidase and neuraminidase 1	20
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)	NOTCH3 gene on chromosome 19	19
Wilson's disease	Intracellular copper transporter ATP7B	13
Huntington's disease	Mutations in the HTT gene cause Huntington disease	4

Expert essay

What is the most efficient way to diagnose dementia in a young person?

Mario Masellis[i]

University of Toronto and Sunnybrook Health Sciences Centre, CANADA

What is young-onset dementia and how common is it?

Young or early-onset dementia refers to a brain condition of progressive deterioration in cognitive and mental abilities that significantly impairs occupational functioning and daily life in individuals under the age of 65 (1). While it is uncommon compared to late-onset dementia (that is over 65), young-onset dementia is still estimated to account for between 2% and 10% of all dementia cases worldwide and carries with it an enormous health and economic burden for individuals, their families and society overall (2). This is because it primarily affects individuals of working age with young families, leading to lost productivity, psychosocial distress, and significant cost to healthcare systems. Given that certain conditions causing or mimicking young-onset dementia have treatments, even if just for symptoms in some cases, it is important to be able to accurately diagnose young-onset dementia, identify its potential aetiology and counsel the individuals and their families. Furthermore, with the anticipated advent of disease-modifying therapies for neurodegenerative diseases, such as Alzheimer's disease, employing an appropriate diagnostic approach will be key to targeting the 'right' treatments to individuals (precision medicine) in the future (1).

How do you diagnose young-onset dementia?

A good clinical history followed by a thorough general and neurological exam are the necessary first steps to an accurate diagnosis. Using a systematic clinical and investigational approach, the goal is to rule out any potentially treatable conditions and to identify associated clinical features that may provide clues to narrowing down the differential diagnosis. Rossor et al. have coined the term 'dementia-plus' to refer to other neurological (for example, parkinsonism, focal weakness, etc.) or non-neurological features (evidence for involvement of other organ systems, such as skin and/or joint changes) that may be observed in association with the primary neurocognitive disorder (3). Special attention should also be paid to family history, as well as infectious (such as Human Immunodeficiency Virus [HIV]) and toxin (for example, heavy alcohol use) exposures.

Cognitive screening should be done as part of this initial assessment. Tests such as the Montreal Cognitive Assessment (4) and/or Mini-Mental State Exam (5), among others, should be employed. Important considerations include validation of the cognitive screening test in the population in which it is intended to be used, including language, education, and cultural factors (6). Specific patterns of cognitive impairment identified on testing may assist with the differential diagnosis. For a comprehensive diagnostic algorithm based on cognitive profile and associated clinical features, please refer to Masellis et al. (1).

Basic blood work looking for potentially treatable causes of cognitive impairment (such as anaemia, vitamin B12 or other vitamin deficiencies, thyroid abnormalities) should be screened in everyone. Brain imaging should also be done to rule out structural abnormalities, such as brain tumours, cerebrovascular disease, or infectious cysts (neurocysticercosis; relevant in low-income countries), and to identify neuroanatomical features of the different causes of dementia. Ideally, this should be done with high-resolution structural Magnetic Resonance Imaging (MRI). If this is not available, then a Computer Axial Tomography (CAT) scan should be the minimum standard. If available, functional brain imaging should also be pursued to investigate for regional perfusion (Single Photon Emission Computed Tomography [SPECT)] or metabolic (Positron Emission Tomography [PET]) signatures of the different types of dementia. Electroencephalogram (EEG) is also useful in ruling out epileptic seizures as a cause or a contributing factor to dementia. Cerebrospinal Fluid (CSF) analysis should be done in the majority of people to exclude inflammatory and infectious causes and to further refine the differential diagnosis. If available, tests such as CSF beta-amyloid, total tau,

i Mario Masellis is supported by the Department of Medicine (Sunnybrook Health Sciences Centre and the University of Toronto), the Sunnybrook Foundation, the Hurvitz Brain Sciences Research Program, and the Sunnybrook Research Institute. He also receives support as co-lead of the Ontario Neurodegenerative Disease Research Initiative funded by the Ontario Brain Institute.

and phospho-tau levels can support a diagnosis of Alzheimer's disease (7). Amyloid and Tau PET may also be of use for determining Alzheimer disease's pathology (7), in particular, but costs limit their routine use in most low- and middle-income countries. Dopamine transporter SPECT may also be helpful in select cases in the differential diagnosis of Lewy body disorders (7). Specialised genetic and biochemical testing for young-onset dementia should be considered based on age at onset, family history, associated clinical features, and brain imaging findings.

What are the causes of young-onset dementia?

While neurodegenerative diseases, such as Alzheimer's disease, are still the most prevalent causes even in this age group, reversible or treatable causes are relatively more prevalent in young-onset dementia compared to late-onset cases. Furthermore, rare genetic or metabolic disorders are also more common in early-onset dementia, especially in those under the age of 35 and treatments may also be available for some of these conditions (8). Therefore, determining a specific familial inheritance pattern is of utmost importance towards guiding appropriate specialised investigations. In these cases, it may also be helpful to refer to a clinical geneticist or genetics counsellor for further genetic and/or biochemical testing.

> **While neurodegenerative diseases, such as Alzheimer's disease, are still the most prevalent causes even in this age group, reversible or treatable causes are relatively more prevalent in young-onset dementia compared to late-onset cases.**

Neurodegenerative and other aetiologies

Early-onset Alzheimer's disease is the most common neurodegenerative cause of dementia in the young. While sporadic cases, those with no strong genetic component, are predominant in this early-onset age group, familial Alzheimer's disease is still more frequent than in late-onset cases. In familial cases, an autosomal dominant pattern of inheritance is seen with mutations observed in one of three genes: presenilin 1 (PSEN1), presenilin 2 (PSEN2), or amyloid precursor protein (APP) (9). These account for less than 2% of all young-onset Alzheimer's cases (10). While a memory deficit is the most common clinical presentation of both early-onset sporadic and familial Alzheimer's disease in the majority of cases, atypical variants with visuospatial, language, or behavioural/executive problems occur more frequently than in late-onset forms (1).

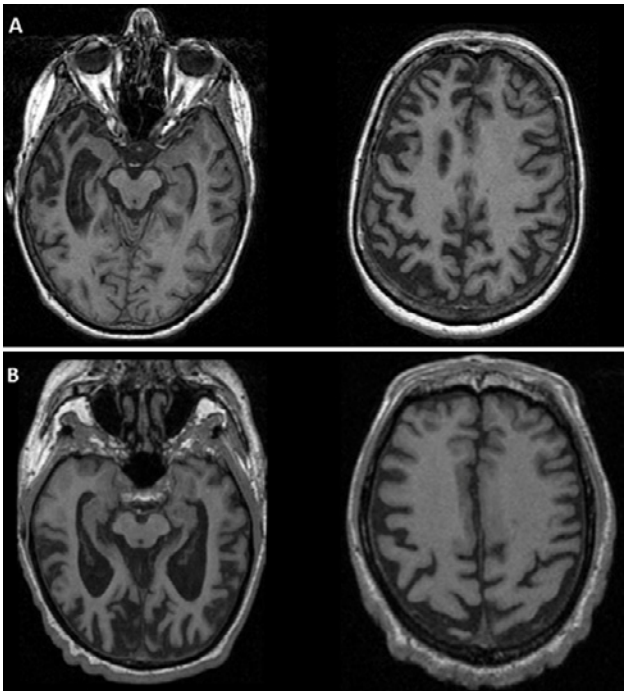


Figure 1. Contrasting atrophy patterns for behavioural variant frontotemporal dementia and early-onset familial Alzheimer's disease. Axial T1 magnetic resonance imaging contrasting atrophy patterns for (a) a patient with behavioural variant frontotemporal dementia due to progranulin (GRN) mutation and (b) a patient with early-onset familial Alzheimer's disease due to presenilin (PSEN1) mutation. (a) Striking asymmetry in frontotemporal and parietal lobes associated with GRN mutations. (b) More symmetrical mesiotemporal and posterior predilection associated with PSEN1 mutations. Reproduced from Masellis M, et al.: Early-onset dementias: diagnostic and etiological considerations. Alzheimer's Research & Therapy 2013, 5(Suppl. 1): S7, under the Creative Commons Attribution License (CC BY 4.0, https://creativecommons.org/licenses/by/4.0/).

Frontotemporal dementia is the second most common neurodegenerative cause of dementia in this age group with its prevalence approaching that of Alzheimer's disease (11). This heterogeneous group of neurodegenerative disorders presents with either prominent behavioural/executive dysregulation (namely, behavioural variant frontotemporal dementia) or language problems (that is, primary progressive aphasia) early on. Frontotemporal dementia is more strongly genetic than young-onset Alzheimer's disease with autosomal dominant mutations observed in the microtubule associated protein Tau (MAPT) and progranulin (GRN) genes, as well as hexanucleotide repeat expansions in the C9orf72 gene; each genetic subtype accounts for ~5 to 10% of all frontotemporal dementia cases (12). Figure 1 demonstrates the utility of structural MRI in distinguishing genetic Alzheimer's disease from genetic frontotemporal dementia.

Parkinson-Lewy body spectrum disorders represent another related group of conditions that can cause dementia in the young, including Parkinson's disease dementia and dementia with Lewy bodies. People may present with motor symptoms that affect their gait, cause muscle rigidity, tremor, and

slowness (parkinsonism), fluctuations in attention and alertness, visual hallucinations and abnormal behaviours while dreaming (13). While Parkinson-Lewy body disorders are most commonly sporadic, mutations or polymorphisms in certain genes, such as alpha-synuclein (SNCA), glucocerebrosidase (GBA1), and apolipoprotein E (APOE), can cause or increase risk for their occurrence (14). All of these neurodegenerative disorders progress relentlessly, resulting in the need for supportive care of those afflicted in the moderate to severe dementia stages and ultimately culminating in death.

The link between poorly controlled cardiovascular risk factors (including hypertension, diabetes, high cholesterol and smoking) and risk for dementia is well-established (15). While pure forms of vascular cognitive impairment are relatively uncommon, small vessel disease of the brain in conjunction with Alzheimer's disease co-pathology (that is, mixed disease) is the most common form of late-onset dementia. While less prevalent, a cause in young-onset cases, especially in high income countries, stroke and dementia are rising in low- to middle-income countries making it an important contributor to mixed disease even in young-onset cases (16). Individuals typically present with deficits in executive functions, psychomotor processing speed, and mental flexibility (namely, fronto-subcortical dementia). Since cardiovascular risk factors are modifiable, there is hope that managing them with medications and lifestyle interventions might reduce the incidence of dementia (16). In addition, some rare genetic disorders, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) due to NOTCH3 gene mutations, should be considered depending on patient and family history, as well as imaging findings (Figure 2).

Rare genetic and/or metabolic conditions, including lysosomal storage diseases, disorders of amino acid and organic acid metabolism, mitochondrial diseases, leukodystrophies, and disorders of metal metabolism can also cause dementia, most often with other associated clinical features, in the young. These have been reviewed in detail elsewhere (17).

