11th COGNITIVE DAY

Proceedings

12th MAY 2023, LJUBLJANA, SLOVENIA

11th COGNITIVE DAY

Proceedings

Published by:
Centre for Cognitive Impairments,
Department of Neurology,
University Medical Centre Ljubljana

Edited by:
Milica Gregorič Kramberger

Proceedings was published at 11th Cognitive Day meeting on 12th May 2023.

Cognitive Day is an annual scientific meeting with international participation organized by Centre for Cognitive Impairments, Department of Neurology, University Medical Centre Ljubljana.

Kataložni zapis o publikaciji (CIP) pripravili v Narodni in univerzitetni knjižnici v Ljubljani

COBISS.SI-ID 152977155
ISBN 978-961-7080-06-3 (PDF)

Contents

List of authors/ lecturers

Stefano F. CAPPA, MD, PhD
Professor of Neurology
Head of Dementia Research Center
IRCCS Mondino Foundation
Director, IUSS Cognitive Neuroscience (ICoN) Center
University School for Advanced Studies (IUSS-Pavia)
Piazza della Vittoria 15, 27100 Pavia, Italy

Eva ZUPANIČ, MD, PhD
Consultant in neurology
Neurology Clinic, University Medical Center,
Ljubljana, Slovenia

Tomaž RUS, MD, PhD
Consultant in neurology
Neurology Clinic, University Medical Center,
Ljubljana, Slovenia

Maria ERIKSDOTTER, MD, PhD
Dean Karolinska Institutet South
Professor, senior consultant in geriatrics
Director SveDem
Dept of Neurobiology, Care Sciences and Society
Karolinska Institutet
Theme Inflammation and Aging,
Karolinska university hospital, Huddinge, Sweden

Eric WESTMAN, MD, PhD
Professor
Head of Division and Acting/Vice Head of Department
Karolinska Institutet
Department of Neurobiology, Care Sciences and Society (NVS)
Division of Clinical Geriatrics
Neo floor 7 | SE 141 83 Huddinge

Ana Verdelho, MD, PhD
Invited Professor of Neurology
Department of Neurosciences
University of Lisbon
Hospital de Santa Maria
Av. Prof. Egas Moniz
Lisbon

Nika ZORKO GARBAJS, MD
Consultant in neurology
Department of Vascular Neurology and Intensive Therapy,
University Medical Centre Ljubljana, Slovenia.

Bojana PETEK, MD
Clinical Institute of Genomic Medicine, University Medical Centre
Ljubljana, Slovenia
Division of Neurogeriatrics, Department of Neurobiology, Care Sciences and
Society, Karolinska Institutet, Stockholm, Sweden

Tom A. FUCHS, MD, PhD
Research Associate, Anatomy and neurosciences
Amsterdam University Medical Center
Netherlands

Preface

Milica G. KRAMBERGER, MD, PhD

Dear fellow colleagues,

it is with great pleasure that I present to you a selection of scientific articles and abstracts for the 11th Cognitive Day international meeting.

In the recent two years the scientific and general society are facing an extremely important time with first emergance of positive results on disease modifying treatment trials for Alzheimer's disease (AD). AD is a neurodegenerative disease, and the aetiology behind 50-70% of all cases of dementia. Due to an ageing population, dementia prevalence is expected to nearly double over the coming three decades, bringing enormous challenges for health and social care systems. There is rapid development in the diagnosis and treatment of AD and other neurodegenerative disorders, across plasma-based biomarkers , pharmacological treatments and non-pharmacological prevention strategies. New strategies for earlier and more accurate detection and diagnosis are emerging.

Patients seen in routine care with a suspected cognitive disorder often have comorbid illnesses, such as cardiovascular and cerebrovascular disorders, type 2 diabetes, and psychiatric disorders. Comorbidities can have a decisive influence on neurodegenerative disease diagnostic investigations and the interpretation of their results, also impact the initiation of treatment.

The Cognitive Day international meetings bring a significant contribution to a process of continuous education and to further improvement of clinical management of patients with cognitive impairments. A great pleasure for us is also the fact that we have longstanding support and the opportunity to host a number of internationally renowned experts from various fields (psychiatry, geriatrics, neurology, psychology, neuroradiology) from several countries.

The primary purpose of this gathering is to provide an active education to all those involved in the management of patients with neurodegenerative diseases and to strengthen activities pursued by a multi-disciplinary team targeting at patients with cognitive and movement impairments. By conducting expert gatherings and with this anthology we would like to inform the readers about the latest findings in the discussed topics.

The contents of this anthology which is also deemed higher education study material, should be an interesting read and helpful to both medical students as well as trainee specialists and various specialists and other members of the multidisciplinary team who encounter such patients in their work.

Sincere thanks to all participating lecturers and everyone involved!

Program

08:30 - 09:00 Registration

09:00 Welcome and introduction
Milica G. KRAMBERGER, Ljubljana, Slovenia

09:05 The clinical assessment of prodromal cognitive decline: the need for new tools?
Stefano CAPPA, Milan, Italy

09:35 Patient/site readiness for a potential new Alzheimer's disease treatment paradigm
Eva ŽUPANIČ, Ljubljana, Slovenia

10:05 - 10:10 Discussion

10:10 Unravelling the heterogeneity in neurodegenerative disorders with the help of neuroimaging,
Eric WESTMAN, Stockholm, Sweden

10:40 Functional brain networks in neurodegenerative disorders
Tomaž RUS, Ljubljana, Slovenia

11:10 - 11:15 Discussion

11:15 - 11:30 Coffee Break

11:30 Vascular cognitive impairment: an opportunity for prevention
Ana FIGUEIRA VERDELHO, Lisbon, Portugal

12:00 Cholinesterase inhibitors: effects on cognition, vascular and renal function and mortality in Alzheimer patients
Mia ERIKSDOTTER, Stockholm, Sweden

12:30 - 12:40 Discussion

12:40 - 13:40 Lunch

13:40 Cognition in Multiple Sclerosis: Evaluation, Treatment, and Brain Networks
Tom FUCHS, Amsterdam, Netherlands

14:10 Statins in patients with dementia-a friend or a foe?
Bojana PETEK Ljubljana, Slovenia

14:40 Association of blood pressure variability with delirium in critically ill
Nika ZORKO GARBAJS, Ljubljana, Slovenia

15:10 - 15:20 Discussion

15:20 Closing remarks

The clinical assessment of prodromal cognitive decline: the need for new tools?

Stefano Cappa

Alzheimer's disease is one of the greatest global health and social care challenges of our time. Its prevention and efficient management are urgent priorities in Western countries. Neuropsychological assessment, included in current diagnostic criteria represents the first step in the diagnostic pathway of patients with suspected Alzheimer's disease. The recent Italian inter-society consensus recommendations (Boccardi et al., 2019) suggest the perform a complete neuropsychological assessment in the T1 phase, which follows the clinical screening phase (T0). At this stage, the suspicion of a possible neurodegenerative disease is formulated by the specialist, thus opening the diagnostic pathway. This phase corresponds to the "specialist phase" of the patient's journey defined by the RAND report (Hlavka et al., 2019). Consensus recommendations include an assessment of the main cognitive domains, ideally with standardized tests with normative values for the Italian population. Beyond the diagnostic phase, neuropsychological assessment plays a key role in the follow-up of the subject, both to assess the natural history and to allow the measurement of the effect of possible treatments (pharmacological and nonpharmacological). With this in mind, computerized approaches capable of evaluating patients with suspected Alzheimer's disease with standardized, objective, and efficient methods on a large scale appear to be of great interest and topicality.
The general concept of "teleneuropsychology" includes different solutions to the problem of remote assessment. Although the Covid-19 pandemic has greatly amplified the demand for this type of service, different situations related to limitations in the availability of services or the characteristics of the population to be evaluated, especially in the case of patients with frail or comorbid conditions, have stimulated research in this area. Particularly in the U.S., the Inter Organizational Practice Committee (IOPC), involving the American Academy of Clinical Neuropsychology/American Board of Clinical Neuropsychology, the National Academy of Neuropsychology, Division 40 of the American Psychological Association, the American Board of Professional Neuropsychology, and the American Psychological Association Services, Inc. (APAS) have been doing important work in reviewing the evidence and providing practical support for the organization of teleneuropsychology activities (Bilder et al., 2020, Hammers et al., 2020).

The solutions adopted have been found to be different. A first level is the administration of tests by telephone (a systematic review can be found in (Carlew et al., 2020). Available evidence indicates a fair applicability of this approach for cognitive screening measures, such as the MOCA (Wong et al., 2015), in surveying large populations given the simplicity of the access mode. However, the same approach appears not to be applicable for the systematic and extensive assessment of major areas of cognitive functioning. At a second level, it is possible to consider the administration of conventional tests in videoconferencing mode. In this regard, two recent reviews of the evidence (Brearly et al., 2017, Marra et al., 2020) concluded for substantial comparability of results between in-person (face-to-face) and administration via web telecommunication platform. The limitations of this approach, which is widely used in this emergency phase, are related on the one hand to the availability of video conferencing systems by the test subject, and on the other hand to the impossibility of performing tests that require motor responses or perceptual processing of complex stimuli. For this reason, this approach privileges verbal tests, thus providing an incomplete overview of the subject's cognitive functioning. Not the least limitation of this approach is the difficulty in standardizing administration procedures and collecting response times.
The most advanced solution for teleneuropsychology is related to the development of computerized neuropsychological batteries implemented in personal computers, laptops or tablets or web-based. This area has undergone tremendous development in recent decades, although the uptake in clinical practice remains relatively limited. The financial burden and reduced availability of technological devices in the elderly population has in fact limited their use for many years. More recent advances in mobile-device technology, with reduced costs and wider dissemination in the general population, including older individuals, have paved the way for a 'desirable large-scale application of teleneuropsychology. In this regard, the aforementioned IOPC as early as 2012 felt the need to provide guidelines with reference to quality standards and complex regulatory issues, with a number of recommendations that still hold true today (Bauer et al., 2012). These include the need for scrutiny of the psychometric goodness of instruments, medical device status, scope of application, technical characteristics of the platform, and aspects of privacy, data security, and reporting. IOPCs'

recommendations are essential in a field that sees, alongside some nonprofit platforms, such as the NIH Toolbox (https://www.healthmeasures.net/explore-measurement-systems/nih-toolbox), numerous commercial products, such as the Cantab (which received FDA clearance as a medical device in 2017) (https://www.cambridgecognition.com/cantab/) or the Philips IntelliSpace Cognition (https://www.usa.philips.com/healthcare/solutions/neurology/digital-cognitive-assessment) (FDA Class II device). Computerized tests lend themselves optimally to remote assessment conditions. They can be administered at home or in a dedicated setting, with assistance from an operator familiar with the procedure but who does not require specialized neuropsychological training. Data collection can be done in different ways depending on the platform used (tablet or PC: administration via app or via web). Data storage can be done on cloud repositories using GDPR-compliant procedures; the software provides correction of scores based on normative data and generation of descriptive performance reports compared to the control group.

BAUER, R. M., IVERSON, G. L., CERNICH, A. N., BINDER, L. M., RUFF, R. M. & NAUGLE, R. I. 2012. Computerized neuropsychological assessment devices: joint position paper of the American Academy of Clinical Neuropsychology and the National Academy of Neuropsychology. Archives of Clinical Neuropsychology, 27, 362-373.

BILDER, R. M., POSTAL, K. S., BARISA, M., AASE, D. M., CULLUM, C. M., GILLASPY, S. R., HARDER, L., KANTER, G., LANCA, M. & LECHUGA, D. M. 2020. InterOrganizational practice committee recommendations/guidance for teleneuropsychology (TeleNP) in response to the COVID-19 pandemic. The Clinical Neuropsychologist, 1-21.

BREARLY, T. W., SHURA, R. D., MARTINDALE, S. L., LAZOWSKI, R. A., LUXTON, D. D., SHENAL, B. V. & ROWLAND, J. A. 2017. Neuropsychological test administration by videoconference: A systematic review and meta-analysis. Neuropsychology Review, 27, 174-186.

CARLEW, A. R., FATIMA, H., LIVINGSTONE, J. R., REESE, C., LACRITZ, L., PENDERGRASS, C., BAILEY, K. C., PRESLEY, C., MOKHTARI, B. & CULLUM, C. M. 2020. Cognitive assessment via telephone: A scoping review of instruments. Archives of Clinical Neuropsychology.

HAMMERS, D. B., STOLWYK, R., HARDER, L. & CULLUM, C. M. 2020. A survey of international clinical teleneuropsychology service provision prior to and in the context of COVID-19. The Clinical Neuropsychologist, 1-17.

MARRA, D. E., HAMLET, K. M., BAUER, R. M. & BOWERS, D. 2020. Validity of teleneuropsychology for older adults in response to COVID-19: A systematic and critical review. The Clinical Neuropsychologist, 1-42.
WONG, A., NYENHUIS, D., BLACK, S. E., LAW, L. S., LO, E. S., KWAN, P. W., AU,

L., CHAN, A. Y., WONG, L. K. & NASREDDINE, Z. 2015. Montreal Cognitive Assessment 5-minute protocol is a brief, valid, reliable, and feasible cognitive screen for telephone administration. Stroke, 46, 1059-1064.

PERSPECTIVE
https://doi.org/10.1038/s43587-022-00269-x
nature aging
Check for updates

Designing the next-generation clinical care pathway for Alzheimer's disease

Harald Hampel[1]✉, Rhoda Au[2], **Soeren Mattke**[3], **Wiesje M. van der Flier**[4], Paul Aisen[5], Liana Apostolova[6], Christopher Chen[7], Min Cho[1], Susan De Santi[1], Peng Gao[1], Atsushi Iwata[8], Ricky Kurzman[1], **Andrew J. Saykin**[9], Stefan Teipel[10,11], Bruno Vellas[12], Andrea Vergallo[1], Huali Wang[13] and Jeffrey Cummings[14]

The reconceptualization of Alzheimer's disease (AD) as a clinical and biological construct has facilitated the development of biomarker-guided, pathway-based targeted therapies, many of which have reached late-stage development with the near-term potential to enter global clinical practice. These medical advances mark an unprecedented paradigm shift and requires an optimized global framework for clinical care pathways for AD. In this Perspective, we describe the blueprint for transitioning from the current, clinical symptom-focused and inherently late-stage diagnosis and management of AD to the next-generation pathway that incorporates biomarker-guided and digitally facilitated decision-making algorithms for risk stratification, early detection, timely diagnosis, and preventative or therapeutic interventions. We address critical and high-priority challenges, propose evidence-based strategic solutions, and emphasize that the perspectives of affected individuals and care partners need to be considered and integrated.

AD is a chronic, nonlinearly progressive, multifactorial neurodegenerative disease that affects multiple domains of an affected individual's life during advanced stage of progression, such as cognition, behavior, functional abilities and social interactions. AD is the most common cause of dementia, accounting for around 60–80% of cases[1]. In 2019, over 50 million people were living with dementia worldwide, and the number is expected to rise to 152 million by 2050, largely driven by the projected increases in low-income and middle-income countries[2]. With population growth and aging, AD is becoming one of the most burdensome and costly diseases facing global society today[3].

Historically, the diagnosis and treatment of AD focused on clinical symptoms. In the past three decades, in vivo biomarker studies identified core pathophysiological alterations—including amyloid and tau—that characterize and underly AD across its decades-long preclinical and prodromal phases. Such evidence has transformed the disease concept from clinically defined to biologically defined (Box 1)[4,5]. This transformation opened the gate to biomarker-guided, molecular pathway-based targeted therapies[6,7]. To date, a new wave of pharmacological compounds targeting AD pathophysiological hallmarks have reached late-stage clinical development with one agent recently approved by the US Food and Drug Administration (FDA) for clinical use in treating AD[8–12].

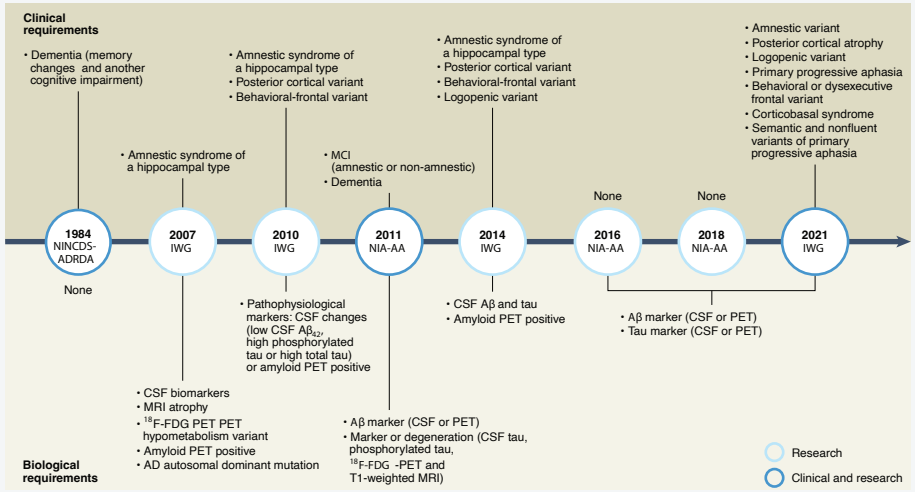
The possibility of detecting AD in its preclinical or prodromal stages and the opportunity of therapeutic intervention to alter clinical progression call for a next-generation global framework of clinical care pathways for individuals with AD. Under this framework, new clinical pathways—which may differ by country and clinical context—must enable timely, accurate and effective detection, diagnosis and treatment of AD at the early stages of mild cognitive impairment (MCI) due to AD and mild AD dementia (collectively defined as early AD hereafter). To this end, in vivo assessment of AD biological continuum (that is, through fluid testing and imaging biomarkers) and ecologically valid/low-threshold assessment of clinical symptomatology through digital health technologies will inevitably play a critical and guiding role in early detection, diagnosis, prognosis and therapeutic decision-making.

It is important to highlight the substantial inequalities in AD and dementia care currently. For example, in the United States, older Black and Hispanic individuals are disproportionally more likely to be affected by AD and other primary dementia disorders, and are more likely to have missed diagnoses, than older white individuals[13]. Various social determinants of health, such as socioeconomic status and educational attainment, also influence cognition and risk of AD[14]. Globally, more than two-thirds of people with dementia live in low-income and middle-income countries; however, the

[1]Neurology Business Group, Eisai, Nutley, NJ, USA. [2]Depts of Anatomy & Neurobiology, Neurology and Epidemiology, Boston University Schools of Medicine and Public Health, Boston, MA, USA. [3]Center for Improving Chronic Illness Care, University of Southern California, San Diego, San Diego, CA, USA. [4]Alzheimer Center Amsterdam, Depts of Neurology and Epidemiology and Data Science, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands. [5]Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, San Diego, CA, USA. [6]Departments of Neurology, Radiology, Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN, USA. [7]Memory Aging and Cognition Centre, Departments of Pharmacology and Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore. [8]Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan. [9]Indiana Alzheimer's Disease Research Center and the Departments of Radiology and Imaging Sciences, Medical and Molecular Genetics, and Neurology, Indiana University School of Medicine, Indianapolis, IN, USA. [10]Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Rostock, Germany. [11]Department of Psychosomatic Medicine, University Medical Center Rostock, Rostock, Germany. [12]University Paul Sabatier, Gerontopole, Toulouse University Hospital, UMR INSERM 1285, Toulouse, France. [13]Dementia Care and Research Center, Peking University Institute of Mental Health (Sixth Hospital), National Clinical Research Center for Mental Disorders, Beijing, China. [14]Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada, Las Vegas (UNLV), Las Vegas, NV, USA. ✉e-mail: harald_hampel@eisai.com

Box 1 | The conceptual transformation of Alzheimer's disease from a clinical–pathological and primarily symptom-based entity to a clinical–biological construct