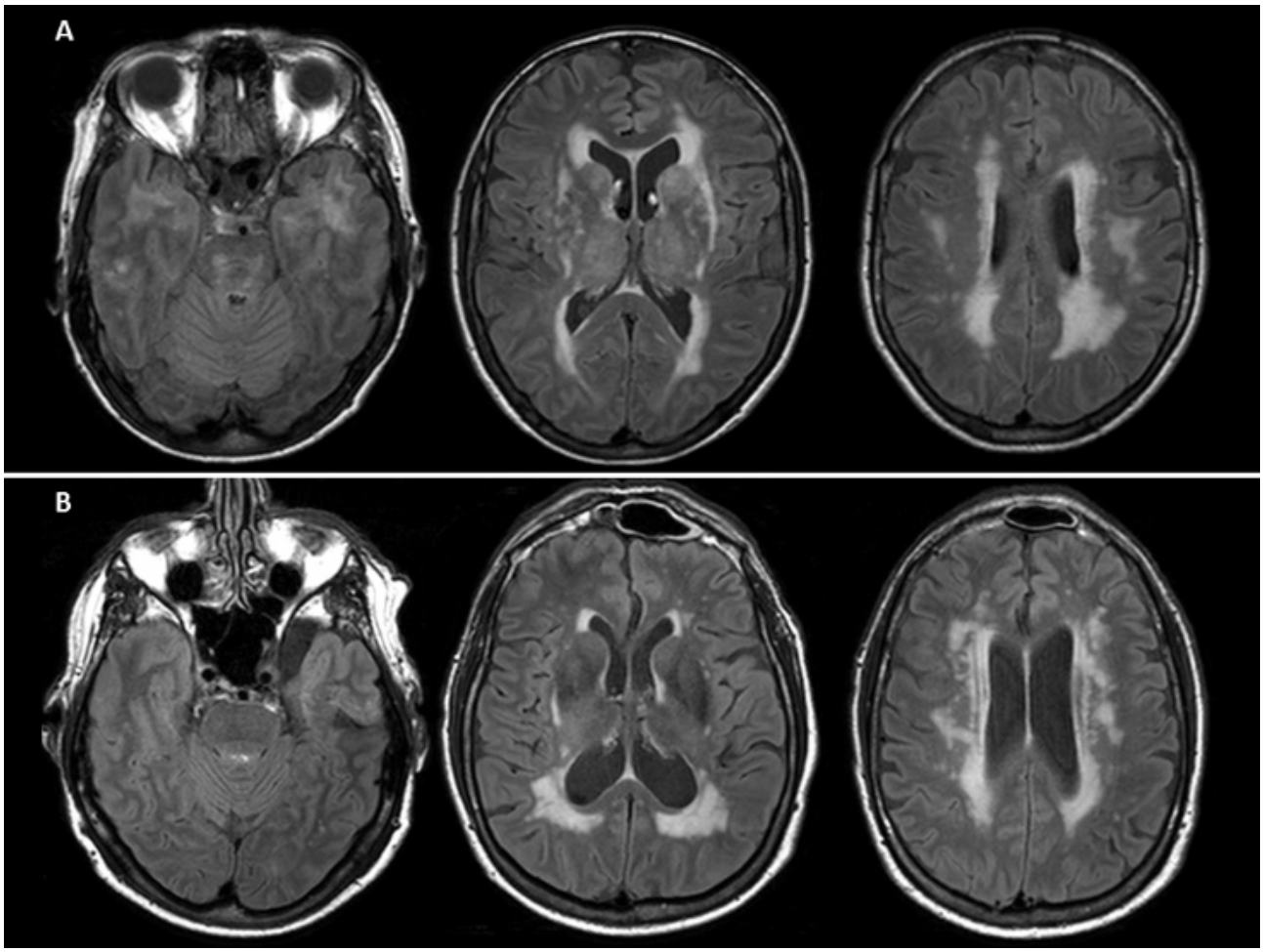


Figure 2. Subcortical ischemic vascular changes in CADASIL and vascular cognitive impairment due to small vessel disease. Axial T2/fluid-attenuated inversion recovery magnetic resonance imaging demonstrating subcortical ischemic vascular changes in (a) a patient with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and (b) a patient with vascular cognitive impairment due to small vessel disease. Anterior temporal lobe involvement distinguishes CADASIL from small vessel disease due to cerebrovascular risk factors. Reproduced from Masellis M, et al.: Early-onset dementias: diagnostic and etiological considerations. Alzheimer's Research & Therapy 2013, 5(Suppl.1):S7, under the Creative Commons Attribution License (CC BY 4.0, https://creativecommons.org/licenses/by/4.0/).

It is important to consider these entities since some, such as Wilson's disease presenting with dementia, parkinsonism and/or psychiatric symptoms, have disease-modifying therapies available.

What should not be missed?

Obstructive sleep apnoea is a common disorder in which recurrent pauses in breathing (apnoeas/hypopneas) during sleep cause intermittent hypoxia, hypercapnia and fragmented sleep (18). This condition can be associated with cognitive impairment. One study demonstrated that 8% of people presenting to a young-onset dementia clinic had obstructive sleep apnoea (19). It is potentially treatable via continuous positive airway pressure (CPAP), which might help with cognitive symptoms, in particular inattention.

The autoimmune encephalopathies are a rare group of potentially steroid-responsive syndromes, often affecting young individuals, presenting with subacute onset of cognitive impairment, and frequently accompanied by psychiatric disturbances, confusion, seizures and cortical T2-weighted signal changes on MRI, most often involving the temporal lobe (20). Auto-antibodies targeting several cell-surface brain receptors or ion channels are the cause of inflammatory brain changes involving limbic structures. These antibodies can be assessed in CSF and plasma/serum, which can aid with specific syndromic diagnosis and initiation of immunomodulating therapies.

Temporal lobe epilepsy can be associated with transient epileptic amnesia, which can mimic the memory symptoms of Alzheimer's disease (21). People may present with altered awareness or cognitive fluctuations in addition to anterograde and retrograde amnesia. This condition can be diagnosed via EEG demonstrating temporal lobe spike and wave activity, and brain MRI showing mesiotemporal sclerosis. There may be some improvement with anticonvulsant therapy, although complete symptom resolution does not always occur.

Special considerations for low- and middle-income countries about treatable causes

While neurodegenerative causes of young-onset dementia are prevalent in low- and middle-income countries, in addition to a higher burden of vascular cognitive impairment as previously mentioned, communicable diseases are an important contributor to cognitive dysfunction due to their higher prevalence. HIV-associated neurocognitive disorder and neurocysticercosis, among others, are potentially treatable causes of cognitive impairment and should be considered on the differential diagnosis of young-onset dementia in these geographical regions (22). The endemic nature of a particular infection should be determined when ordering specific microbiological diagnostic tests.

In summary, young-onset dementia poses unique challenges for afflicted individuals, their families, healthcare systems and society on the whole. A rational diagnostic approach is necessary to first ensure that treatable contributing factors or causes of dementia are excluded, and then to determine the specific neurodegenerative, heredodegenerative or genetic metabolic aetiologies. Access to genetic counselling and other specialised care services should be provided by healthcare systems. Treatment or reduction of 12 potentially modifiable risk factors for late-onset dementia (namely head injury, excess alcohol consumption, air pollution, lower education, hypertension, smoking, diabetes, obesity, physical inactivity, depression, social isolation, and hearing impairment) may prevent dementia or delay its onset (23), especially for younger individuals with risk factors and lacking a strong family history suggestive of a genetic disorder.

References

1. Masellis M, Sherborn K, Neto PR, et al. Early-onset dementias: Diagnostic and etiological considerations. Alzheimer's Res. Ther. Alzheimers Res Ther; 2013. https://pubmed.ncbi.nlm.nih.gov/24565469/.
2. World Alzheimer Report. 2009. www.deutsche-alzheimer.de.
3. Rossor MN, Fox NC, Mummery CJ, Schott JM, Warren JD. The diagnosis of young-onset dementia [online]. Lancet Neurol. Lancet Neurol; 2010. p. 793–806. https://pubmed.ncbi.nlm.nih.gov/20650401/.
4. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment [online].
5. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res [online serial]. J Psychiatr Res; 1975;12:189–198. https://pubmed.ncbi.nlm.nih.gov/1202204/.
6. Perry W, Lacritz L, Roebuck-Spencer T, et al. Population Health Solutions for Assessing Cognitive Impairment in Geriatric Patients. Clin Neuropsychol [online serial]. Routledge; 2018;32:1193–1225. https://pubmed.ncbi.nlm.nih.gov/30396329/.
7. Brisson M, Brodeur C, Létourneau-Guillon L, et al. CCCDTD5: Clinical role of neuroimaging and liquid biomarkers in patients with cognitive impairment. Alzheimer's Dement Transl Res Clin Interv [online serial]. Wiley; 2020;6. https://pubmed.ncbi.nlm.nih.gov/33532543/.
8. Kelley BJ, Boeve BF, Josephs KA. Young-Onset Dementia Demographic and Etiologic Characteristics of 235 Patients [online]. https://jamanetwork.com/.
9. Wu L, Rosa-Neto P, Hsiung GYR, et al. Early-onset familial alzheimer's disease (EOFAD) [online]. Can. J. Neurol. Sci. Canadian Journal of Neurological Sciences; 2012. p. 436–445. https://pubmed.ncbi.nlm.nih.gov/22728850/.
10. Jarmolowicz AI, Chen HY, Panegyres PK. The patterns of inheritance in early-onset dementia: Alzheimer's disease and frontotemporal dementia. Am J Alzheimers Dis Other Demen [online serial]. SAGE Publications Inc.; 2015;30:299–306. https://pubmed.ncbi.nlm.nih.gov/25147204/.

11. Coyle-Gilchrist ITS, Dick KM, Patterson K, et al. Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes. Neurology [online serial]. Lippincott Williams and Wilkins; 2016;86:1736–1743. https://pubmed.ncbi.nlm.nih.gov/27037234/.
12. Greaves C V., Rohrer JD. An update on genetic frontotemporal dementia [online]. J. Neurol. Dr. Dietrich Steinkopff Verlag GmbH and Co. KG; 2019. p. 2075–2086. https://pubmed.ncbi.nlm.nih.gov/31119452/.
13. McKeith IG, Boeve BF, DIckson DW, et al. Diagnosis and management of dementia with Lewy bodies [online]. Neurology Lippincott Williams and Wilkins; 2017. p. 88–100. Accessed at: https://pubmed.ncbi.nlm.nih.gov/28592453/.
14. Sanghvi H, Singh R, Morrin H, Rajkumar AP. Systematic review of genetic association studies in people with Lewy body dementia [online]. Int. J. Geriatr. Psychiatry John Wiley and Sons Ltd; 2020. p. 436–448. https://pubmed.ncbi.nlm.nih.gov/31898332/.
15. Moorhouse P, Rockwood K. Vascular cognitive impairment: current concepts and clinical developments [online]. Lancet Neurol. Lancet Neurol; 2008. p. 246–255. https://pubmed.ncbi.nlm.nih.gov/18275926/.
16. Hachinski V, Einhäupl K, Ganten D, et al. Preventing dementia by preventing stroke: The Berlin Manifesto [online]. Alzheimer's Dement. Elsevier Inc.; 2019. p. 961–984. https://pubmed.ncbi.nlm.nih.gov/31327392/.
17. Ridha B, Josephs KA. Young-onset dementia: A practical approach to diagnosis [online]. Neurologist Lippincott Williams and Wilkins; 2006. p. 2–13. https://pubmed.ncbi.nlm.nih.gov/16547442/.
18. Rosenzweig I, Glasser M, Polsek D, Leschziner GD, Williams SCR, Morrell MJ. Sleep apnoea and the brain: A complex relationship [online]. Lancet Respir. Med. Lancet Publishing Group; 2015. p. 404–414. https://pubmed.ncbi.nlm.nih.gov/25887982/.
19. Panegyres PK, Frencham K. Course and causes of suspected dementia in young adults: A longitudinal study. Am J Alzheimers Dis Other Demen [online serial]. Weston Medical Publishing; 2007;22:48–56. https://pubmed.ncbi.nlm.nih.gov/17534002/. Accessed June 8, 2021.
20. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis [online]. Lancet Neurol. Lancet Publishing Group; 2016. p. 391–404. https://pubmed.ncbi.nlm.nih.gov/26906964/.
21. Baker J, Savage S, Milton F, et al. The syndrome of transient epileptic amnesia: a combined series of 115 cases and literature review. Brain Commun [online serial]. Oxford University Press (OUP); 2021;3. https://pubmed.ncbi.nlm.nih.gov/33884371/.
22. Bergen DC, Silberberg D. Nervous System Disorders A Global Epidemic [online]. Arch Neurol 2002. Accessed at: https://jamanetwork.com/.
23. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission [online]. Lancet Lancet Publishing Group; 2020. p. 413–446. https://pubmed.ncbi.nlm.nih.gov/32738937/.

Expert essay

Particular challenges for diagnosing Alzheimer's disease in young people under 65

Pauline Olivieri,[1] Leonardo Cruz de Souza,[2] Julien Lagarde,[1] Marie Sarazin[1]

[1] Department of Neurology of Memory and Language, GHU Paris Psychiatry and Neurosciences, Hôpital Sainte Anne, F-75014, Paris, Université de Paris, F-75006 Paris, FRANCE
[2] School of Medicine, Federal University of Minas Gerais, Belo Horizonte, BRAZIL

Clinical presentation

Aside from the typical amnestic presentation, individuals with young-onset Alzheimer's disease have, more often than those with late-onset Alzheimer's disease, an atypical non-amnestic syndrome with executive, language, or visuo-spatial dysfunction (1). Among the atypical clinical presentations, the most frequent is the biparietal syndrome characterised by a visuospatial deficit, apraxia, agraphia, logopenic aphasia and deficit of auditory-verbal short-term memory. The other most frequent atypical presentation of young-onset Alzheimer's disease is logopenic variant primary progressive aphasia (LPA), posterior cortical atrophy (PCA) or Benson's syndrome and the behavioural/dysexecutive variant. In LPA, language deficit is the initial symptom, characterised by repeated pauses that disrupt the flow of the conversation and the generation of phonologic errors, associated with deficit in sentence repetition. In PCA, visuospatial deficit is the initial symptom, and individuals then develop features of Balint syndrome (ocular apraxia, optic ataxia, and simultanagnosia), Gerstmann syndrome (acalculia, agraphia, finger agnosia, and left-right disorientation), visual agnosia, and transcortical sensory aphasia, whereas episodic memory is preserved or only mildly impaired. The behavioural/dysexecutive variant of Alzheimer's disease is defined by a predominant dysexecutive syndrome which is frequently associated with frontal behavioural symptoms (1). These clinical features can lead to a misdiagnosis of behavioural variant frontotemporal dementia. In young-onset Alzheimer's disease, the initial complaint is not always purely cognitive. In a recent study, 32% of young people with a diagnosis of Alzheimer's disease had an atypical complaint, leading to an initial diagnosis of a burnout syndrome. Among those with young-onset Alzheimer's disease who had a professional activity (70%), a burnout-like syndrome was the first diagnosis in almost half of the cases (2). These people had an inability to carry out concurrent professional tasks, leading to a reduction of professional efficacy and severe anxiety, in the absence of overt language, memory, gestural, visuo-spatial disorders, or other neurological signs. Their family members did not report any specific cognitive abnormality. Because of these atypical clinical presentations, an Alzheimer's disease diagnosis is not the always the first to be ascribed to such young individuals and young-onset Alzheimer's disease cases are often referred to other specialists before neurologists. Instead, should they receive an initial diagnosis of burnout, they are usually referred to psychiatrists and followed for several years before the first neurological evaluation. Also, it is common for patients with PCA to be referred to several ophthalmologists before the first neurological evaluation. The diagnosis of young-onset Alzheimer's disease is delayed by about a 1.6-years average compared to people with late-onset Alzheimer's disease (3), due in part to theses atypical clinical presentations and not to anosognosia, which is less pronounced in young individuals. The rapidity of clinical decline is also one of the main elements differentiating young- and late-onset. Several studies indicate that these early-onset patients have a more aggressive disease course (4).