- In 1984, diagnostic criteria for AD were first defined by the US NINCDS-ADRDA[137].
  - Definitive AD: diagnosis requires autopsy.
  - Probable AD: Clinical entity; discordance between clinical diagnosis and AD-type neuropathology at postmortem showed approximately 30% mismatch[138,139].
  - Atypical phenotypes show different patterns of progression[24,140].
- In 2007, the IWG defined AD as a clinical–biological entity.
  - AD defined by specific clinical phenotypes and in vivo fluid and neuroimaging biomarkers.
  - Definition broadened and included the pre-dementia stages[141].
  - By 2016, the IWG expanded the natural history for AD recommending classifications of the preclinical/presymptomatic stages and atypical presentations[24,142,143].
- In 2010, the NIA-AA working groups formulated three research diagnostic criteria based on cognitive changes and pathophysiological evidence using biomarkers. These included the dementia phase of AD, the symptomatic pre-dementia phase (MCI) of AD, and the asymptomatic, preclinical phase of AD[144–146].
- In 2016, the AT(N) research framework was developed (Table 1)[147].
  - 'A' = Aβ biomarker (amyloid PET or CSF $A\beta_{42}$ or $A\beta_{42/40}$ ratio)
  - 'T' = tau pathology biomarker (CSF p-tau or tau PET)
  - 'N' = neurodegeneration or neuronal injury (CSF total tau, ^{18}F-FDG-PET, or structural MRI)
  - ATX(N): 'X' = additional novel pathophysiological markers[9].
- In 2018, an NIA-AA research framework update defined AD by biomarkers alone and not clinical symptoms[5].
  - AD: neuropathological or biomarker evidence of the disease (that is, amyloid plaques and pathological tau deposits).
  - Created a six-stage clinical scheme of the AD continuum[5,147].
- IWG argued AD diagnosis should include positive biomarkers (that is, amyloid-positive and tau-positive) and specific AD clinical phenotypes, whereas cognitively unimpaired individuals with positive biomarkers should be considered 'at risk for progression to AD'[4].
- In 2018, the FDA staging system for AD was developed to facilitate treatment development in the early stages[148].
  - Stage 1: normal cognition and biomarker evidence of AD.
  - Stage 2: cognitive symptoms detectable with very sensitive assessments and biomarker evidence of AD.
  - Stage 3: easily demonstrable cognitive abnormalities; functional deficits detectable only with sensitive measures and biomarker evidence of AD.
  - Stages 4–6: mild, moderate and severe dementia[148].



Evolution of the diagnostic criteria for Alzheimer's disease. This timeline highlights key milestones in the development and updates to the diagnostic criteria for AD, the biological and clinical requirements that accompany their use, and their applicability in research and clinical settings. ADRDA, Alzheimer's Disease and Related Disorders Association (now the Alzheimer's Association) Work Group. IWG, International Working Group; NIA-AA, US National Institute on Aging and Alzheimer's Association; NINCDS, National Institute of Neurological and Communicative Disorders and Stroke. Cognitively unimpaired individuals are considered at risk for AD. Schematic is based on the information in ref.[4].

Table 1 | ATX(N) biomarkers and their contexts of use in Alzheimer's disease [5,8,9,136]

AT(N)	Imaging	CSF	Blood	FDA Class
A/amyloid	Amyloid PET	$A\beta_{42}$, $A\beta_{42}/A\beta_{40}$	$A\beta_{42}/A\beta_{40}$	Diagnostic monitoring
T/tau	Tau PET	p-tau_{181}, p-tau_{217}	p-tau_{181}, p-tau_{217}	Prognostic monitoring
N/neurodegeneration	MRI, FDG PET	NfL, tau	NfL, tau, GFAP	Pharmacodynamic monitoring
ATX(N) examples	SV2A PET, microglial PET, astrocytosis PET	Synaptic analytes, inflammatory measures	Synaptic analytes, inflammatory measures	Pharmacodynamic monitoring

The various biomarkers under the AT(N) system can be measured by neuroimaging or by detection in blood and CSF. ATX(N) demonstrates the dynamic and evolving nature of the AT(N) classification system where the X component represents additional biomarkers, for example, inflammatory biomarkers, that improve classification, based on the pathophysiology of disease.

condition is often underdiagnosed and undertreated due to various factors such as lack of awareness, stigma and limited health care resources[15]. One key priority is to achieve access and equity of care for the growing number of people living with the disease[16].

In this Perspective, we describe a blueprint for transitioning from the current clinical symptom-focused and inherently late-stage management of AD to a biomarker-guided and digitally facilitated clinical care pathway that focuses on detection and intervention at early stages of the disease. We will address critical hurdles to the practical implementation of such a paradigm shift. We emphasize that patient and care partner perspectives must be considered and become central when developing and implementing a new clinical care pathway for AD.

Defining the next-generation clinical care pathway for Alzheimer's disease

At present in a routine clinical setting, AD is often detected at the mild-to-moderate dementia stage. Diagnosis is usually based on clinical symptoms without biomarker confirmation, and pharmacological treatment options are largely limited to those addressing the symptoms of AD dementia, such as cholinergic and glutamatergic modulators approved two decades ago to mitigate cognitive and behavioral/psychological symptoms. Non-pharmacological treatments have shown promise in preventing cognitive decline; for example, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) demonstrated that a multidomain intervention aimed at reducing lifestyle-related and vascular-related risk factors was effective at preventing cognitive decline among older individuals at risk for dementia[17]. This landmark study has led to the development of the World-Wide FINGERS network aiming to adapt, test and optimize the FINGER model for risk reduction and prevention of cognitive decline across different countries and settings[18].

Emerging treatments targeting AD-associated pathophysiology are directed at earlier stages of the disease and aim at maintaining cognition and function[11]. Early intervention may allow the affected individual to function at the highest level longer. The availability of such emerging treatments necessitates the identification of individuals with early-stage AD in routine clinical settings beyond academic and/or trial centers. Early detection of AD could empower affected individuals and their care partners to make decisions about future treatment and care proactively, and to anticipate and adapt to the cognitive and behavioral changes associated with disease progression[19].

However, multiple hurdles to early detection and early intervention exist in routine clinical practice. Affected persons and family may not understand the early signs of AD and how they differ from normal aging, and may avoid seeking medical attention due to the stigma associated with dementia diagnosis[20]. Currently across the globe, the rate of undetected dementia is as high as ~60%[21,22], with diagnosis of MCI being a rare exception rather than the norm. It is crucial for clinicians as well as patients and families to recognize the importance of early detection and diagnosis, and not overlook the early symptoms of AD or mislabel these as normal aging[23]. With these barriers in mind, we describe the next-generation clinical care pathway for AD and its implementation in daily clinical practice requiring innovation in health care system infrastructures and workflow and bridging of the general public into a participatory framework of medicine.

Summary of key steps in future clinical care pathway for Alzheimer's disease. *First-line diagnostic workup: primary care.* The first step of the next-generation clinical care pathway for AD (Fig. 1) involves a potentially affected individual or family members noticing subtle changes in cognition and/or behavior and proactively seeking medical and/or psychological consultation in a primary care setting. It may also be possible to detect changes during a routine visit.

The first-line medical assessment consists of recording family and medical history to assess for risk factors for AD (family history for neurodegenerative diseases, diabetes, history of traumatic brain injury, and so on) or other causes of reversible/irreversible cognitive impairment (for example, cerebrovascular and cardiocerebrovascular diseases, psychiatric disorders, metabolic/endocrinological diseases with neurological manifestations, cancer and its treatments, and potentially, neurological consequences of coronavirus disease 2019)[5,24–26]. Assessments may be collected digitally to facilitate both patient experience and clinician workflow.

Physical examination (general and neurological) can identify signs of central and autonomous nervous system impairment that may suggest non-AD diagnoses (for example, early psychosis, bradykinesia, postural reflexes, involuntary movements, severe orthostatic hypotension and others)[5,24]. Digital assessments of bradykinesia, tremor and blood pressure may augment clinical evaluations. First-line medical evaluation would continue to include laboratory tests to identify other potential causes of reversible/irreversible cognitive impairment, such as routine blood tests for vitamin B_{12} deficiency and hypothyroidism, electrolyte imbalance, severe anemia, hepatic and renal diseases, and, when appropriate, screening tests for infectious diseases such as syphilis and human immunodeficiency virus.

Quick, easy-to-use and validated clinical assessment tools can be used to identify impairment in cognition, function and behavior. Such tools already exist, including the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) or Mini Cognitive Assessment Instrument (Mini-Cog) for assessing cognition, the Instrumental Activities of Daily Living (IADL) or Functional Activities Questionnaire (FAQ) for assessing daily function, and the Neuropsychiatric Inventory Questionnaire (NPI-Q) for assessing behavior[27]. However, primary care physicians (PCPs) often have substantial time constraints and may require training and support to evaluate individuals with such methods. Moreover, many of the standard instruments are impacted by linguistic, cultural, educational and demographic factors, and referral to specialists for more in-depth neuropsychological evaluation may be required for accurate diagnosis in certain situations[28]. In the future,

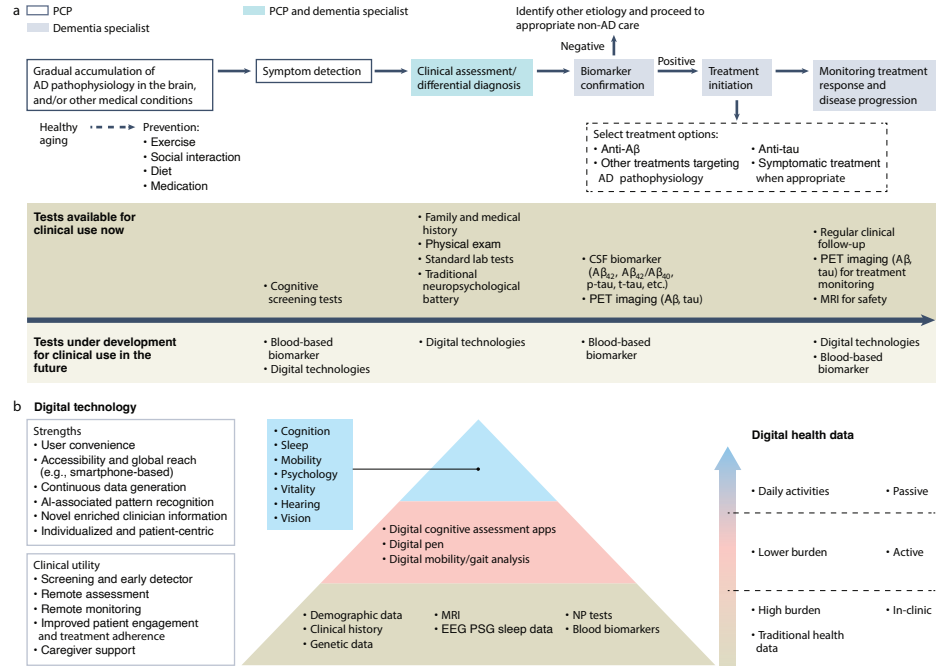


Fig. 1 | The next-generation clinical care pathway for Alzheimer's disease. a, An overarching illustration. The next-generation clinical care pathway begins with healthy aging and participation in preventive lifestyle measures to slow or prevent accumulation of AD pathophysiology, with the goal of extending healthspan across populations. Symptom detection, triggered by concerned individuals or family members, or detected during a routine wellness visit, may involve cognitive testing and, in the future, blood-based biomarkers and digitally based assessments. This will be accompanied by clinical assessments involving standard laboratory tests and physical examination. Any recorded cognitive impairment will be confirmed with standardized biomarker tests. Individuals with confirmed disease will proceed to treatment initiation with relevant AD therapy followed by long-term monitoring, of which digital technologies and blood-based biomarkers will play a key role in the future.b, Digital health technologies in future AD clinical care and the path toward a precision monitoring and detection platform. A precision monitoring and detection platform will require a transformation from the traditional data collection methods to the inclusion of digital technologies. This will include active engagement technologies that require individual interaction and engagement to passive engagement technologies that collect data in the background while the individuals keep to their daily routine. AI, artificial intelligence; EEG, electroencephalogram; NP, neuropsychiatric; PSG, polysomnography.

low-threshold digital assessment tools for measuring cognitive performance will be needed[27,29,30]. In addition, blood-based biomarkers of AD pathophysiology—currently under clinical validation and/or qualification—may also be used in the primary care setting in the future to better inform referral to AD specialists who would be in charge of the second-line diagnostic workup and therapeutic decision-making[29,31–34].

Second-line diagnostic workup and therapeutic decision-making: Alzheimer's disease specialist. In the AD specialist setting with a neurologist, geriatrician or geriatric psychiatrist, a more comprehensive clinical evaluation will determine if the clinical presentation is consistent with AD. Specialist assessment is particularly important in complex cases with atypical presentation, early-onset or rapid progression[35]. Brain computerized tomography (CT) and magnetic resonance imaging (MRI) are recommended to identify structural explanations for cognitive impairment, such as neoplasm, past stroke or hydrocephalus, to name a few[36]. Atrophy patterns of the brain can provide first signs for the presence of a neurodegenerative disease[35].

The second-line diagnostic workup is characterized by in vivo demonstration of AD hallmark pathophysiological changes reflected by the amyloid/tau/neurodegeneration (AT(N)) classification system, that is, proteinopathies involving amyloid-β (Aβ) and tau pathways, axonal damage and neuronal loss (Table 1)[5]. In the medium to long term, blood-based biomarkers may evolve from triage tools to confirmatory biomarkers comparable to the current standard of amyloid positron emission tomography (PET) or cerebrospinal fluid (CSF) biomarkers. It is important to exclude any amnestic cognitive syndromes without Aβ and tau pathology such as limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC)[37,38]. Currently, this is only possible by excluding AD specific pathology; in the future, positive biomarkers for TDP-43 in the CSF may become available[39].

In situations where AD is excluded as the cause for cognitive impairment, the path for the individual would be redirected toward non-AD conditions. A diagnosis of AD would require discussions between the clinician and the individual/family for prognosis. The most critical prognostic outcomes to individuals and their care partners are related to cognitive decline, dependency and physical health[40].

Therapeutic interventions will consist of agents targeting AD-associated pathophysiology, although at present patients must be aware that these treatments are unlikely to stop or reverse cognitive decline. These therapies will likely be given in combination with existing symptomatic treatments (cholinesterase inhibitors or memantine), and likely guided by the profile of biomarker and behavioral or functional changes[11,41]. Treatment continuation, cessation or dose adjustment will be determined based on clinical and biological factors[42,43].

In the future when treatments for preclinical (presymptomatic) stages of AD become available, identifying such populations will become critical. At such time, a personalized, multidimensional approach to the diagnosis of preclinical AD should be considered for the best chance of diagnosis and progression prediction. This will likely include identifying genetic risk factors associated with AD and abnormalities in fluid and neuroimaging AD biomarkers; in particular, periodic screening with blood-based biomarkers of AD pathophysiology ($A\beta_{42/40}$ and phosphorylated tau (p-tau) species) in appropriate populations should be considered[44]. Such a complex approach has several outstanding issues such as diagnostic accuracy, cost of diagnosis and treatment relative to benefit) yet without consensus on when a preclinical diagnosis of AD is indicated and how it should be performed[22,45,46]. Consensus process in the future should involve clinical and biomarker experts, but also patient advocacy groups and representatives of regulatory agencies and payers. In addition to pharmacological interventions, multidomain lifestyle interventions could prove beneficial over the long term in such populations, which may include modifications of diet, exercise, sleep and social and cognitive stimulation[47].

Communication with patients and their care partners. Patient and care partner perspectives must be considered when developing and implementing the next-generation clinical care pathway for AD[48–51]. Their collective involvement is essential to provide insight into possible gaps in existing health services[48–50]. Qualitative studies have revealed the need for: (1) early diagnosis through a well-organized process, (2) a notably shorter pathway to accessing support services for their current needs and care goals, (3) easily accessible, adequate and clear information about cognitive testing, medications, disease progression, finances and behavior, (4) effective disease management by highly knowledgeable and experienced clinicians, and (5) good communication skills of clinicians[48]. Individuals at risk for AD or with early AD and their families will need substantial health literacy to understand and apply the increasingly complex and nuanced information such as risk prediction, early detection and prognosis for decision-making on health-related issues. Overall health literacy can vary substantially, and effective and clear communication from clinicians with empathy and sensitivity to individual needs and preferences is critical[52]. In the context of diagnosis and therapeutic workup, among a number of informative topics, clinicians must effectively communicate the rationale for biomarker testing, the results and implications for treatment and to set appropriate expectations, as treatments that target AD-associated pathophysiology are likely to slow clinical decline without noticeable improvement in symptoms[53,54]. Involving the patient and care partner to understand what matters to them regarding health, cognitive, behavioral and functional status as a measure of treatment success and developing a tool for this purpose is equally important[55,56]. In addition, patient and care partner preference in how they would like to be informed must be taken into consideration.

Use of biomarkers in clinical care of Alzheimer's disease

The incorporation of biomarkers represents a major innovation in the next-generation clinical care pathway for AD, supporting screening, diagnosis and disease staging as well as predicting the rate of progression, determining prognosis and assisting therapeutic decision-making[9]. Established Aβ biomarkers such as those measured by PET imaging or CSF analysis should be used to assess the presence of amyloid pathology and is mostly used today in specialized and tertiary care for diagnostic confirmation and therapeutic decision-making. Three radioligands for amyloid PET have been approved by the US FDA and European Medicines Agency (EMA) for amyloid plaque imaging in cognitively impaired individuals being clinically evaluated for AD and other causes of cognitive decline. These include ^{18}F-florbetapir[57], ^{18}F-flutemetamol[58] and ^{18}F-florbetaben[59]. Amyloid PET was validated against the gold standard of neuropathology, has undergone extensive standardization and has been widely used in AD clinical trials[34]. The appropriate use criteria for amyloid PET are available, providing guidance to clinicians on the types of patients and clinical circumstances in which amyloid PET should be used[60,61]. Interestingly, an applied study showed relevant clinical benefit of amyloid PET imaging even for individuals who did not meet the appropriate use criteria[62]. The Imaging Dementia-Evidence For Amyloid Scanning (IDEAS) study provided evidence that amyloid PET positively impacts diagnostic accuracy and certainty as well as patient management[63]. As such, amyloid PET is likely to be the first choice for clinical use in the context of anti-Aβ agents, especially in the United States and Europe. However, the limited availability of PET scanners, radioligand manufacturing centers and nuclear medicine teams, as well as the high cost and lack of reimbursement are all factors that constrain its global use in routine clinical practice[34,64].

CSF biomarker analysis for $A\beta_{42}$ has been developed and standardized using certified reference materials and methods[65]. The CSF $A\beta_{42/40}$ ratio is highly concordant with amyloid PET, and evidence suggests that Aβ abnormalities may be detected in CSF earlier than by amyloid PET. Both the FDA and the EMA have encouraged further study of CSF biomarkers in the context of clinical AD diagnostics[34,65]. The appropriate use criteria for lumbar puncture and CSF testing during the diagnostic workup of AD have been established[66], and further recommendations to optimize the safety profile of lumbar puncture are available[67]. Recommendations and protocols to standardize the pre-analytical aspects of CSF biomarker testing for AD are also established[68,69].

Besides Aβ, development of tau biomarkers has also advanced markedly. Various tau PET radioligands could chart the spatial spreading of tau pathophysiology in vivo, which tightly correlates with cognitive and functional outcomes across AD clinical stages[34,70]. Flortaucipir F18 was recently approved in the United States for imaging tau pathology in individuals with cognitive impairment who are being evaluated for AD, and several other investigational tau tracers are being actively studied[34,70]. Among several contexts of use of tau biomarkers[71–73], monitoring downstream biological effects on tau pathways following anti-Aβ treatment and guiding future anti-Aβ and tau combination therapies represent two unique opportunities[34].

As PET imaging is expensive and of limited availability, and CSF sampling may be considered invasive, the rapidly advancing blood-based biomarkers for AD are particularly promising, given the broad availability, scalability and cost-effectiveness of blood tests globally (Box 2). Plasma $A\beta_{42/40}$ shows great promise in accurately reflecting amyloid PET and CSF $A\beta_{42/40}$ results[74–76]. A mass spectrometry-based plasma $A\beta_{42/40}$ test achieved an accuracy of 0.81 (area under the receiver operating characteristic (ROC) curve) in predicting brain amyloid status, and has recently received Clinical Laboratory Improvement Amendments certification[77]. Besides Aβ, plasma p-tau181, p-tau217 and p-tau231 are emerging as accurate,

Box 2 | Strengths and limitations of each biomarker modality

Modality	Strengths	Limitations
PET	• Localization of amyloid or tau • Quantification of pathology load; qualitative reading program for clinical practice • Regulatory approval of Aβ PET tracers for in vivo detection of A β • Regulatory approval of tau PET tracer for in vivo detection of tau pathology	• Limited access/high cost • Each biomarker scanned for separately • Exposure to radioactivity • Infrastructure requirements including cyclotrons to manufacture the tracer, scanners and software for quantitative analysis of the scans (in research setting)
CSF	• More cost-effective than PET • Multiple biomarkers from one draw • More accessible and scalable than PET • Lumipulse G β-amyloid ratio (1-42/1-40) in vitro diagnostic test received FDA approval	• No localization • Invasive due to the need for lumbar puncture • Pre-analytical factors (for example, how samples are collected and stored) could affect results
Blood	• More cost-effective than PET and CSF • More accessible and scalable than PET and CSF • Multiple biomarkers in one drop of blood • Less invasive than CSF testing • Easily repeated measurements over time	• No localization • Additional validation required to confirm accuracy • Not yet available for clinical use • Pre-analytical factors (for example, how samples are collected and stored) could affect results

specific and accessible biomarkers for detecting early AD-related pathophysiology[78–84]. In the near term, blood-based biomarkers reflecting core AD pathophysiology have the potential to serve as screening and triage tools to identify those who should be tested with more resource-demanding techniques such as PET imaging and/or CSF biomarker analysis. It will be important to define standard diagnostic pathways following a positive blood biomarker test, including the development of an evidence base for predictive accuracy within a primary care setting, provision of access to specialized care, and determination of thresholds of positivity that will guide the use of new treatments targeting AD pathophysiology[9,32,85]. In the future, blood-based biomarkers may be developed for other contexts of use such as to predict disease risk, track disease progression and monitor treatment response[9,32].