Structural brain and fluorodeoxyglucose-positron emission tomography imaging

The clinical presentation differences corroborate with brain atrophy and glucose hypometabolic patterns that are distinctive in extent and location between young- and late-onset Alzheimer's disease. On magnetic resonance imaging (MRI), young-onset Alzheimer's disease shows greater neocortical atrophy, particularly in parietal cortex, with preserved hippocampal volumes relative to LOAD (5). In LPA, MRI shows atrophy and decreased metabolism in the left temporo-parietal junction, while in PCA presentation, neuroimaging shows predominant areas of atrophy and hypometabolism from parieto-occipital cortex. Patients with the behavioural/dysexecutive variant of Alzheimer's disease manifest mild prefrontal atrophy, associated to moderate bilateral atrophy in temporoparietal regions. MRI studies suggest that functional connectivity changes differ in young- and late-onset Alzheimer's disease, the former being mainly driven by an early involvement of fronto-parietal networks (6). Progressive changes of neural networks are present before neuronal loss and regional atrophy and could contribute to the occurrence

of non-cognitive inaugural complaint before the onset of more classic cortical cognitive signs. This hypothesis will need to be tested in dedicated studies including imaging data.

Pathophysiological biomarkers

For young patients with an atypical non-amnestic presentation, the diagnosis of Alzheimer's disease is possible by using pathophysiological biomarkers such as cerebrospinal fluid (CSF) biomarkers or amyloid/tau positron emission tomography (PET) imaging.

Cerebrospinal Fluid (CSF) biomarkers

The profile of CSF biomarkers is the same: amyloid β42 (Aβ) peptide levels are decreased, and total tau and phospho-tau levels are increased in CSF. Some studies suggest phenotypic variations in these CSF biomarkers, particularly lower tau levels in PCA (7), but this has not been confirmed across studies and with neuropathology.

Amyloid and tau PET biomarkers

The extent and distribution of tau pathology measured by PET differed between young- and late-onset Alzheimer's disease, with tau aggregation in widespread neocortical regions (prefrontal and parietal cortex) in young-onset Alzheimer's disease while the pattern of tau deposition was more confined to the temporal regions in late-onset Alzheimer's disease, in line with neuropathological studies showing that damage to limbic structures may be a prominent feature of late but not of young-onset Alzheimer's disease (8). The regional pattern of tau pathology measured by PET was congruent with clinical presentation of the disease: high uptake was found in left temporo-parietal cortex in LPA and in parieto-occipital cortex in PCA. Similarly, people with the behavioural/dysexecutive variant of Alzheimer's disease exhibit temporoparietal pattern of tau uptake. The tau PET imaging pattern was inversely correlated with regional cortical hypometabolism assessed by FDG-PET. In addition, PET imaging confirms neuropathological studies, showing that the tauopathy is initially more severe and progresses faster in young-onset Alzheimer's disease than late-onset, supporting the idea that the disease is more aggressive in individuals with young-onset (9).

In contrast to the regional tau accumulation revealed by PET imaging, amyloid deposition was present diffusely throughout the neocortex, independent of clinical presentation and with no differences between young- and late-onset (10). Amyloid PET is especially useful in the differentiation of young-onset Alzheimer's disease from other dementias of early-onset.

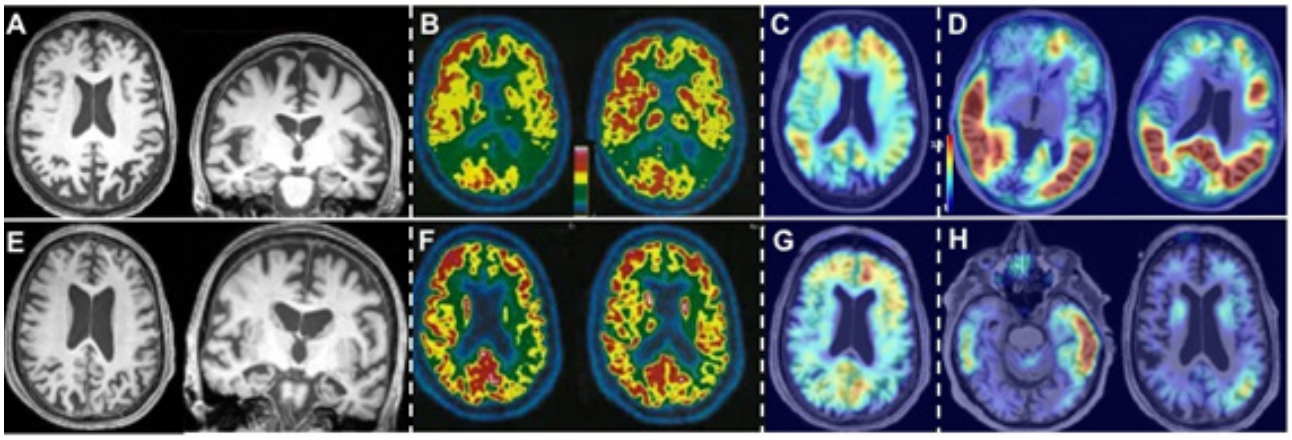


Illustration of the imaging features in a young and an older patient with Alzheimer's disease.

Top row: 53-year-old patient with Alzheimer's disease (CDR=0.5, estimated disease duration = 3 years). Bottom row: 80-year-old patient with Alzheimer's disease (CDR = 0.5, estimated disease duration = 6 years). Brain MRI shows a biparietal atrophy, with relatively preserved hippocampi in the young-onset patient (A), and a more pronounced hippocampal atrophy in the late-onset patient (E). FDG-PET shows a marked parietal hypometabolism in young-onset Alzheimer' s disease (B), which is less pronounced in late-onset (F). The pattern of amyloid deposition is comparable in young- and late-onset patients (C, G). Tau tracer binding is more diffuse and more pronounced in the young-onset patient, extending to the temporo-parietal cortex, while it remains more restricted to the temporal lobes in the patient with late-onset dementia (D, H).

The amyloid and tau PET images are from the Shatau7-IMATAU study funded by the French Ministry of Health (PHRC-2013–0919), CEA, Foundation pour la recherche sur la maladie d'Alzheimer, Institut de Recherches Internationales Servier, France-Alzheimer.

Genetic: Autosomal dominant transmission

Familial Alzheimer's disease with autosomal dominant transmission is rare, only 1.6% of the total young-onset population carries a presenilin 1 (PSEN1), presenilin 2 (PSEN2), or amyloid precursor protein (APP) gene mutation (11). These three pathogenic mutations, which lead to aberrant cleavage or aggregation of the APP, explain three quarters of autosomal dominant cases: Dominant Alzheimer's disease: (PSEN1 in 52% of cases), APP (mutation in 9% and duplication in 7%) and PSEN2 in 6% (12). In these genetic forms, Alzheimer's disease most often begins before the age of 60 with a typical hippocampal amnesia in 84% of cases, but atypical cognitive forms are also described and should not be ignored, such as spastic paraparesis, early myoclonus, seizures, dysarthria, pseudobulbar affect, more extensive amyloid angiopathy.

Therapeutic management

It is crucial to diagnose young-onset Alzheimer's disease as early as possible, in order to provide the most appropriate care, such as specific medication based on acetylcholinesterase inhibitors or memantine, rehabilitation, adaptation of the workspace when possible and also to avoid the prescription of contraindicated treatment such as anticholinergic antidepressants. The consideration of medico-social and psychosocial complications is essential for young patients, who often still have a professional activity and young children.

Moreover, the early diagnosis of young-onset Alzheimer's disease is a challenge to enable these people to participate in therapeutic trials, as their symptoms are often too pronounced at the time of diagnosis to be included.

References

1. Mendez MF. Early-Onset Alzheimer Disease. Neurol Clin 2017;35:263.
2. Olivieri P, Hamelin L, Lagarde J, Hahn V, Guichart-Gomez E, Roué-Jagot C, et al. Characterization of the initial complaint and care pathways prior to diagnosis in very young sporadic Alzheimer's disease. Alzheimer's Res Ther 2021;13:90. https://doi.org/10.1186/s13195-021-00829-0.
3. Van Vliet D, De Vugt ME, Bakker C, Pijnenburg YAL, Vernooij-Dassen MJFJ, Koopmans RTCM, et al. Time to diagnosis in young-onset dementia as compared with late-onset dementia. Psychol Med 2013;43:423–32. https://doi.org/10.1017/S0033291712001122.
4. Koedam ELGE, Lauffer V, Van Der Vlies AE, Van Der Flier WM, Scheltens P, Pijnenburg YAL. Early-versus late-onset Alzheimer's disease: More than age alone. J Alzheimer's Dis 2010;19:1401–8. https://doi.org/10.3233/JAD-2010-1337.
5. Ossenkoppele R, Cohn-Sheehy BI, La Joie R, Vogel JW, Möller C, Lehmann M, et al. Atrophy patterns in early clinical stages across distinct phenotypes of Alzheimer's disease. Hum Brain Mapp 2015;36:4421–37. https://doi.org/10.1002/hbm.22927.
6. Gour N, Felician O, Didic M, Koric L, Gueriot C, Chanoine V, et al. Functional connectivity changes differ in early and late-onset alzheimer's disease. Hum Brain Mapp 2014;35:2978–94. https://doi.org/10.1002/hbm.22379.
7. Teng E, Yamasaki TR, Tran M, Hsiao JJ, Sultzer DL, Mendez MF. Cerebrospinal fluid biomarkers in clinical subtypes of early-onset alzheimer's disease. Dement Geriatr Cogn Disord 2014;37:307–14. https://doi.org/10.1159/000355555.
8. Schöll M, Ossenkoppele R, Strandberg O, Palmqvist S, Jögi J, Ohlsson T, et al. Distinct 18F-AV-1451 tau PET retention patterns in early- and late-onset Alzheimer's disease. Brain 2017;140:2286–94. https://doi.org/10.1093/brain/awx171.
9. Sintini I, Martin PR, Graff-Radford J, others. Longitudinal tau-PET uptake and atrophy in atypical Alzheimer's disease. NeuroImage Clin n.d.;23:3.
10. De Souza LC, Corlier F, Habert MO, Uspenskaya O, Maroy R, Lamari F, et al. Similar amyloid-β burden in posterior cortical atrophy and Alzheimer's disease. Brain 2011;134:2036–43. https://doi.org/10.1093/brain/awr130.
11. Jarmolowicz AI, Chen HY, Panegyres PK. The patterns of inheritance in early-onset dementia: Alzheimer's disease and frontotemporal dementia. Am J Alzheimers Dis Other Demen 2015;30:299–306. https://doi.org/10.1177/1533317514545825.
12. Nicolas G, Wallon D, Charbonnier C, Quenez O, Rousseau S, Richard AC, et al. Screening of dementia genes by whole-exome sequencing in early-onset Alzheimer disease: Input and lessons. Eur J Hum Genet 2016;24:710–6. https://doi.org/10.1038/ejhg.2015.173.

Expert essay

Alzheimer's disease diagnosis in Down syndrome: challenges and opportunities

Juan Fortea,[1] André Strydom[2]

[1] Sant Pau Memory Unit, Neurology Department, Hospital de la Santa Creu i Sant Pau – Biomedical Research Institute Sant Pau – Universitat Autònoma de Barcelona, Barcelona, SPAIN
[2] Institute of Psychology, Psychiatry and Neuroscience, King's College London, London, UNITED KINGDOM

Down syndrome is the most frequent cause of intellectual disability of genetic origin. There are approximately 5.8 million people living with Down syndrome in the world. The life expectancy of adults with Down syndrome has dramatically increased over the last decades due to improved healthcare, and now approaches 60 years of age in high income countries (1). Consequently, age-associated comorbidities are emerging, most importantly Alzheimer´s disease (2).

Virtually all adults with Down syndrome develop the hallmarks of Alzheimer´s disease pathology by age 40, and the lifetime risk of dementia is estimated to be well over 90% (3). Dementia is rare before the age of 40, but its incidence and prevalence exponentially increase thereafter to over 80% in those over the age of 65 (Figure 1) with a median age at dementia diagnosis ranging between the ages of 53 and 55 (3,4). Dementia due to Alzheimer´s disease is now the main cause of death in adults with Down syndrome. This strong association is mainly due to the triplication of amyloid precursor protein gene (1–3).

Clinical challenges

The clinical presentation of Alzheimer's disease in Down syndrome is now recognised as similar to that of sporadic Alzheimer's disease, with early declines in episodic memory as well as declines in attention and in executive functions. These are followed by declines in other cognitive abilities and the development of functional, behavioural, and neurological symptoms (5,6). The diagnosis of mild cognitive impairment or prodromal Alzheimer's disease requires a change in cognition reported by the carer (cognitive complaints by adults with Down syndrome are rare) based on decline from previous performance. As in the general population, dementia is diagnosed when activities of daily living are clearly affected and need to have changed from premorbid functioning. The variable degree of premorbid intellectual disability problematises these definitions. First, there are different degrees of cognitive functioning due to the variable levels of intellectual disability, which complicates the formal definition of mild cognitive impairment or prodromal Alzheimer's disease. Similarly, many individuals with Down syndrome have longstanding impairments in daily activities, complicating the definition of Alzheimer's disease dementia. Prodromal Alzheimer's disease might impact on functionality earlier in Down syndrome than in the general population due to lower cognitive and functional reserve (1).

Clinicians with expertise in the diagnosis of Alzheimer's disease are able to make accurate diagnoses despite the difficulties in assessing the Alzheimer's disease-related cognitive impairment and the absence of validated operatised clinical diagnostic criteria, if they consider the individual's baseline functioning, and exclude other causes of decline (1). People with Down syndrome usually score at floor in the neuropsychological test batteries used in the general population; therefore, adapted tests are required (1,2). Using these adapted tests, recent research suggests that population norms are feasible if the subjects are stratified by the level of intellectual disability (7). Another important recommendation is to consider the within-person longitudinal change on tests if data is available on the personal best level of achievement. One limitation of the most current adapted tests, however, is that most adults with Down syndrome with severe intellectual disability cannot perform these tests. Other measures of cognitive functioning and dementia symptoms should be used for these individuals, including carer reported tools (1).

Comorbidities frequently found in adults with Down syndrome pose another important clinical challenge. Early symptoms can be mistaken as part of lifelong impairments or obscured by coexisting medical comorbidities that might affect cognition, such as obstructive sleep apnoea, hypothyroidism and depression. Conversely, given the early age of onset of dementia, the differential diagnosis rarely includes other neurodegenerative dementias (1,2).

Finally, the lack of awareness from families, carers and clinicians represents another important challenge, which is currently delaying or impeding Alzheimer's disease diagnoses in adults with Down syndrome. Consultations often only occur when activities of daily living are substantially

affected, or when behavioural problems emerge, hence early descriptions of a behavioural or frontal subtype as the main clinical presentation in Down syndrome.

Alzheimer's disease biomarkers offer new opportunities

Biomarkers are revolutionising the diagnosis of Alzheimer's disease in the general population. Several biomarkers have been approved by regulatory agencies and are increasingly included in clinical guidelines. In Down syndrome, however, promising results on these biomarkers have yet to be applied in clinical diagnosis.

There are few studies with cerebrospinal fluid biomarkers in Down syndrome, but all have consistently shown the typical biochemical Alzheimer's disease signature with a 50% reduction in the β-amyloid 42/40 ratio and a two-fold increase phosphorylated tau levels in symptomatic patients (8).

Blood-based biomarkers are now feasible due to the development of ultrasensitive technologies, and well tolerated in individuals with Down syndrome. Plasma neurofilament light (NfL) levels have excellent diagnostic and prognostic performances (8–10). NfL levels are not specific to Alzheimer's disease, but they are highly indicative of symptomatic Alzheimer's disease in the context of Down syndrome (8–10). This is due to the aforementioned fact that other neurodegenerative disorders are exceedingly rare. Novel plasma phosphorylated-tau assays have been recently developed and have high accuracy for Alzheimer's disease diagnosis (1). Adults with Down syndrome have higher plasma Aβ concentrations than euploid controls, but these biomarkers have not yet proven to be useful for diagnosing symptomatic Alzheimer's disease (1). Of note, there are no reports in Down syndrome with the novel mass spectrometry techniques that accurately detect brain amyloidosis in sporadic Alzheimer's disease.

Imaging biomarkers have also been used in the Down Syndrome population. The atrophy pattern in the MRI and the brain hypometabolism associated with Alzheimer's disease shows the same regional pattern of hypometabolism in Down syndrome as seen in sporadic Alzheimer's disease involving the medial temporal, parietal, praecuneus and posterior cingulate regions (1–3). Amyloid PET studies also show a similar pattern of amyloid deposition to that described in sporadic Alzheimer's disease (1–3). There are only a very small number of studies using tau PET tracers in Down Syndrome, but the available data also shows a typical Alzheimer's disease pattern (1).

Of note, these biomarkers changes begin 20 years before symptom onset and the natural history of Alzheimer's disease in Down syndrome follows a predictable sequence of events in biomarker changes in a strikingly similar order and timing to that described in autosomal dominant Alzheimer's disease (3).

In summary, there are challenges leading to clinical underdiagnosis and/or misdiagnosis. However, accurate clinical diagnoses are possible, and biomarkers have potential for Alzheimer's disease diagnosis in this population. In the future, population-based screening for Alzheimer's disease in Down syndrome may substantially increase detection. Such programmes should target those adults with Down syndrome over 35–40 years of age (1), and include plasma biomarkers, which have the potential to become useful and cost-effective screening tools. Accurate diagnoses are the essential first step towards timely access to treatment (which is now becoming available) and care planning.

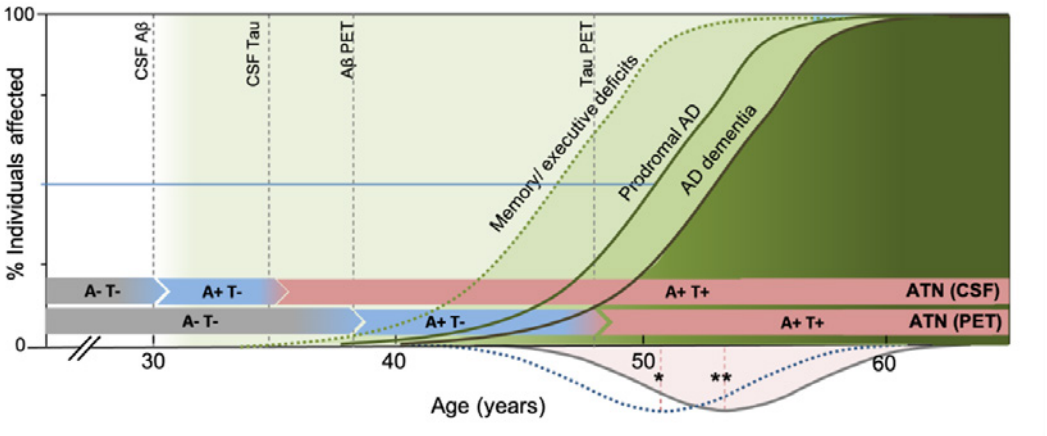


Figure 1. The arrows reflect the timing for the earliest changes in CSF and PET biomarkers. The model shows the clinical progression of Alzheimer's disease in people with Down Syndrome. Subtle memory/executive deficits may start from age 35, prodromal Alzheimer's disease occurs at a median age of 51 years (*) and dementia at age 54 (**) years of age. The Gaussians bellow the X-axis reflect density of prodromal and Alzheimer's disease dementia diagnosis in Fortea et al. (3) The vertical dotted lines reflect the earliest biomarker changes for the amyloid and tau biomarkers in the same paper.

References

1. Fortea J, Zaman S, Hartley S, Rafii M, Head E, Carmona-Iragui M. Down syndrome-associated Alzheimer's disease. Lancet Neurol Under Rev; 2021.
2. Strydom A, Coppus A, Blesa R, Danek A, Fortea J, Hardy J, et al. Alzheimer's disease in Down syndrome: An overlooked population for prevention trials. Alzheimer's Dement Transl Res Clin Interv 2018;4:703–13. https://doi.org/10.1016/j.trci.2018.10.006.
3. Fortea J, Vilaplana E, Carmona-Iragui M, Benejam B, Videla L, Barroeta I, et al. Clinical and biomarker changes of Alzheimer's disease in adults with Down syndrome: a cross-sectional study. Lancet 2020;395:1988–97. https://doi.org/10.1016/S0140-6736(20)30689-9.
4. Hithersay R, Startin CM, Hamburg S, Mok KY, Hardy J, Fisher EMC, et al. Association of Dementia with Mortality among Adults with Down Syndrome Older Than 35 Years. JAMA Neurol 2019;76:152–60. https://doi.org/10.1001/jamaneurol.2018.3616.
5. Startin CM, Hamburg S, Hithersay R, Al-Janabi T, Mok KY, Hardy J, et al. Cognitive markers of preclinical and prodromal Alzheimer's disease in Down syndrome. Alzheimer's Dement 2019;15:245–57. https://doi.org/10.1016/j.jalz.2018.08.009.
6. Hithersay R, Baksh RA, Startin CM, Wijeratne P, Hamburg S, et al. Optimal age and outcome measures for Alzheimer's disease prevention trials in people with Down syndrome. Alzheimer's Dement 2021;17:595–604. https://doi.org/10.1002/alz.12222.
7. Benejam B, Videla L, Vilaplana E, Barroeta I, Carmona-Iragui M, Altuna M, et al. Diagnosis of prodromal and Alzheimer's disease dementia in adults with Down syndrome using neuropsychological tests. Alzheimer's Dement Diagnosis, Assess Dis Monit 2020;12:1. https://doi.org/10.1002/dad2.12047.
8. Fortea J, Carmona-Iragui M, Benejam B, FernándezS, Videla L, Barroeta I, et al. Plasma and CSF biomarkers for the diagnosis of Alzheimer's disease in adults with Down syndrome: a cross-sectional study. Lancet Neurol 2018;17:860–9. https://doi.org/10.1016/S1474-4422(18)30285-0.
9. Carmona-Iragui M, Alcolea D, Barroeta I, Videla L, Muñoz L, Van Pelt K, et al. Prognostic performance and longitudinal changes in plasma Neurofilament light levels in adults with Down syndrome: a multicentre longitudinal study. Lancet Neurol 2021;In press.
10. Strydom A, Heslegrave A, Startin CM, Mok KY, Hardy J, Groet J, et al. Neurofilament light as a blood biomarker for neurodegeneration in Down syndrome. Alzheimer's Res Ther 2018;10:39. https://doi.org/10.1186/s13195-018-0367-x.

Conclusions

Young-onset dementia can be seen as particularly cruel as it strikes individuals before the age of 65, young people in their prime with jobs, children and an active social and physical life. It contradicts what most people associate with this age group, namely, that it is an 'old person' condition that young people need not concern themselves with.

Although half of these cases are attributable to the onset of various dementias, other rarer underlying causes may be at play when young-onset is diagnosed. As some of these causes are treatable or reversible (for example, a person who has suffered repeated head trauma or abused alcohol and drugs) referring these individuals to specialised centres, such as memory clinics or a hospital's neurology department, is especially critical.

This is part of the reason a young-onset diagnosis can be an especially long, complex and difficult journey. By ensuring they are not misdiagnosed, which further exacerbating the symptoms, pinpointing these other factors is necessary to orient the management of the case. This includes providing the appropriate and effective therapies or medication in a timely manner.