Biomarkers reflecting other components of AD-related pathophysiology, such as neuronal injury/neurodegeneration (CSF total tau and neurofilament light chain (NfL), volumetric MRI), synaptic dysfunction (CSF neurogranin, ^{18}F-fluorodeoxyglucose (FDG)-PET and synaptic vesicle glycoprotein 2A (SV2A) PET) and inflammation (CSF chitinase-3-like protein (YKL-40), glial fibrillary acidic protein (GFAP) and soluble triggering receptor expressed on myeloid cells 2 (TREM2), translocator protein (TSPO) PET and monoamine oxidase B (MAO-B) PET) are emerging, but are not yet ready for clinical implementation (Table 1)[34].

It is worth noting that a sizable portion of individuals with AD exhibit comorbid pathologies such as vascular lesions or intracellular inclusions of TDP-43 (refs. [86,87]). There is an urgent need for research to develop imaging and fluid biomarkers for common co-pathologies such as TDP-43, α-synuclein and other misfolded proteins. Further studies are needed to understand how comorbid pathologies contribute to the biological and clinical progression of AD, and how to factor these in during the clinical management of patients. In addition, biomarker data on individuals aged 85 and older (oldest old) are scarce; given that age is the greatest risk factor for late-onset AD and considering the pace of population aging worldwide, more research is needed to map the biomarker landscape in this population[13]. Similarly, more biomarker research on middle-age, at-risk populations is needed given the importance for prevention efforts in such populations (Box 3).

Although biomarkers form the cornerstone for the next-generation clinical care pathway for AD, their use is currently limited in clinical practice. Clinicians may be reluctant to discuss biomarkers to avoid burdening their patients, perhaps in part because there are still uncertainties regarding the clinical utility of a biomarker-based diagnosis. These uncertainties may result in some clinicians steering their patients away from further biomarker testing[88]. Moreover, clinicians vary in their approach to informing a patient they have early disease, with about one-half of clinicians preferring not to use the term MCI[88]. Web-based tools are emerging to support clinicians and patients with decisions on diagnostic testing, interpretation of individually tailored biomarker test results, and the communication of test results to individuals and their families[89]. Clinicians should receive appropriate education and practical training on the use of new tools and assessments[5,67,90].

Use of digital health technologies in clinical care pathway

The rise of digital health technologies represents another major opportunity to improve the AD clinical care pathway (Fig. 1). Such technologies are particularly poised for early detection/case finding and tracking longitudinal disease progression and/or treatment response.

The transition from traditional cognitive testing to nonintrusive digital assessment offers several advantages. First, nonintrusive testing offers ecological validity owing to the patient assessment in their normal environment and outside the hospital setting. Second, thanks to its convenience, digital assessments can be more frequent as compared to traditional in-clinic assessments, thus allowing documentation of, and control for, day-to-day variations in cognitive function. Third, assessment of everyday activities as a surrogate indicator of abstract cognitive functions increases the functional relevance of the patient assessment. And finally, zero-effort technologies provide access to patients outside standard cognitive testing, such as individuals with advanced stages of dementia, those with reduced hearing, or those who are illiterate[42]. Digital cognitive testing also has the potential to overcome the socioeconomic and cultural biases embedded in some traditional neuropsychological tests.

In the near term, digital health technologies that require active input from the user to assess changes in cognition, function and quality of life are under development[29,42,91]. In the long term, the rapid progress in sensor-based technologies, including mobile and wearable devices (smartphones and smart watches) may support increasingly early detection of subtle changes associated with AD onset (for example, speech/language, oculomotor skills and movement) in a continuous, passive and unobtrusive manner (that is, digital biomarkers). This will enable risk assessment, screening and disease prediction with little or no active engagement by the participants[42,91–98]. As an example, the Oregon Center for Aging & Technology (ORCATECH)/Collaborative Aging Research Using

Box 3 | Glossary

Biomarker
Usually refers to a group of broad medical characteristics that can be objectively measured as an indicator of the body's normal biological processes, or as an indicator of pathogenic processes and response to therapy. To qualify as a biomarker, a characteristic must be measurable, quantifiable, accurate and reproducible.

Context of use
In relation to biomarkers, this usually refers to the description of the biomarker's specified and appropriate use and how the biomarker is applied in drug development and clinical care.

Digital biomarker
Clinically meaningful and objective physiological and behavioral data that can be measured using digital and sensor-based technologies, including mobile and wearable devices such as smartphones and smart watches.

Digital health technologies
These refer to technologies that require the use of computers, connectivity, software and sensors for health care and all its related uses.

Functional Activities Questionnaire (FAQ)
A screening tool for evaluating difficulties in activities of daily living that allow an individual to care for themselves. The main distinguishing feature of the FAQ is that, unlike the IADL, it measures more basic tasks such as eating and bathing.

Instrumental Activities of Daily Living (IADL)
This assesses the ability or need for assistance to perform activities that allow an individual to live independently in a community and to improve quality of life. Domains assessed include cooking, cleaning, transportation, laundry and managing finances.

Mini Cognitive Assessment Instrument (Mini-Cog)
Compared to other cognitive screening tools, this is a relatively quicker 3-min test to screen for cognitive impairment in older adults in both the community and health care settings. The test uses a three-item recall test for memory and a clock-drawing test.

Mini-Mental State Examination (MMSE)
An 11-question measure widely used to test cognitive function among the older population; it includes a systematic and thorough test of five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. Of a maximum score of 30, 23 or lower is indicative of cognitive impairment.

Montreal Cognitive Assessment (MoCA)
A rapid screening tool for mild cognitive dysfunction that assesses cognitive domains including attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations and orientation. Of a maximum score of 30, below 26 is indicative of cognitive impairment. This is considered a good screening tool for persons who score above the cutoff for MMSE.

Neuropsychiatric Inventory Questionnaire (NPI-Q)
An informant-based test for assessing behavior. It assesses neuropsychiatric symptoms including delusions, hallucinations, aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviors, night-time behavioral disturbances and appetite/eating disturbances.

Patient journey
A term usually used to refer to a patient's experience throughout an episode of care. This may entail the entire scope of events of patient experiences within a health care ecosystem, including undergoing regular checkups and receiving treatment.

Polygenic risk score
A score related to the risk of developing a disease, estimated based on the total number of changes or variations in an individual's genes that are related to the disease. This has potential to improve personalized disease risk prediction using genetic data.

Sensor technologies
Sensor technologies require the use of sensors to detect physical, chemical or biological properties of an individual and convert them into readable and meaningful information.

Technology (CART) platform utilizes ambient technologies and wearables to longitudinally monitor cognition, physical mobility, sleep and the level of social engagement in the homes of older adults[99]. Such data can be integrated and analyzed to find meaningful behaviors that identify people at different stages of cognitive decline[100]. Digital health technologies will play a central role in an integrated care model (for example, the Integrated Care for Older People (ICOPE) recommended by the World Health Organization) that not only focuses on cognition but also addresses other functions that maintain brain research, such as mobility, psychology, vitality, hearing and vision[101–103].

Important considerations for the use of digital technologies include privacy issues, specificity and sensitivity to AD versus other causes of cognitive impairment or dementia, user friendliness, reliability, costs and access, among others[42,104]. Once in clinical practice, the ultimate goal of digital health technologies is to facilitate patient self-management and maintain people living independently for as long as possible[42,105,106].

Challenges and potential solutions: a holistic perspective

With biomarker-guided, pathway-based targeted therapies emerging, modeling studies predict that health care systems in many regions/countries will not be able to meet the demand of patients for diagnosis and treatment of AD[107–110]. In the United States, ~15 million individuals with MCI would need to be evaluated by specialists, undergo diagnostic testing and pursue treatment[107]. Current estimates show that the expected caseload of patients will result in long average wait times for specialist visits (~50 months) with many patients developing AD dementia while on waiting lists[107,111]. The strained capacity of memory specialists will limit access to diagnosis and treatment[107,111].

There are additional obstacles to meet the demand of people with AD. Although some countries have dementia plans in place, the emphasis is often on the management of patients with descriptive dementia syndromes and does not adequately address prodromal symptomatic MCI, and etiology in general or early-stage disease[112–114]. Coverage of services is also limited, especially for routine use of confirmatory biomarker tests. For countries with the capacity to absorb increases in service demand, there may not be an incentive to scale up patient volume due to budgetary considerations[112]. Moreover, there will be challenges keeping pace with the necessary infrastructure to accommodate recommended procedures, such as adding PET tracer manufacturing capacity and installing PET scanners, increasing the volume of biomarker testing,

ensuring sufficient availability and accessibility to infusion centers and having the necessary infrastructure for monitoring treatment safety and efficacy[112,115,116]. Other potential issues also include clinician capacity and capabilities; recent reports show a limited number of dementia specialists in the United States, Canada, Europe and Japan, and clinicians may be reluctant to evaluate a patient for a decline in cognitive function if they don't feel adequately trained or believe that there are no therapeutic advantages to identifying a decline in cognitive function[112,113].