Additional references

1. Ayodele T, Rogaeva E, Kurup JT, Beecham G, Reitz C. Early-Onset Alzheimer's Disease: What Is Missing in Research? Curr Neurol Neurosci Rep. 2021;21(2):4. https://www.ncbi.nlm.nih.gov/pubmed/33464407.
2. Hendriks S, Peetoom K, Bakker C, van der Flier WM, Papma JM, Koopmans R, et al. Global Prevalence of Young-Onset Dementia: A Systematic Review and Meta-analysis. JAMA Neurol. 2021. https://www.ncbi.nlm.nih.gov/pubmed/34279544.
3. O'Malley M, Parkes J, Stamou V, Lafontaine J, Oyebode J, Carter J. Young-onset dementia: scoping review of key pointers to diagnostic accuracy. BJPsych Open. 2019;5(3). https://dx.doi.org/10.1192/bjo.2019.36.
4. Rossor MN, Fox NC, Mummery CJ, Schott JM, Warren JD. The diagnosis of young-onset dementia. The Lancet Neurology. 2010;9(8):793-806. https://dx.doi.org/10.1016/s1474-4422(10)70159-9.
5. Antonarakis SE, Skotko BG, Rafii MS, Strydom A, Pape SE, Bianchi DW, et al. Down syndrome. Nat Rev Dis Primers. 2020;6(1):9. https://www.ncbi.nlm.nih.gov/pubmed/32029743.
6. Fortea J, Vilaplana E, Carmona-Iragui M, Benejam B, Videla L, Barroeta I, et al. Clinical and biomarker changes of Alzheimer's disease in adults with Down syndrome: a cross-sectional study. The Lancet. 2020;395(10242):1988-97.
7. Serrano-Pozo A, Das S, Hyman BT. APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. The Lancet Neurology. 2021;20(1):68-80.
8. McKee AC. The Neuropathology of Chronic Traumatic Encephalopathy: The Status of the Literature. Seminars in Neurology. 2020;40(04):359-69. https://dx.doi.org/10.1055/s-0040-1713632.
9. McKee AC, Cairns NJ, Dickson DW, Folkerth RD, Dirk Keene C, Litvan I, et al. The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. Acta Neuropathol. 2016;131(1):75-86. https://dx.doi.org/10.1007/s00401-015-1515-z.
10. McKee AC, Stein TD, Nowinski CJ, Stern RA, Daneshvar DH, Alvarez VE, et al. The spectrum of disease in chronic traumatic encephalopathy. Brain. 2013;136(1):43-64. https://dx.doi.org/10.1093/brain/aws307.
11. Smith DH, Johnson VE, Trojanowski JQ, Stewart W. Chronic traumatic encephalopathy – confusion and controversies. Nat Rev Neurol. 2019;15(3):179-83. https://dx.doi.org/10.1038/s41582-018-0114-8.
12. Nutt DJ, King LA, Phillips LD. Drug harms in the UK: a multicriteria decision analysis. The Lancet. 2010;376(9752):1558-65.
13. Aarsland D, Creese B, Politis M, Chaudhuri KR, Ffytche DH, Weintraub D, et al. Cognitive decline in Parkinson disease. Nat Rev Neurol. 2017;13(4):217-31. https://www.ncbi.nlm.nih.gov/pubmed/28257128.
14. Piguet O, Hornberger M, Mioshi E, Hodges JR. Behavioural-variant frontotemporal dementia: diagnosis, clinical staging, and management. The Lancet Neurology. 2011;10(2):162-72. https://dx.doi.org/10.1016/s1474-4422(10)70299-4.
15. Surmeier DJ, Obeso JA, Halliday GM. Selective neuronal vulnerability in Parkinson disease. Nat Rev Neurosci. 2017;18(2):101-13. https://www.ncbi.nlm.nih.gov/pubmed/28104909.
16. Salloway S, Hong J. CADASIL syndrome: a genetic form of vascular dementia. J Geriatr Psychiatry Neurol. 1998;11(2):71-7. https://www.ncbi.nlm.nih.gov/pubmed/9877528.
17. Maclean AV, Woods R, Alderson LM, Salloway SP, Correia S, Cortez S, et al. Spontaneous lobar haemorrhage in CADASIL. J Neurol Neurosurg Psychiatry. 2005;76(3):456-7. https://www.ncbi.nlm.nih.gov/pubmed/15716553.

18. Mancuso M, Arnold M, Bersano A, Burlina A, Chabriat H, Debette S, et al. Monogenic cerebral small-vessel diseases: diagnosis and therapy. Consensus recommendations of the European Academy of Neurology. Eur J Neurol. 2020;27(6):909-27. https://www.ncbi.nlm.nih.gov/pubmed/32196841.
19. Salvarani C, Brown RD, Hunder GG. Adult primary central nervous system vasculitis. The Lancet. 2012;380(9843):767-77.
20. Hajj-Ali RA, Singhal AB, Benseler S, Molloy E, Calabrese LH. Primary angiitis of the CNS. The Lancet Neurology. 2011;10(6):561-72.
21. Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. The Lancet Neurology. 2008;7(4):327-40.
22. Graus F, Dalmau J. Paraneoplastic neurological syndromes in the era of immune-checkpoint inhibitors. Nat Rev Clin Oncol. 2019;16(9):535-48. https://www.ncbi.nlm.nih.gov/pubmed/30867573.
23. Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser M-G. Cadasil. The Lancet Neurology. 2009;8(7):643-53.
24. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. The Lancet Neurology. 2016;15(4):391-404.
25. Das SK, Ray K. Wilson's disease: an update. Nat Clin Pract Neurol. 2006;2(9):482-93. https://www.ncbi.nlm.nih.gov/pubmed/16932613.
26. Tabrizi SJ, Flower MD, Ross CA, Wild EJ. Huntington disease: new insights into molecular pathogenesis and therapeutic opportunities. Nat Rev Neurol. 2020;16(10):529-46. https://www.ncbi.nlm.nih.gov/pubmed/32796930.

Chapter 24
Costs factors in diagnosing dementia

Serge Gauthier, Anders Wimo

Key points

- Adequate training of medical students and family practitioners is the most cost-effective approach for a timely and accurate diagnosis of dementia.
- Costs associated with a timely and accurate diagnosis are preferable to a delayed or inaccurate diagnosis that impedes a structured management of the condition.
- In relation to the emergence of biomarkers leading to an earlier and more specific diagnosis of dementia, further work is required to find cost-effective ways to orient people towards the best diagnostic pathways.

General background

When the cost factors in diagnosing dementia were studied in 1998, the main finding was that the human element, meaning the clinician's time, was the most important component, yet the least expensive when compared to costs associated with blood tests and structural brain imaging (1). In 2014, Wimo et al (2) carried out a detailed cost analysis on the diagnosis of dementia, including a breakdown of each diagnostic procedure and anticipating the proposed biological diagnosis of Alzheimer disease using the Amyloid, Tau, Neurodegeneration (ATN) framework (3).

Diagnostic costs have been studied in Sweden (4,5) and in Germany (6), highlighting the variability of costs based on the type of cognitive impairment and the setting (community setting versus a specialised clinic).

Survey results

The 1,111 multidisciplinary clinicians who responded to this survey were from high income (62%) and low- and middle-income countries (38%) using the 2021 World Bank listings of countries as reference. Most were working under a public healthcare system (50%), a good many in a mixed public and private system (30%), and the minority in private only systems (20%). When questioned about whether costs were a limiting factor in using specific diagnostic tests if they were available in their country, the main obstacle reported was with amyloid PET imaging (32%), followed by FDG-PET (29%), CT/MRI (18%), genetic testing (17%), CSF analysis for amyloid and tau proteins (14%). Costs were not a factor in referring a young person with dementia to a specialised clinic (2%), nor were they the primary issue in accepting to use novel blood biomarkers (14%) or in using remote cognitive testing (2%).

Among the 2,327 persons with dementia and their carers who replied to their survey, only 19% raised financial constraints as a major issue in getting a diagnosis, compared to lack of information provided about dementia (41%).

Additional considerations

When preparing this World Alzheimer Report, an effort was made to document the current costs of a dementia diagnosis. Most of the clinicians who replied indicated that the costs were covered by their country or state public healthcare system and that they were unaware of the specific costs. Thus, a worldwide cost analysis is needed for diagnostic procedures associated with dementia. A template is proposed in Tables 1a and 1b using the Province of Quebec's current costs per medical visit for people over the age of 65 in an outpatient clinic setting within the public healthcare system, as well as laboratory procedures in the public healthcare system or in private facilities. Costs are in Canadian Dollars unless otherwise indicated. Further work is clearly necessary in order to promote cost effective ways that orient people concerned with cognitive decline towards the best diagnostic pathway.

Comparing diagnostic pathways using current costs in Quebec versus costs published in 2014 by Wimo et al., with Swedish cost data is pertinent (Table 2) (2). Of note, from a clinical perspective, the sequence of events would be PC, SCE, NP, MRI, then CSF or PET.

The current costs of diagnosing dementia for people over the age 65 is lowest when most of the diagnosis is handled by family practitioners and emphasis is placed on history, physical examination, basic cognitive testing, the minimal required laboratory tests to exclude common comorbidities, and one brain imaging study (CT or MRI, the latter being preferable). In Quebec, these costs would include two visits with a family practitioner, bloods and a CT (total $198.30) or an MRI ($484.30).

In people younger than 65, there is a broader differential diagnosis that usually requires a referral to a neurologist with additional expertise in early-onset dementias. There will be additional laboratory tests and likely a spinal fluid examination (see Chapter 23). In Quebec, these total costs include two visits to a family practitioner and a referral to a neurologist providing two visits, one MRI, one FDG-scan and either a spinal fluid study (total $2,108.00) or a PET-amyloid scan (total $4,503.00). Special blood tests on a case-by-case basis are not included.

If a biological diagnosis for the cause of the dementia is the result of Alzheimer's disease, access to new anti-amyloid therapies may be needed. Thus, specific biomarkers studies are required to confirm amyloid positivity, and there is a need to validate a cost-effective algorithm such as the one proposed in Table 3 using APOE genotyping ($43) as a starting point. The high (95+) amyloid positivity in APOE4 4/4 has been reported by Degenhardt et al., 2016 (7). Elevated P-Tau 181 plasma levels are promising as surrogate to CSF analysis (8,9) and PET imaging (10), and the cost is expected to be less that CSF analysis. This algorithm may prove particularly useful when diagnosing people over the age of 70 (11).

Finally, if the person is clinically diagnosed as having mild cognitive impairment, the diagnostic approach will differ if there is a wait and see approach, taking advance of secondary prevention through control of vascular risk factors and emphasis on heath lifestyles (Diagnostic pathway 1 in Table 2), versus a disease-modifying drug requiring full clinical and etiologic work-up (Diagnostic pathways 13 and 15 in Table 2). As highlighted by Wimo et al in 2014, false positives and false negatives may have more consequences at that stage (2).

Current costs of dementia diagnosis related to visits (Table 1a) and procedures (Table 1b) in a hospital outpatient clinic, in the province of Quebec, Canada, under a universal publicly funded Medicare system.

Table 1a. Assessments by physicians (First visit and one follow-up visit for persons over the age of 65)

	First Visit	Follow-up Visit
Family practitioner	100.00	50.00
Neurologist	320.00	77.00
Psychiatrists	359.00	140.00
Geriatricians	350.00	250.00
Geneticists	323.00	105.00
	PUBLIC	PRIVATE
Assessments by other healthcare professionals		
Genetic counsellor	140.00	Not available
Neuropsychologist	500.00	2,300.00

Table 1b. Laboratory tests

	PUBLIC	PRIVATE
Blood Tests		
Complete Blood Count (CBC)	1.30	52.00
Sedimentation rate	1.60	39.00
Thyroid Stimulation Hormone (TSH)	1.60	89.00
T4	1.80	79.00
Electrolytes	2.10	69.00
Calcium	0.80	35.00
Blood Urea Nitrogen (BUN)	0.70	29.00
Creatinine	0.70	37.00
Glycemia	0.70	37.00
Haemoglobin A1c (HbA1c)	3.20	62.00
Alanine Aminotransferase (ALT)	0.70	31.00
B12	2.50	62.00
Folate	3.30	59.00
Cholesterol total, HDL, LDL, Triglycerides	5.30	79.00
Homocysteine	10.80	129.00
Syphilis serology	3.50	69.00
Human Immunodeficiency Virus (HIV) screen	4.90	69.00
Electroencephalography (EEG)		
Routine awake EEG	300.00	450.00
Spinal Fluid		
Lumbar puncture (procedure and kit)	205.00	205.00
Measure of A-Beta, Total tau and P-Tau	400.00	1349.00USD
Brain imaging		
Non contrast computer tomography (CT)	34.00	300.00
Non contrast magnetic resonance imaging (MRI)	320.00	650.00
Positron Emission Tomography (PET) with fluorodeoxyglucose (PET-FDG)	636.00	1,750.00
PET with amyloid ligand florbetaben	3,000.00	Not available
Genetic Testing		
APOE	43.00	219.00
PS1, PS2, APP	890.00 USD	890.00 USD

Prices are in Canadian Dollars unless otherwise indicated.