With these obstacles and challenges, there is a pressing need to determine the essential steps toward system preparedness for the next-generation AD clinical care pathway. Primary care is a critical entry point into health care systems with a larger number of general providers compared with specialist services[107,112]. Better tools are being developed to identify and triage patients in the primary care setting[29]. Digital health technologies, including digital cognitive assessments, have the potential to detect early cognitive decline and monitor progression, while the emerging blood-based biomarkers—following analytical and clinical validation—could be used to enhance the likelihood of AD as the etiology of the observed cognitive decline[31,32,42,97,117]. To this end, a study showed that a brief cognitive test in combination with a blood-based biomarker test of AD pathophysiology at the primary care level can substantially improve triaging in primary care and lead to reduced waiting times for a specialist visit during the diagnostic process[31]. Besides diagnostic evaluation, prognostic information including the risk of disease progression is important to guide treatment decisions. For example, for cardiovascular diseases, the American Heart Association and the American College of Cardiology have issued predictive equations to guide treatment decisions based on projected risk of cardiovascular events; similar tools for AD could give clinicians a holistic view of a patient's risk of progression[118]. To this end, the Interceptor Project in Italy is monitoring a group of patients with early-stage cognitive decline to determine factors from the initial evaluation of the patient that could predict progression[119].

Telehealth will be an essential component of the next-generation pathway by providing coordinated care between a patient, care partners and clinicians (that is, nurse, PCP and specialist), and will allow access to memory care and remote monitoring in individuals who cannot leave home, or in those without adequate transportation or living in a rural area[120]. More defined hub and spoke arrangements linking PCPs to specialists through telehealth and related technologies may facilitate care by coordinated teams.

Better care models and incentives are needed to increase a PCP's involvement in AD care. For example, cognitive screening is a mandatory requirement of the driver's license renewal process for older people in Japan, while walk-in clinics are available for screening and consultation in memory centers in Korea[110]. The emergence of telecare-enabled specialist support has helped to empower PCP sites in the United States[107]. In addition, accountability schemes have emerged as incentives, such as use of age-adjusted dementia diagnosis rates as a quality measure for general practitioners in the United Kingdom[112].

Specialty care for AD will need to evolve to accommodate a shift from the current focus on diagnosis often at late stages of the disease and counseling to more emphasis on diagnosing the disease at early stages and offering new treatments that target the underlying pathophysiology. For example, memory clinics have been logistically located near general hospitals in the United Kingdom to provide one-stop, large-scale practices that can handle all aspects of care with biomarker testing, differential diagnosis and infusion therapy[112]. Agile learning health care systems will be required to adjust continuously to new and emerging therapies for AD and related disorders.

Ethnic, socioeconomic and racial disparities have been identified in people with AD[121–123]. Differences in risk factors (for example, genetics, comorbid cardiovascular disease or metabolic syndrome) between races may play a role in the incidence and prevalence of AD, while cultural factors (for example, lack of access to medical care, trust issues between marginalized groups and the health care system) may influence diagnosis and treatment[121–123]. Inherent biases may exist in cognitive screening tools that complicate the diagnosis of AD in less educated groups[121] and there is an underrepresentation of marginalized groups in clinical research and clinical trials[122,124,125]. Improving diverse participation in clinical research and clinical trials is paramount to understanding how factors like race, ethnicity, socioeconomic status, gender, sexual orientation, education and culture interact with biological factors associated with AD[122,125–129]. The next-generation clinical care pathway will need to address the issue of diversity as well as social determinants of health to optimize equity of care for all individuals with AD[121–125].

Conclusions and perspectives

The conceptualization of AD as a clinical–biological construct and the emerging biomarker-guided pathway-based treatments targeting AD-associated pathophysiology highlight the importance and urgency of developing and implementing a global framework for the next-generation AD clinical care pathway. Detecting the disease at its initial and early stages will be crucial, and primary care will have an important role in case finding. Utilizing a 'memory care enabled' workforce including nurse practitioners, community health workers and geriatric care managers may reduce the burden and complete reliance on the PCPs as the gateway to diagnosis and care[130]. Diagnosis will include biomarker assessments, which will also guide the initiation of treatment as well as monitoring of treatment response, dose adjustments, and treatment continuation or cessation. Including patients and care partners early in the development process will ensure acceptance and accessibility of novel pathways and technology for those most affected. Although patient and public involvement has been utilized in other medical specialties such as oncology and pediatrics, a pragmatic approach needs to be adapted and transformed for AD clinical care.

The successful development and implementation of the next-generation AD clinical care pathway outlined above depends on close interaction and cross-functional collaboration with stakeholders including regulators, pharmaceutical and biotechnology industry, policymakers, and payors. While the current paper centered on the clinician and patient as well as the care partner perspective, optimization of the clinical care pathway needs to be complemented by the health system and cost viewpoints. Both perspectives need to be integrated in the near future once a clinical care pathway addressing the most urgent needs of patients and family has been agreed on by health care system stakeholders.

The next-generation clinical care pathway for AD must address the critical issues of diversity and inclusion to ensure health equity for the enormous and rapidly growing number of AD patients across the globe. A starting point is to ensure more inclusive participation in observational biomarker research and in clinical trials so that therapeutic approaches will be broadly applicable and available. The new pathway needs to be adapted to local resources and capabilities to maximize the health benefit for patients. From there it will become clear that the next step is to devise the roadmap toward a transformation to precision neurology—a holistic and synergistic approach to AD care that encompasses genetic, biological (that is, biomarker), clinical and environmental profiling of individual patients to guide the development of individualized treatment schemes and ultimately, prevention and extension of brain healthspan[131–135].

Received: 7 March 2022; Accepted: 7 July 2022;
Published online: 19 August 2022

References

1. Alzheimer's Association. 2018 Alzheimer's disease facts and figures. *Alzheimers Dement.* **14**, 367–429 (2018).
2. GBD 2019 Dementia Forecasting Collaborators Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health* **7**, e105–e125 (2022).
3. Scheltens, P. et al. Alzheimer's disease. *Lancet* **397**, 1577–1590 (2021).
4. Dubois, B. et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. *Lancet Neurol.* **20**, 484–496 (2021).
5. Jack, C. R. Jr. et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* **14**, 535–562 (2018).
6. Aisen, P. S., Vellas, B. & Hampel, H. Moving towards early clinical trials for amyloid-targeted therapy in Alzheimer's disease. *Nat. Rev. Drug Discov.* **12**, 324 (2013).
7. Hampel, H. et al. The amyloid-β pathway in Alzheimer's disease. *Mol. Psychiatry* **26**, 5481–5503 (2021).
8. Cummings, J. The National Institute on Aging-Alzheimer's Association Framework on Alzheimer's disease: application to clinical trials. *Alzheimers Dement.* **15**, 172–178 (2019).
9. Hampel, H. et al. Developing the ATX(N) classification for use across the Alzheimer disease continuum. *Nat. Rev. Neurology* **17**, 580–589 (2021).
10. US Food and Drug Administration. FDA's decision to approve new treatment for Alzheimer's Disease (2021).
11. Cummings, J., Lee, G., Zhong, K., Fonseca, J. & Taghva, K. Alzheimer's disease drug development pipeline: 2021. *Alzheimer's Dement.* **7**, e12179 (2021).
12. Biogen. Aduhelm (aducanumab-avwa) [package insert]. US Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf (2021).
13. Alzheimer's Association. 2021 Alzheimer's disease facts and figures. *Alzheimers Dement.* **17**, 327–406 (2021).
14. Majoka, M. A. & Schimming, C. Effect of social determinants of health on cognition and risk of Alzheimer disease and related dementias. *Clin. Ther.* **43**, 922–929 (2021).
15. Ferri, C. P. & Jacob, K. S. Dementia in low-income and middle-income countries: different realities mandate tailored solutions. *PLoS Med.* **14**, e1002271 (2017).
16. Hampel, H. & Lista, S. Dementia: the rising global tide of cognitive impairment. *Nat. Rev. Neurol.* **12**, 131–132 (2016).
17. Ngandu, T. 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* **385**, 2255–2263 (2015).
18. Kivipelto, M. et al. World-Wide FINGERS Network: a global approach to risk reduction and prevention of dementia. *Alzheimers Dement.* **16**, 1078–1094 (2020).
19. Alzheimer's Association. 2019 Alzheimer's disease facts and figures. *Alzheimers Dement.* **15**, 321–387 (2019).
20. Dubois, B., Padovani, A., Scheltens, P., Rossi, A. & Dell'Agnello, G. Timely diagnosis for Alzheimer's disease: a literature review on benefits and challenges. *J. Alzheimers Dis.* **49**, 617–631 (2016).
21. Eichler, T. et al. Rates of formal diagnosis in people screened positive for dementia in primary care: results of the DelpHi-Trial. *J. Alzheimers Dis.* **42**, 451–458 (2014).
22. Lang, L. et al. Prevalence and determinants of undetected dementia in the community: a systematic literature review and a meta-analysis. *BMJ Open* **7**, e011146 (2017).
23. Toepper, M. Dissociating normal aging from Alzheimer's disease: a view from cognitive neuroscience. *J. Alzheimers Dis.* **57**, 331–352 (2017).
24. Dubois, B. et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol.* **13**, 614–629 (2014).
25. Mandelblatt, J. S. et al. Cognitive effects of cancer and its treatments at the intersection of aging: what do we know; what do we need to know? *Semin. Oncol.* **40**, 709–725 (2013).
26. Spudich, S. & Nath, A. Nervous system consequences of COVID-19. *Science* **375**, 267–269 (2022).
27. Porsteinsson, A. P., Isaacson, R. S., Knox, S., Sabbagh, M. N. & Rubino, I. Diagnosis of early Alzheimer's disease: clinical practice in 2021. *J. Prev. Alzheimers Dis.* **8**, 371–386 (2021).
28. Ng, K. P. et al. The influence of language and culture on cognitive assessment tools in the diagnosis of early cognitive impairment and dementia. *Expert Rev. Neurother.* **18**, 859–869 (2018).
29. Sabbagh, M. N. et al. Early detection of mild cognitive impairment in primary care. *J. Prev. Alzheimers Dis.* **7**, 165–170 (2020).
30. Rhodius-Meester, H. F. M. et al. cCOG: a web-based cognitive test tool for detecting neurodegenerative disorders. *Alzheimer's Dement.* **12**, e12083 (2020).
31. Mattke, S., Cho, S. K., 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.* **12**, e12081 (2020).
32. Hampel, H. et al. Blood-based biomarkers for Alzheimer disease: mapping the road to the clinic. *Nat. Rev. Neurol.* **14**, 639–652 (2018).
33. Teunissen, C. E. et al. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. *Lancet Neurol.* **21**, 66–77 (2022).
34. Zetterberg, H. & Bendlin, B. B. Biomarkers for Alzheimer's disease—preparing for a new era of disease-modifying therapies. *Mol. Psychiatry* **26**, 296–308 (2021).
35. Gauthier, S., Rosa-Neto, P., Morais, J. & Webster, C. World Alzheimer Report 2021: journey through the diagnosis of dementia. *Alzheimer's Disease International* https://www.alzint.org/resource/world-alzheimer-report-2021/ (2021).
36. Robinson, L., Tang, E. & Taylor, J. P. Dementia: timely diagnosis and early intervention. *BMJ* **350**, h3029 (2015).
37. Nelson, P. T. et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. *Brain* **142**, 1503–1527 (2019).
38. Graus, F. et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol.* **15**, 391–404 (2016).
39. Scialo, C. 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.* **2**, fcaa142 (2020).
40. Mank, A. et al. Identifying relevant outcomes in the progression of Alzheimer's disease; what do patients and care partners want to know about prognosis? *Alzheimer's Dement.* **7**, e12189 (2021).
41. Hane, F. T. et al. Recent progress in Alzheimer's disease research, part 3: diagnosis and treatment. *J. Alzheimers Dis.* **57**, 645–665 (2017).
42. Kourtis, L.C., Regele, O.B., Wright, J.M. & Jones, G.B. Digital biomarkers for Alzheimer's disease: the mobile/wearable devices opportunity. *NPJ Digit. Med.* **2**, 9 (2019).
43. Ritchie, C. W. et al. The Edinburgh Consensus: preparing for the advent of disease-modifying therapies for Alzheimer's disease. *Alzheimer's Res. Ther.* **9**, 85 (2017).
44. Keshavan, A. et al. Population-based blood screening for preclinical Alzheimer's disease in a British birth cohort at age 70. *Brain* **144**, 434–449 (2021).
45. Frozza, R. L., Lourenco, M. V. & De Felice, F. G. Challenges for Alzheimer's disease therapy: insights from novel mechanisms beyond memory defects. *Front Neurosci.* **12**, 37 (2018).
46. Khan, T. K. An algorithm for preclinical diagnosis of Alzheimer's disease. *Front. Neurosci.* **12**, 275 (2018).
47. Kivipelto, M., Mangialasche, F. & Ngandu, T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. *Nat. Rev. Neurol.* **14**, 653–666 (2018).
48. Prorok, J. C., Horgan, S. & Seitz, D. P. Health care experiences of people with dementia and their caregivers: a meta-ethnographic analysis of qualitative studies. *CMAJ* **185**, E669–E680 (2013).
49. Frank, C. & Forbes, R. F. A patient's experience in dementia care: using the 'lived experience' to improve care. *Can. Fam. Physician* **63**, 22–26 (2017).
50. Kowe, A. et al. Stakeholder involvement in dementia research: a qualitative approach with healthy senior citizens and providers of dementia care in Germany. *Health Soc. Care Community* **30**, 908–917 (2020).
51. Kunneman, M. et al. Patients' and caregivers' views on conversations and shared decision making in diagnostic testing for Alzheimer's disease: the ABIDE project. *Alzheimer's Dement.* **3**, 314–322 (2017).
52. Rostamzadeh, A. et al. Health literacy in individuals at risk for Alzheimer's dementia: a systematic review. *J. Prev. Alzheimers Dis.* **7**, 47–55 (2020).
53. Fruijtier, A. D. et al. What patients want to know, and what we actually tell them: the ABIDE project. *Alzheimer's Dement.* **6**, e12113 (2020).
54. Fruijtier, A. D. et al. ABIDE Delphi study: topics to discuss in diagnostic consultations in memory clinics. *Alzheimer's Res. Ther.* **11**, 77 (2019).
55. DiBenedetti, D. B. et al. Assessing what matters most to patients with or at risk for Alzheimer's and care partners: a qualitative study evaluating symptoms, impacts, and outcomes. *Alzheimers Res. Ther.* **12**, 90 (2020).
56. Tochel, C. et al. What outcomes are important to patients with mild cognitive impairment or Alzheimer's disease, their caregivers, and health-care professionals? a systematic review. *Alzheimers Dement.* **11**, 231–247 (2019).
57. Amyvid (florbetapir F18 injection) [highlights of prescribing information]. US Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202008s000lbl.pdf (2012).
58. Vizamyl (flutemetamol F18 injection) [highlights of prescribing information]. US Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203137s000lbl.pdf (2013).