Table 2. Comparison of 2014 costs in Sweden to current costs in Quebec for different diagnostic pathways when Alzheimer`s disease is suspected.

Diagnostic	Sequence of tests	Costs in 2014	Costs in 2021
Pathway		*in Sweden (US$)*	*In Quebec (US$)*
Dia 1	PC	860	160
Dia xvf2	PC+SCE	1330	481
Dia 3	PC+SCE+MRI	1700	740
Dia 4	PC+SCE+CSF	2130	970
Dia 5	PC+SCE+NP	1870	885
Dia 6	PC+SCE+PET	2760	2906
Dia 7	PC+SCE+MRI+CSF	2500	1229
Dia 8	PC+SCE+MRI+NP	2240	1144
Dia 9	PC+SCE+MRI+PET	3130	3165
Dia 10	PC+SCE+CSF+NP	2670	1375
Dia 11	PC+SCE+CSF+PET	3560	3395
Dia 12	PC+SCE+NP+PET	3300	3311
Dia 13	PC+SCE+MRI+CSF+NP	3040	1633
Dia 14	PC+SCE+MRI+CSF+PET	3930	3654
Dia 15	PC+SCE+MRI+NP+PET	3670	3569
Dia 16	PC+SCE+CSF+NP+PET	4100	3800
Dia 17	PC+SCE+MRI+CSF+NP+PET	4470	4058

Dia, diagnostic pathway; PC, primary care (includes two clinical examinations, basic laboratory tests, computed tomography scan); SCE, specialist two clinical examinations (neurologist rate for the 2021 data); MRI, magnetic resonance imaging; CSF, spinal tap, kit and cost of analysis; NP, neuropsychological examination; PET, positron emission tomography for amyloid.

Table 3. Proposal to streamline the biological diagnosis of dementia due to Alzheimer's disease

- APOE 4/4 = A (+) very high (95%+) probability; no need for CSF or amyloid PET
- APOE 4/3 = A (+) moderate to high probability; requires plasma p-Tau 181 – if elevated, no need for CSF or PET
- APOE 4/3 with normal plasma p-Tau 181 or APOE3/3 = A (+) moderate probability, requires CSF or PET

Conclusions

A timely and accurate diagnosis of dementia entails some costs, but they are offset by a delayed or inaccurate diagnosis that impedes a structured management of the condition.

Comparing global healthcare systems and developing optimal diagnostic pathways from a cost perspective is vital. That said, the approach must also account for a time-effective clinician approach that incorporates time to provide necessary information to people with cognitive decline and their families.

Additional references

1. Gauthier S. Costs of diagnostic procedures. In: Wimo A, Jönsson B, Karlsson G, Winblad B, editors. Health Economics of Dementia. John Wiley & Sons Ltd; 1998. p. 269–73.
2. Wimo A, Ballard C, Brayne C, Gauthier S, Handels R, Jones RW, et al. Health economic evaluation of treatments for Alzheimer's disease: Impact of new diagnostic criteria. J Intern Med [Internet]. 2014 [cited 2021 Jul 12];275(3):304–16. https://pubmed.ncbi.nlm.nih.gov/24605810/
3. Jack CR, Bennett DA, Blennow K, Carrillo MC, Feldman HH, Frisoni GB, et al. A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. Vol. 87, Neurology. 2016. p. 539–47.
4. Wimo A, Religa D, Edlund AK, Winblad B, Eriksdotter M, Spångberg K. Costs of diagnosing dementia: Results from SveDem, the Swedish Dementia registry. Int J Geriatr Psychiatry [Internet]. 2013 Oct [cited 2021 Jul 12];28(10):1039–44. https://pubmed.ncbi.nlm.nih.gov/23440702/
5. Jedenius E, Wimo A, Strömqvist J, Jönsson L, Andreasen N. The cost of diagnosing dementia in a community setting. Int J Geriatr Psychiatry [Internet]. 2010 May [cited 2021 Jul 12];25(5):476–82. https://pubmed.ncbi.nlm.nih.gov/19685441/
6. Michalowsky B, Flessa S, Hertel J, Goetz O, Hoffmann W, Teipel S, et al. Cost of diagnosing dementia in a German memory clinic. Alzheimer's Res Ther [Internet]. 2017 Aug 22 [cited 2021 Jul 12];9(1). https://pubmed.ncbi.nlm.nih.gov/28830516/
7. Degenhardt EK, Witte MM, Case MG, Yu P, Henley DB, Hochstetler HM, et al. Florbetapir F18 PET Amyloid Neuroimaging and Characteristics in Patients With Mild and Moderate Alzheimer Dementia. Psychosomatics. 2016 Mar 1;57(2):208–16.
8. Alcolea D, Delaby C, Muñoz L, Torres S, Estellés T, Zhu N, et al. Use of plasma biomarkers for AT(N) classification of neurodegenerative dementias. J Neurol Neurosurg Psychiatry [Internet]. 2021 [cited 2021 Jul 12]; https://pubmed.ncbi.nlm.nih.gov/34103344/
9. Hansson O. Biomarkers for neurodegenerative diseases [Internet]. Vol. 27, Nature Medicine. Nature Publishing Group; 2021 [cited 2021 Jul 12]. p. 954–63. https://www.nature.com/articles/s41591-021-01382-x
10. Tissot C, Kunach P, Therriault J, Benedet A, Pascoal T, Ashton N, et al. Comparing tau status determined via plama pTau181, pTau 231 and [18F]MK6240 PET. Neurol [Submitted]. 2021;
11. Ossenkoppele R, Jansen WJ, Rabinovici GD, Knol DL, van der Flier WM, van Berckel BNM, et al. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. JAMA [Internet]. 2015 May 19 [cited 2021 Jul 12];313(19):1939–49. https://pubmed.ncbi.nlm.nih.gov/25988463/

Part VI

The future of the diagnosis of dementia

Chapter 25
New challenges and opportunities in the diagnosis of dementia

Claire Webster

- Clinicians recognise the need to make their practice more efficient in the diagnosis of dementia.
- New blood biomarkers may facilitate diagnosis of the causes of dementia.
- Medical and health science university faculties must integrate new insights and knowledge about diagnosis and management of dementia.

General background

This concluding Chapter summarises some of the important emerging themes based on the survey responses and expert essays. This is encouraging news, as primary care physicians express interest in adapting their clinical practice to incorporate biomarker screening and become more specialised in the diagnostic and post diagnosis management process. Unfortunately, the current reality is that there are roadblocks still in place that prevent individuals from obtaining a diagnostic assessment easily. These include a lack of awareness regarding the signs and symptoms of the condition; public fear and stigma associated with the diagnosis; problematic geographical locations, lack of adequate transportation to reach clinicians; insufficient numbers of trained healthcare experts in dementia; limited access to free public healthcare and the financial costs related to medical care.

Survey results

Among the 1,111 multidisciplinary clinicians who responded to the survey, most (75%) ranked the increased numbers of people who will seek a diagnosis given the ever-ageing population as the major challenge facing dementia diagnosis in the future. This was followed by people seeking a diagnosis based on self-testing results from web-based symptoms checklists or cognitive tests (44%), new disease-modifying therapies (43%), and direct-to-consumer genetic testing (22%). When asked what would make clinical practice more efficient when diagnosing people with cognitive decline, validated blood tests to confirm the aetiology of dementia was first (71%), followed by cognitive scales better adapted to various cultures and languages (67%), validated on-line algorithm taking into account clinical, laboratory and brain imaging information (59%), cognitive scales validated for telemedicine (52%) and self-screen cognitive, functional and behavioural scales completed prior to the clinical assessment (44%) were the top answers (Table 1).

Many of the 101 national Alzheimer associations who completed the survey indicated that their country has (37%), or is developing (23%), a National Dementia Plan. Most of the existing National Dementia Plans have a segment devoted to diagnosis, but few include a specific target for diagnosis rates or collect information about the number of newly diagnosed people with dementia (25%). Only 33 countries have easy access to healthcare professionals for all people concerned about their memory or cognitive changes, with 55 of the 101 associations citing that access is limited due to: a lack of clinicians (47%); people's fear of a dementia diagnosis (46%); costs (33%); or other reasons (16%) (Table 2).

In terms of knowledge sharing with the populations they represent, nearly all associations provide information about the warning signs of dementia (98%) and about reducing the risk of dementia (95%). Many provide information about diagnosis on their website (61%).

Table 1. List of choices by clinicians to make clinical practice more efficient in the diagnosis of dementia in order of priority

- Validated blood test to confirm aetiology of dementia.
- Cognitive scales better adapted to various cultures and languages.
- Validated on-line algorithms to combine clinical and laboratory data for individuals.
- Cognitive scales validated for telemedicine.
- Self-screening for cognition, function and behaviour prior to the clinical assessment.

Table 2. Alzheimer associations' list of reasons to explain the limited access to healthcare professionals, in order of importance

- Lack of clinicians.
- People's fear about a dementia diagnosis.
- Costs.

Expert essay

New challenges and opportunities in the diagnosis of dementia

Anders Wimo

Department of NVS, Centre of Alzheimer Research, Section of Neurogeriatrics, Karolinska Institutet, SWEDEN

The first point of contact in healthcare for people with symptoms that make them question whether they have an emerging dementia disorder is, in most cases, a primary care physician (GP, family practitioner, family physician) (1,2). Primary care can be organised and financed in many different ways – it can be public or private. Primary care physicians can work more or less alone or in teams with many variations of staff, and the out-of-pocket expenses can be low or high. The commission for primary care can be broad or rather narrow. Being a primary care physician can be a speciality like other specialities (neurology, internal medicine, etc.), but physicians can also start working in a primary care setting after completing medical school.

The prerequisites for this first contact can vary quite a bit, depending on where in the world you live. In general, primary care physicians work with and follow patients regularly, and, when needed, refer them to specialists. Thus, primary care should be the optimal care level for this first appointment.

> **In many countries, primary care physicians see several patients per hour, perhaps 6–10, and it is not possible to make an accurate dementia diagnosis in 10 minutes.**

In an ideal scenario, the primary care physician has known the individual and the family well for many years. The physician is experienced and well-educated in dementia. They have blocked off plenty of time for the appointment (approximately, one hour). A family member or friend should accompany and be present, termed medically as an 'informant' (this is with the patient's consent). A structured case history is collected. A set of cognitive tests, such as Mini-Mental State Exam (MMSE), Montreal Cognitive Assessment (MoCA), or clock drawing test is conducted, perhaps by another member of the dementia care team at the primary care centre. A base laboratory test is analysed and following a CT scan, a follow-up visit takes place. If needed, the individual is referred to a specialist. Unfortunately, this ideal scenario is rarely the case, and dementia often goes under-diagnosed in primary care (3).

Barriers to a making a diagnosis

Lack of competence, training and skills in dementia as well as negative attitudes towards dementia diagnostic work-ups by primary care physicians are often regarded as significant barriers (4). This is, of course, a problem, although to varying degrees (5). Dementia education geared towards primary care physicians is essential and has proven effective (6).

However, there are still two other aspects that needs attention.

First, in many countries, primary care physicians see several patients per hour, perhaps 6–10, and it is not possible to make an accurate dementia diagnosis in 10 minutes. This way of working is often related to significant demands and pressure caused by extensive patient lists (5).

Second, the remuneration system is often linked to a payment per visit structure. The more patients seen, the more money the practice earns. Such payment systems are extremely counterproductive for proper dementia management in primary care (4).

To date, there are many primary care physicians who can manage the assessment and post diagnosis process of their patients with a suspected dementia without needing to make referrals, as they have an ideal structure in place.

However, we are now facing a new situation with two arms which are closely linked: the diagnostic process is moving from dementia to pre-dementia states. Currently in primary care clinical practice, a diagnosis such as mild cognitive impairment (MCI) is not actually the goal, but rather a consequence of the diagnostic process that results in an MCI diagnosis. This is because the individual did not fulfil the criteria for dementia. However, in research, and at many memory clinics, there is a particular focus on the

pre-dementia Alzheimer's disease diagnosis. Besides the current diagnostic tools (brain imaging with MRI, PET, CSF, neuropsychology), blood-based markers for Alzheimer's disease are on their way, and such markers will likely be made available in primary care (7). However, for the moment, it is difficult to anticipate their role. The second arm is the hope for disease-modifying treatments (DMT), particularly for Alzheimer's disease (8). Since we know that the brain damaging process has been ongoing for many years before criteria for a dementia diagnosis are fulfilled, the arrival of disease-modifying treatments will demand a pre-dementia diagnosis of Alzheimer's disease.