59. Neuraceq (florbetaben F18 injection) [highlights of prescribing information]. US Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204677s000lbl.pdf (2014).
60. Johnson, K. A. 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. *Alzheimers Dement.* **9**, e1–e16 (2013).
61. Johnson, K. A. et al. Update on appropriate use criteria for amyloid PET imaging: dementia experts, mild cognitive impairment, and education. Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging. *Alzheimers Dement.* **9**, e106–e109 (2013).
62. Altomare, D. et al. Quantitative appraisal of the Amyloid Imaging Taskforce appropriate use criteria for amyloid-PET. *Alzheimers Dement.* **14**, 1088–1098 (2018).
63. Rabinovici, G. D. et al. Association of amyloid positron emission tomography with subsequent change in clinical management among medicare beneficiaries with mild cognitive impairment or dementia. *JAMA* **321**, 1286–1294 (2019).
64. Tousi, B. & Sabbagh, M. N. Editorial: a time of transition of Alzheimer's disease in the advent of anti-amyloid monoclonal antibodies. *Neurol. Ther.* **10**, 409–413 (2021).
65. Zetterberg, H. & Blennow, K. Moving fluid biomarkers for Alzheimer's disease from research tools to routine clinical diagnostics. *Mol. Neurodegener.* **16**, 10 (2021).
66. Shaw, L. M. et al. Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosis of Alzheimer's disease. *Alzheimers Dement.* **14**, 1505–1521 (2018).
67. Hampel, H. et al. State-of-the-art of lumbar puncture and its place in the journey of patients with Alzheimer's disease. *Alzheimers Dement.* **18**, 159–177 (2021).
68. Hansson, O. et al. Pre-analytical protocol for measuring Alzheimer's disease biomarkers in fresh CSF. *Alzheimers Dement* **12**, e12137 (2020).
69. Vanderstichele, H. et al. Standardization of preanalytical aspects of cerebrospinal fluid biomarker testing for Alzheimer's disease diagnosis: a consensus paper from the Alzheimer's Biomarkers Standardization Initiative. *Alzheimers Dement.* **8**, 65–73 (2012).
70. Tauvid (flortaucipir F 18 injection) [highlights of prescribing information]. US Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212123s000lbl.pdf (2020).
71. Moscoso, A. et al. Longitudinal associations of blood phosphorylated Tau181 and neurofilament light chain with neurodegeneration in Alzheimer disease. *JAMA Neurol.* **78**, 396–406 (2021).
72. Chen, S. D. et al. Longitudinal plasma phosphorylated tau 181 tracks disease progression in Alzheimer's disease. *Transl. Psychiatry* **11**, 356 (2021).
73. Moscoso, A. et al. Time course of phosphorylated-tau181 in blood across the Alzheimer's disease spectrum. *Brain* **144**, 325–339 (2021).
74. Janelidze, S. et al. Plasma beta-amyloid in Alzheimer's disease and vascular disease. *Sci. Rep.* **6**, 26801 (2016).
75. Schindler, S. E. et al. High-precision plasma beta-amyloid 42/40 predicts current and future brain amyloidosis. *Neurology* **93**, e1647–e1659 (2019).
76. Nakamura, A. et al. High performance plasma amyloid-beta biomarkers for Alzheimer's disease. *Nature* **554**, 249–254 (2018).
77. West, T. et al. A blood-based diagnostic test incorporating plasma Abeta42/40 ratio, ApoE proteotype, and age accurately identifies brain amyloid status: findings from a multi cohort validity analysis. *Mol. Neurodegener.* **16**, 30 (2021).
78. Barthelemy, N.R., Horie, K., Sato, C. & Bateman, R.J. Blood plasma phosphorylated-tau isoforms track CNS change in Alzheimer's disease. *J. Exp. Med.* **217**, e20200861 (2020).
79. Janelidze, S. 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.* **26**, 379–386 (2020).
80. Karikari, T. K. 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.* **19**, 422–433 (2020).
81. Mielke, M. M. et al. Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography. *Alzheimers Dement.* **14**, 989–997 (2018).
82. Palmqvist, S. et al. Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. *JAMA* **324**, 772–781 (2020).
83. Thijssen, E. H. et al. Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration. *Nat. Med.* **26**, 387–397 (2020).
84. Ashton, N. J. et al. Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology. *Acta Neuropathol.* **141**, 709–724 (2021).
85. Ashton, N. J. 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* **48**, 2140–2156 (2021).
86. Langa, K. M., Foster, N. L. & Larson, E. B. Mixed dementia: emerging concepts and therapeutic implications. *JAMA* **292**, 2901–2908 (2004).
87. McAleese, K. E. et al. TDP-43 pathology in Alzheimer's disease, dementia with Lewy bodies and ageing. *Brain Pathol.* **27**, 472–479 (2017).
88. Visser, L. N. C. et al. Clinicians' communication with patients receiving a MCI diagnosis: the ABIDE project. *PLoS ONE* **15**, e0227282 (2020).
89. van Maurik, I. S. et al. Development and usability of ADappt: web-based tool to support clinicians, patients and caregivers in the diagnosis of mild cognitive impairment and Alzheimer disease. *JMIR Form. Res.* **3**, e13417 (2019).
90. Chiotis, K. et al. Clinical validity of increased cortical uptake of amyloid ligands on PET as a biomarker for Alzheimer's disease in the context of a structured 5-phase development framework. *Neurobiol. Aging* **52**, 214–227 (2017).
91. Sabbagh, M. N. et al. Early detection of mild cognitive impairment in an at-home setting. *J. Prev. Alzheimers Dis.* **7**, 171–178 (2020).
92. Stroud, C., Onnela, J. P. & Manji, H. Harnessing digital technology to predict, diagnose, monitor, and develop treatments for brain disorders. *NPJ Digit. Med.* **2**, 44 (2019).
93. Au, R., Ritchie, M., Hardy, S., Ang, T. F. A. & Lin, H. Aging well: using precision to drive down costs and increase health quality. *Adv. Geriatr. Med. Res.* **1**, e190003 (2019).
94. Seelye, A. et al. Embedded online questionnaire measures are sensitive to identifying mild cognitive impairment. *Alzheimer Dis. Assoc. Disord.* **30**, 152–159 (2016).
95. Kirste, T. et al. Detecting the effect of Alzheimer's disease on everyday motion behavior. *J. Alzheimers Dis.* **38**, 121–132 (2014).
96. Lüdtke, S., Hermann, W., Kirste, T., Beneš, H. & Teipel, S. An algorithm for actigraphy-based sleep/wake scoring: comparison with polysomnography. *Clin. Neurophysiol.* **132**, 137–145 (2021).
97. Sabbagh, M. N. et al. Rationale for early diagnosis of mild cognitive impairment supported by emerging digital technologies. *J. Prev. Alzheimers Dis.* **7**, 158–164 (2020).
98. Chen, R. et al. Developing measures of cognitive impairment in the real world from consumer-grade multimodal sensor streams. in *Proceedings of the 25th ACM SIGKDD International Conference on Knowledge Discovery & Data Mining* 2145–2155 (2019).
99. Beattie, Z. et al. The Collaborative Aging Research Using Technology Initiative: an open, sharable, technology-agnostic platform for the research community. *Digit. Biomark.* **4**, 100–118 (2020).
100. Wu, C. Y. et al. Unobtrusive sensing technology detects ecologically valid spatiotemporal patterns of daily routines distinctive to persons with mild cognitive impairment. *J. Gerontol. A Biol. Sci. Med. Sci.* glab293 (2021).
101. Piau, A. et al. Intrinsic capacitiy monitoring by digital biomarkers in integrated care for older people (ICOPE). *J. Frailty Aging* **10**, 132–138 (2021).
102. Takeda, C., Guyonnet, S., Sumi, Y., Vellas, B. & Araujo de Carvalho, I. Integrated care for older people and the implementation in the INSPIRE Care Cohort. *J. Prev. Alzheimers Dis.* **7**, 70–74 (2020).
103. Tavassoli, N. et al. Implementation of the WHO integrated care for older people (ICOPE) programme in clinical practice: a prospective study. *Lancet Healthy Longev.* **3**, 394–404 (2022).
104. van Gils, A. M. et al. Assessing the views of professionals, patients and care partners concerning the use of computer tools in memory clinics: International Survey Study. *JMIR Form. Res.* **5**, e31053 (2021).
105. McAlearney, A. S. et al. High Touch and High Tech (HT2) proposal: transforming patient engagement throughout the continuum of care by engaging patients with portal technology at the bedside. *JMIR Res. Protoc.* **5**, e221 (2016).
106. Hampel, H. & Vergallo, A. The Sars-CoV-2 pandemic and the brave new digital world of environmental enrichment to prevent brain aging and cognitive decline. *J. Prev. Alzheimers Dis.* **7**, 294–298 (2020).
107. Liu, J. L., Hlavka, J. P., Hillestad, R. & Mattke, S. Assessing the Preparedness of the US Health Care System Infrastructure for an Alzheimer's Treatment (RAND Corporation, 2017).
108. Hlavka, J. P., Mattke, S. & Liu, J. L. Assessing the preparedness of the health care system infrastructure in six European countries for an Alzheimer's treatment. *Rand Health Q.* **8**, 2 (2019).
109. Mattke, S., Hlavka, J. P., Yoong, J., Wang, M. & Goto, R. Assessing the preparedness of the Japanese health care system infrastructure for an Alzheimer's treatment. (USC Dornsife: Center for Economic and Social Research, 2019).
110. Jun, H., Cho, S. K., Yoong, J. & Mattke, S. Assessing the preparedness of the Korean health care system infrastructure for an Alzheimer's treatment. (USC Dornsife: Center for Economic and Social Research, 2020).