Since the US Federal Drug Administration has recently (June 2021) given aducanumab a conditional approval for the treatment of Alzheimer´s disease, the situation will likely change in a dramatic way, at least in the US. We have yet to know how it will change in other parts of the world. We also do not know if 'filters' or restrictions will be applied to the accessibility of aducanumab. Nevertheless, this new US situation, combined with improved techniques, particularly for pre-dementia Alzheimer's disease diagnosis, will undoubtedly change the role of primary care in the diagnosis of dementia. If we assume that US approval will be followed in other parts of the world, or that other disease-modifying treatments will enter the market, people with subjective and/or slight memory problems may seek primary care more frequently, with the hope and demand for treatment for an eventual Alzheimer's disease diagnosis. The use of blood markers in combination with some cognitive tests in primary care (hopefully also responsive in pre-dementia states), may make referrals to specialists for additional assessment increase dramatically. However, and as shown in the reports from RAND (9,10), the readiness for such a heightened demand is inadequate in most countries. The diagnostic infrastructure is not prepared for a large increase in demand for pre-dementia (and early dementia) Alzheimer's disease diagnostics.

The fact that there have been no disease-modifying treatments on the market is perhaps the main reason primary care physicians are sceptical about pre-dementia Alzheimer's disease diagnostics along with, for example, blood-based biomarkers (11). The argument that an early diagnosis is not only linked to drug treatment, but also presents possibilities for early prevention (12), is probably not a solid argument for many primary care physicians. Prevention of dementia is, to a great extent, linked to cardiovascular risk factors, and this is already a major aspect of the work conducted in primary care. Therefore, even if the risk of dementia is appended, it does not impact the work all that much.

> **The diagnostic infrastructure is not prepared for a large increase in demand for pre-dementia (and early dementia) Alzheimer's disease diagnostics.**

Be aware that this is the situation in high income countries. In low- and middle-income countries, the situation is entirely different. The primary care infrastructure is limited, the diagnostic capacity for dementia is scarce, and primary care physicians are more engaged in managing conditions other than dementia. The accessibility to current Alzheimer's disease related drugs is already limited (13), and the expected price of a disease-modifying treatment will probably make it more or less impossible to obtain for the vast majority of people with Alzheimer's disease in low- and middle-income countries.

Another aspect to consider is that even if the sensitivity and specificity of new blood-based diagnostic tests is high (say 90%), the positive predictive values on a population level (with a prevalence of, say 10%), such as in primary care, is low (about 50%) (14). Though the arrival of blood-based biomarkers (in combination with cognitive tests) is considered progress for those of us who work in primary care, the label is important: 'at risk' of Alzheimer's disease does not conclude that people have Alzheimer's disease before the diagnosis is confirmed with more comprehensive tests at specialist clinics. And a great number of people who are referred to memory clinics, where the Alzheimer's disease diagnosis was yet to be confirmed, will be referred back to primary care, in an anxious state.

References

1. Fougère B, Vellas B, Delrieu J, Sinclair AJ, Wimo A, Herman CJ, et al. The Road Ahead to Cure and Prevent Alzheimer's Disease: Implementing Prevention into Primary Care. J Prev Alzheimer's Dis [Internet]. 2015 [cited 2021 Jul 12];2(3):199–211. https://pubmed.ncbi.nlm.nih.gov/29226945/.
2. Thyrian JR, Hoffmann W, Eichler T. Editorial: Early Recognition of Dementia in Primary Care- Current Issues and Concepts. Curr Alzheimer Res [Internet]. 2017 Dec 21 [cited 2021 Jul 12];15(1):2–4. https://pubmed.ncbi.nlm.nih.gov/29320981/.
3. International AD. World Alzheimer Report 2011: The Benefits of Early Diagnosis and Intervention [Internet]. 2011 [cited 2021 Jul 12]. www.alz.co.uk/worldreport2011.
4. Koch T, Iliffe S. Rapid appraisal of barriers to the diagnosis and management of patients with dementia in primary care: A systematic review. BMC Fam Pract [Internet]. 2010 [cited 2021 Jul 12];11. https://pubmed.ncbi.nlm.nih.gov/20594302/.
5. Giezendanner S, Monsch AU, Kressig RW, Mueller Y, Streit S, Essig S, et al. General practitioners' attitudes towards early diagnosis of dementia: A cross-sectional survey. BMC Fam Pract [Internet]. 2019 May 20 [cited 2021 Jul 12];20(1). https://pubmed.ncbi.nlm.nih.gov/31109304/.

6. Casey AN, Islam MM, Schütze H, Schütze H, Parkinson A, Yen L, et al. GP awareness, practice, knowledge and confidence: Evaluation of the first nation-wide dementia-focused continuing medical education program in Australia. BMC Fam Pract [Internet]. 2020 Jun 10 [cited 2021 Jul 12];21(1). https://pubmed.ncbi.nlm.nih.gov/32522153/.
7. Hansson O. Biomarkers for neurodegenerative diseases [Internet]. Vol. 27, Nature Medicine. Nature Publishing Group; 2021 [cited 2021 Jul 12]. p. 954–63. https://www.nature.com/articles/s41591-021-01382-x.
8. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: A priority for European science and society [Internet]. Vol. 15, The Lancet Neurology. Lancet Neurol; 2016 [cited 2021 Jul 12]. p. 455–532. https://pubmed.ncbi.nlm.nih.gov/26987701/.
9. Hlavka J, Mattke S, Liu J. Assessing the Preparedness of the Health Care System Infrastructure in Six European Countries for an Alzheimer's Treatment. 2018.
10. Liu J, Hlavka J, Hillestad R, Mattke S. Assessing the Preparedness of the U.S. Health Care System Infrastructure for an Alzheimer's Treatment. Santa Monica, Calif.: RAND Corporation. 2017.
11. Sannemann L, Müller T, Waterink L, Zwan M, Wimo A, Stomrud E, et al. General practitioners' attitude toward early and pre-dementia diagnosis of AD in five European countries – A MOPEAD project survey. Alzheimer's Dement Diagnosis, Assess Dis Monit [Internet]. 2021 Jan [cited 2021 Jul 12];13(1). /pmc/articles/PMC7901232/.
12. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. Lancet [Internet]. 2015 Jun 6 [cited 2021 Jul 12];385(9984):2255–63. https://pubmed.ncbi.nlm.nih.gov/25771249/.
13. Suh GH, Wimo A, Gauthier S, O'Connor D, Ikeda M, Homma A, et al. International price comparisons of Alzheimer's drugs: A way to close the affordability gap. Int Psychogeriatrics [Internet]. 2009 Dec [cited 2021 Jul 12];21(6):1116–26. https://pubmed.ncbi.nlm.nih.gov/19735595/.
14. Wimo A. What are the difficulties of implementing innovative pharmacy practice models in the care of patients with dementia? [Internet]. Vol. 21, Expert Review of Pharmacoeconomics and Outcomes Research. Taylor & Francis; 2021 [cited 2021 Jul 12]. p. 1–4. https://www.tandfonline.com/doi/abs/10.1080/14737167.2021.1848551.

Expert essay

Defining Alzheimer's disease biologically

Clifford R. Jack

Mayo Clinic, Rochester, MN, UNITED STATES

Diagnostic criteria for Alzheimer's disease

The first formal, widely accepted diagnostic criteria for Alzheimer's disease were the NINDS-ADRDSA (National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association) criteria published in 1984 (1). A diagnosis of probable Alzheimer's disease could be made in life after certain exclusions, while a diagnosis of definite Alzheimer's disease could only be made at autopsy. These criteria made complete sense at the time because they were developed in the pre-biomarker era. Because they were well-formulated, they have been widely used in both research and clinical practise for over a quarter of a century. They are still widely used in modern clinical practise. Unfortunately, the critical distinction between probable and definite Alzheimer's disease made by the NINDS-ADRDSA workgroup is often ignored and, as a result, a non-specific clinical syndrome (typically an amnestic dementia) is commonly equated with Alzheimer's disease which is a specific disease with a specific pathological definition (2).

Biomarker era

Biomarkers for Alzheimer's disease are either fluid or positron emission tomography (PET) imaging. It is difficult to pick a specific date marking the beginning of the era of Alzheimer's disease biomarkers, but review articles describing cerebrospinal fluid (CSF) biomarkers already appeared in the early 2000s (3,4). Magnetic resonance (MR) and fluorodeoxyglucose-positron emission tomography (FDG-PET) had been used since the 1980s to study dementia; however, these modalities are not specific for Alzheimer's disease, thus the first true disease specific Alzheimer's disease imaging biomarker was amyloid PET introduced in 2004 (5). Tau PET was introduced some years later (6). Many research groups around the world have incorporated Alzheimer's disease biomarkers into their research programmes which has resulted in a large literature base relating observed clinical symptoms in research participants to contemporaneous biomarker indicators of neuropathology. These clinical-biomarker studies revealed three important discrepancies between the 1984 NINDS-ADRDSA (1) definition of probable Alzheimer's disease and biomarker findings. First, what was labelled probable Alzheimer's disease on clinical grounds was often not supported by biomarkers. Second, individuals given non-Alzheimer's disease clinical diagnoses sometimes had Alzheimer's disease by biomarker findings. Third, many cognitively unimpaired individuals had considerable Alzheimer's disease pathology by biomarkers. These clinical-pathologic discrepancies had been noted in neuropathologic studies (7,8), but the advantage of biomarkers is the ability to link contemporaneous clinical and biological findings (rather than waiting, sometimes years, for autopsy), as well as the ability to follow individuals over time with serial biomarker-clinical correlations.

The application of biomarkers to clinical research led to the formulation of biomarker-based disease models. A common model holds that different pathologic features of Alzheimer's disease do not arise simultaneously but rather co-evolve in a staggered offset manner (9). Specifically, Alzheimer's disease biomarker abnormalities begin with those of amyloid, then tau, then neurodegeneration. Overt clinical symptoms appear last in the sequence, many years after the onset of biomarker evident amyloidosis, and symptoms are most closely linked with tau and neurodegeneration (9).

Revised diagnostic criteria incorporating biomarkers

Two different groups have published revised diagnostic criteria for Alzheimer's disease that incorporate biomarkers. The International Work Group (IWG) has published a series of criteria centred around the idea that a diagnosis of Alzheimer's disease requires biomarker evidence of the disease plus overt clinical symptoms (10–12). Individuals with abnormal biomarkers who are asymptomatic (except for familial mutation carriers) are labelled 'at risk' for Alzheimer's disease. The second group to publish diagnostic guidelines was the National Institute on Aging-Alzheimer's Association (NIA-AA). Three different NIA-AA work groups each published guidelines in 2011, one for preclinical Alzheimer's disease, for mild cognitive impairment, and one for dementia (13–15). Each of these three documents was internally consistent; however, there were conceptual inconsistencies between them.

NIA-AA research framework

The NIA-AA commissioned another working group in 2016 to address inconsistencies between the three 2011 documents and to incorporate advances in the field (for example the development of tau PET) that had not been present when the 2011 guidelines were developed. The document produced by this group was labelled the NIA-AA research framework (16). Some of the key principles underlying the research framework were the concepts of syndrome and biology should be separated. An amnestic dementia and Alzheimer's disease are not synonymous. The former is a non-specific clinical syndrome that may be due to a variety of pathologies; in reality, amnestic dementia or mild cognitive impairment in elderly people is usually due to a combination of pathologies (17). In contrast, Alzheimer's disease is one specific pathologic entity which is defined by plaques and tangles (2). The term Alzheimer's disease should be used to describe the biologically defined entity which can be ascertained either at autopsy or in living people by biomarkers, not by a clinically defined syndrome(s).

Operationalisation of biomarkers in the NIA-AA research framework was based on the AT(N) construct (18) in which biomarkers are placed into three general groups based on the nature of the pathologic process that each maps onto. Accepted biomarkers at the time the research framework was developed were either CSF or imaging. Biomarkers of β-amyloid plaques (labelled 'A)' were cortical amyloid PET ligand binding or low CSF Aβ42 (or 42/40). Biomarkers of fibrillar tau (labelled 'T') were elevated cerebrospinal fluid phosphorylated tau (P-tau) and cortical tau PET ligand binding. Biomarkers of neurodegeneration or neuronal injury (labelled '(N)') were cerebrospinal fluid total tau (T-tau), FDG PET hypometabolism and atrophy on MRI. The (N) group was placed in parenthesis to denote the fact that these biomarkers, like clinical symptoms, are not specific for Alzheimer's disease and thus are used for disease staging but not for definitive diagnosis (16).

Plasma Alzheimer's disease biomarkers

Diagnostic biomarkers that were accepted, validated, and widely used in research and in some clinical settings at the time the NIA AA research framework was being developed were either cerebrospinal fluid or PET imaging; thus, making a biological definition in vivo required testing that was either invasive or expensive. This was explicitly identified in the research framework document 16 as a significant limitation to widespread adoption of a biologically based definition of Alzheimer's disease. However, around that time and shortly after the research framework was published in 2018, papers began appearing that showed very promising diagnostic performance for plasma biomarkers in the A category, specifically plasma Aβ 42/40 (19–21), and for biomarkers in the (N) category, particularly plasms NfL (22–27). Very recently, plasma measures of ptau181 and ptau217 have shown very promising diagnostic performance (28–33). The development of plasma Alzheimer's disease biomarkers has ushered in a new age in which a biologically based diagnosis of Alzheimer's disease can be generally available non-invasively and inexpensively – blood can be drawn anywhere and sent to central labs for analysis – and can be widely implemented for both research and clinical diagnostic purposes.

Disease-modifying therapy

A second major recent development in the field has been the approval by the Federal Drug Administration (FDA) of the first disease-modifying treatment for Alzheimer's disease. Aduhelm (aducanumab) received accelerated approval for treatment of people with Alzheimer's disease who are in the mild cognitive impairment or early dementia stage. FDA approval was based on reduction in amyloid PET in treated patients on the assumption that amyloid reduction was likely to be of benefit. Further studies are required to prove clinical benefit. Although specific guidance on how a diagnosis of Alzheimer's disease should be verified was not provided in the FDA package insert, the phase 3 clinical trials of aducanumab required documentation of Alzheimer's disease pathology either by amyloid PET or cerebrospinal fluid biomarkers for entry.

“ The development of plasma Alzheimer's disease biomarkers has ushered in a new age in which a biologically based diagnosis of Alzheimer's disease can be generally available non-invasively and inexpensively – blood can be drawn anywhere and sent to central labs for analysis – and can be widely implemented for both research and clinical diagnostic purposes.

In summary, these two transformative developments, plasma biomarkers and disease-modifying treatments, will interact in a reinforcing manner to reshape the field. The first ever disease-modifying treatment is now a reality. It is likely that clinicians will initially use either amyloid PET or cerebrospinal fluid biomarkers to document the presence of Alzheimer's disease in patients who are being considered for treatment. However, plasma biomarkers are predicted to play an increasingly prominent role in diagnosis once clinicians gain greater experience with them. Thus, it seems reasonable to predict that plasma biomarkers will make a biological diagnosis of Alzheimer's disease practical on a wide scale at a moment in time when the ability to make a biological diagnosis in clinical practise is needed to indicate which individuals will benefit from newly approved amyloid lowering therapeutically.

References

1. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group* under the auspices of department of health and human services task force on Alzheimer's disease. Neurology. 1984;
2. Hyman BT, Phelps CH, Beach TG, others. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement. 2012;8(1):1–13.
3. Blennow K. Cerebrospinal Fluid Protein Biomarkers for Alzheimer's Disease. NeuroRx. 2004;1(2):213–25.
4. Blennow K, Hampel H. CSF markers for incipient Alzheimer's disease. Lancet Neurol. 2003;2(10):605–13.
5. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging Brain Amyloid in Alzheimer's Disease with Pittsburgh Compound-B. Ann Neurol. 2004 Mar;55(3):306–19.
6. Chien DT, Szardenings AK, Bahri S, Walsh JC, Mu F, Xia C, et al. Early clinical PET imaging results with the novel PHF-tau radioligand [F18]-T808. J Alzheimer's Dis. 2014;38(1):171–84.
7. Price JL, Davis PB, Morris JC, White DL. The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. Neurobiol Aging. 1991;12(4):295–312.
8. Beach TG, Monsell SE, Phillips LE, Kukull W. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005-2010. J Neuropathol Exp Neurol [Internet]. 2012;71(4):266–73. https://dx.doi.org/10.1097/nen.0b013e31824b211b.
9. Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013;12(2):207–16.
10. Dubois B, Feldman HH, Jacova C, DeKosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol. 2007;6(8):734–46.
11. Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing research diagnostic criteria for Alzheimer's disease: The IWG-2 criteria. Vol. 13, The Lancet Neurology. 2014. p. 614–29.
12. Dubois B, Villain N, Frisoni GB, Rabinovici GD, Sabbagh M, Cappa S, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. Lancet Neurol. 2021;20(6):484–96.
13. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement [Internet]. 2011 May 1 [cited 2021 Jul 19];7(3):280–92. https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1016/j.jalz.2011.03.003.
14. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement [Internet]. 2011 May 1 [cited 2021 Jul 19];7(3):270–9. https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1016/j.jalz.2011.03.008.
15. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement [Internet]. 2011;7(3):263–9. https://dx.doi.org/10.1016/j.jalz.2011.03.008.
16. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's Dement [Internet]. 2018;14(4):535–62. https://www.ncbi.nlm.nih.gov/pubmed/29653606.
17. Schneider JA, Arvanitakis Z, Bang W, DA. B. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology. 2007;69:2197–204.
18. Jack CR, Bennett DA, Blennow K, Carrillo MC, Feldman HH, Frisoni GB, et al. A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. Vol. 87, Neurology. 2016. p. 539–47.
19. Ovod V, Ramsey KN, Mawuenyega KG, Bollinger JG, Hicks T, Schneider T, et al. Amyloid β concentrations and stable isotope labeling kinetics of human plasma specific to central nervous system amyloidosis. Alzheimer's Dement. 2017;13(8):841–9.
20. Nabers A, Perna L, Lange J, others. Amyloid blood biomarker detects Alzheimer's disease. EMBO Mol Med. 2018;10:5.
21. Nakamura A, Kaneko N, Villemagne VL, Kato T, Doecke J, Doré V, et al. High performance plasma amyloid-β biomarkers for Alzheimer's disease. Nature [Internet]. 2018;554(7691):249–54. https://doi.org/10.1038/nature25456.
22. Zhou W, Zhang J, Ye F, Xu G, Su H, Su Y, et al. Plasma neurofilament light chain levels in Alzheimer's disease. Neurosci Lett. 2017;650:60–4.
23. Mattsson N, Andreasson U, Zetterberg H, Blennow K, Weiner MW, Aisen P, et al. Association of plasma neurofilament light with neurodegeneration in patients with Alzheimer disease. JAMA Neurol [Internet]. 2017 May 1 [cited 2021 Jul 22];74(5):557–66. https://pubmed.ncbi.nlm.nih.gov/28346578/.
24. Lewczuk P, Ermann N, Andreasson U, Schultheis C, Podhorna J, Spitzer P, et al. Plasma neurofilament light as a potential biomarker of neurodegeneration in Alzheimer's disease. Alzheimer's Res Ther. 2018;10(1):1.
25. Mattsson N, Cullen NC, Andreasson U, Zetterberg H, Blennow K. Association between Longitudinal Plasma Neurofilament Light and Neurodegeneration in Patients with Alzheimer Disease. JAMA Neurol. 2019;76(7):791–9.
26. Mielke MM, Syrjanen JA, Blennow K, Zetterberg H, Vemuri P, Skoog I, et al. Plasma and CSF neurofilament light: Relation to longitudinal neuroimaging and cognitive measures. Neurology. 2019;93(3):E252–60.
27. Quiroz YT, Zetterberg H, Reiman EM, Chen Y, Su Y, Fox-Fuller JT, et al. Plasma neurofilament light chain in the presenilin 1 E280A autosomal dominant Alzheimer's disease kindred: a cross-sectional and longitudinal cohort study. Lancet Neurol. 2020;19(6):513–21.
28. Mielke MM, Hagen CE, Xu J, Chai X, Vemuri P, Lowe VJ, et al. Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography. Alzheimer's Dement. 2018;14(8):989–97.
29. Karikari TK, Pascoal TA, Ashton NJ, Janelidze S, Benedet AL, Rodriguez JL, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. Lancet Neurol [Internet]. 2020;19(5):422–33. https://doi.org/10.1016/S1474-4422(20)30071-5.
30. Janelidze S, Berron D, Smith R, Strandberg O, Proctor NK, Dage JL, et al. Associations of Plasma Phospho-Tau217 Levels with Tau Positron Emission Tomography in Early Alzheimer Disease. Vol. 78, JAMA Neurology. JAMA Neurol; 2021. 149–156 p.
31. Janelidze S, Mattsson N, Palmqvist S, Smith R, Beach TG, Serrano GE, et al. Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. Nat Med [Internet]. 2020;26(3):379–86. https://doi.org/10.1038/s41591-020-0755-1.
32. Thijssen EH, La Joie R, Wolf A, Strom A, Wang P, Iaccarino L, et al. Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration. Nat Med. 2020;26(3):387–97.
33. Palmqvist S, Janelidze S, Quiroz YT, Zetterberg H, Lopera F, Stomrud E, et al. Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. JAMA – J Am Med Assoc [Internet]. 2020;324(8):772–81. https://doi.org/10.1001/jama.2020.12134.

Conclusions

When reviewing the totality of the information drawn together in this Chapter, and indeed the entire report, it is evident that receiving a diagnostic assessment for dementia should ideally begin at the primary care level. That said, this is precisely where the barriers to getting such a diagnosis exist. All the amassed survey responses converge to offer an inclusive behind-the-scenes look at what physicians, people with dementia and their carers experience.

From a clinician perspective, a lack of competence and training regarding dementia coupled with a high patient load and remuneration systems that do not encourage lengthy consultations contribute to the complications. Alternatively, from an individual's viewpoint, lack of recognition of potential signs of dementia along with perceived stigma and fear, costs, difficulties with remote locations and scarce transportation also play their part in delaying a diagnosis.

Nonetheless, there is a movement towards change. Primary care physicians have expressed interest in the potential for biomarker screening tests while the proliferation of self-testing kits point to a heightened awareness by people questioning their symptoms.

However, the ageing population and the influx of people seeking a definitive diagnosis based on the genetic risks indicated by these kits will present major challenges for clinicians, including the shift towards diagnosing pre-dementia states. This is why the advent of validated blood tests to confirm aetiology is being so enthusiastically supported. Cost-efficient, non-invasive and easily implemented – it is hoped that this trifecta of benefits will make dementia diagnosis on a wide-scale a new reality.

Report conclusions

This World Alzheimer Report has addressed a range of topics as the contributing expert authors have looked through various clinician lenses into the world of dementia.

These different perspectives have one goal – to increase the efficacy of the diagnostic process. Ranging from validated blood tests towards an aetiologic diagnosis (Chapter 13); cognitive scales that are better adapted to various cultures and languages (Chapter 6); validated online algorithms (Chapter 14); cognitive scales validated for telemedicine (Chapter 6); and self-screening tests prior to clinical assessment (Chapters 4, 5, 6), this is an impressive collection.

One of the common theme centres on the importance of clinical assessment initiated online and the potential use, and advantages, of available web-based algorithms. The interest in blood tests as a way to streamline the aetiologic work-up regarding the cause of dementia would be cost-effective, as argued in Chapter 24, but the routine use of APOE genotyping would require training in the disclosure of genetic information, as examined in Chapter 15.

Although not yet an issue for most clinicians around the world, the diagnosis of a dementia with no evidence of amyloid build-up as discussed in Chapter 17, means a broader differential diagnosis for which we are still lacking longitudinal information.

The key role of primary care practitioners, as summarised by Anders Wimo, requires education about the diagnosis and management of dementia in medical schools and throughout practice.

Forward thinking...

Alzheimer's disease and related disorders have no cure yet – and as the population ages and more people are diagnosed, we need to ensure that the public is better educated about the signs and symptoms of dementia. This would prompt individuals to consult healthcare professionals more, as well as gain a better understanding of how to manage their illness. The responsibilities entailed with this disease are considerable. It requires a rigorous commitment in an all-encompassing and dynamic world. That is why it is often referred to as a journey and it is precisely why governments also have an essential role to play. There is a pressing need to develop public awareness campaigns that educate, enact policies that bring about change, create programmes that expand accessibility and endorse support systems that assist all the many carers. The world needs to embrace health literacy about dementia – not only increasing an individual's opportunity to get their foot in the door, but while there, obtain a variety of dementia support and information they can understand and rely on. Empowering this concept will ensure the best quality of care, safety and dignity of the person who is diagnosed.

> **“ There is a pressing need to develop public awareness campaigns that educate, enact policies that bring about change, create programs that expand accessibility and endorse support systems that assist all the many carers.**

Medical schools across the globe have an equally important responsibility to better educate students today so that they may be better healthcare professionals tomorrow. This is not simply relegated to understanding the various diagnostic options, but most importantly, how to assist an individual and their carer on the best ways to navigate their post-care in a progressively complex medical environment. Dementia is now one of the leading causes of death, and there exists an ethical imperative in the medical community to properly arm citizens around the world with all the necessary knowledge and skills they require, as well as actively engage them in their own healthcare needs. Only in this way can post-care become optimal care.

Alzheimer's Disease International:
The International Federation of
Alzheimer's Disease and Related
Disorders Societies, Inc. is
incorporated in Illinois, USA, and is a
501(c)(3) not-for-profit organization

Alzheimer's Disease International
57A Great Suffolk Street
London SE1 0BB
UK
Tel: +44 20 79810880
www.alz.co.uk

Alzheimer's Disease International