111. Mattke, S. & Hanson, M. Expected wait times for access to a disease-modifying Alzheimer's treatment in the United States. *Alzheimers Dement.* **18**, 1071–1074 (2021).
112. Mattke, S., Ullrich, A. & Wang, M. Implications of Alzheimer's treatment for organization and payment of medical practices in the EU-5 countries. (USC Dornsife: Center for Economic and Social Research, 2020).
113. Mattke, S. & Wang, M. Implications of Alzheimer's treatment for organization and payment of medical practices in the United States. (USC Dornsife: Center for Economic and Social Research, 2020).
114. Prince, M., Comas-Herrera, A, Knapp, M, Guerchet, M. & Karagiannidou, M. World Alzheimer Report 2016: improving healthcare for people living with dementia: coverage, quality and costs now and in the future. (Alzheimer's Disease International, 2016).
115. Sperling, R. A. et al. Amyloid-related imaging abnormalities (ARIA) in amyloid modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. *Alzheimers Dement.* **7**, 367–385 (2011).
116. Liu, J. L., et al. Assessing the preparedness of the Canadian health care system infrastructure for an Alzheimer's treatment (RAND Corporation, 2019).
117. Au, R. K., Kolachalama V. B., Paschalidis, I. C. H. Redefining and validating digital biomarkers as fluid, dynamic multi-dimensional digital signal patterns. *Front. Digit. Health* **3**, 751629 (2022).
118. Lloyd-Jones, D. M. et al. Use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease: a special report from the American Heart Association and American College of Cardiology. *Circulation* **139**, e1162–e1177 (2019).
119. Rossini, P. M. et al. The Italian INTERCEPTOR Project: from the early identification of patients eligible for prescription of antidementia drugs to a nationwide organizational model for early Alzheimer's disease diagnosis. *J. Alzheimers Dis.* **72**, 373–388 (2019).
120. National Institute on Aging. Telehealth: improving dementia care. https://www.nia.nih.gov/news/telehealth-improving-dementia-care (2020).
121. Chin, A. L., Negash, S. & Hamilton, R. Diversity and disparity in dementia: the impact of ethnoracial differences in Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* **25**, 187–195 (2011).
122. US Department of Health and Human Services. Racial and ethnic disparities in Alzheimer's Disease: a literature review. https://aspe.hhs.gov/sites/default/files/migrated_legacy_files//138596/RacEthDis.pdf (2014).
123. Vega, I. E., Cabrera, L. Y., Wygant, C. M., Velez-Ortiz, D. & Counts, S. E. Alzheimer's disease in the Latino community: intersection of genetics and social determinants of health. *J. Alzheimers Dis.* **58**, 979–992 (2017).
124. McKindra, L. Dementia researchers issue urgent call for more diversity in clinical trial participation. (University of Kansas Medical Center, 2021).
125. Wilkins, C. H., Schindler, S. E. & Morris, J. C. Addressing health disparities among minority populations: why clinical trial recruitment is not enough. *JAMA Neurol.* **77**, 1063–1064 (2020).
126. Anderson, J. G., Flatt, J. D., Jabson Tree, J. M., Gross, A. L. & Rose, K. M. Characteristics of sexual and gender minority caregivers of people with dementia. *J. Aging Health* **33**, 838–851 (2021).
127. Ferretti, M. T. et al. Optimal Alzheimer's disease detection and diagnosis under the sex and gender lens: a crucial step towards precision neurology. in *World Alzheimer Report 2021: Journey through the diagnosis of dementia.* Alzheimer's Disease International, 238–241 (2021).
128. Ferretti, M. T. et al. Sex differences in Alzheimer disease—the gateway to precision medicine. *Nat. Rev. Neurol.* **14**, 457–469 (2018).
129. Fredriksen-Goldsen, K. I., Jen, S., Bryan, A. E. B. & Goldsen, J. Cognitive impairment, Alzheimer's disease and other dementias in the lives of lesbian, gay, bisexual and transgender (LGBT) older adults and their caregivers: needs and competencies. *J. Appl Gerontol.* **37**, 545–569 (2018).
130. Galvin, J. E. et al. Early stages of Alzheimer's disease: evolving the care team for optimal patient management. *Front. Neurol.* **11**, 592302 (2020).
131. Hampel, H., Lista, S. & Khachaturian, Z. S. Development of biomarkers to chart all Alzheimer's disease stages: the royal road to cutting the therapeutic Gordian Knot. *Alzheimers Dement.* **8**, 312–336 (2012).
132. Hampel, H. et al. PRECISION MEDICINE—the golden gate for detection, treatment and prevention of Alzheimer's disease. *J. Prev. Alzheimers Dis.* **3**, 243–259 (2016).
133. Hampel, H. et al. A precision medicine framework using artificial intelligence for the identification and confirmation of genomic biomarkers of response to an Alzheimer's disease therapy: analysis of the blarcamesine (ANAVEX2-73) phase 2a clinical study. *Alzheimer's Dement.* **6**, e12013 (2020).
134. Hampel, H., Vergallo, A., Perry, G., Lista, S. & Alzheimer Precision Medicine Inititaive. The Alzheimer Precision Medicine Initiative. *J. Alzheimers Dis.* **68**, 1–24 (2019).
135. Altomare, D. et al. Brain Health Services: organization, structure, and challenges for implementation. a user manual for Brain Health Services—part 1 of 6. *Alzheimers Res. Ther.* **13**, 168 (2021).
136. Cummings, J. The role of biomarkers in Alzheimer's disease drug development. *Adv. Exp. Med. Biol.* **1118**, 29–61 (2019).
137. McKhann, G. et al. 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* **34**, 939–944 (1984).
138. Beach, T. G., Monsell, S. E., Phillips, L. E. & Kukull, W. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005–2010. *J. Neuropathol. Exp. Neurol.* **71**, 266–273 (2012).
139. Kovacs, G. G. et al. Non-Alzheimer neurodegenerative pathologies and their combinations are more frequent than commonly believed in the elderly brain: a community-based autopsy series. *Acta Neuropathol.* **126**, 365–384 (2013).
140. Graff-Radford, J. et al. New insights into atypical Alzheimer's disease in the era of biomarkers. *Lancet Neurol.* **20**, 222–234 (2021).
141. Dubois, B. et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol.* **6**, 734–746 (2007).
142. Dubois, B. et al. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol.* **9**, 1118–1127 (2010).
143. Dubois, B. et al. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimers Dement.* **12**, 292–323 (2016).
144. Albert, M. S. 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. *Alzheimers Dement.* **7**, 270–279 (2011).
145. McKhann, G. M. 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. *Alzheimers Dement.* **7**, 263–269 (2011).
146. Sperling, R. A. 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. *Alzheimers Dement.* **7**, 280–292 (2011).
147. Jack, C. R. et al. A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. *Neurology* **87**, 539–547 (2016).
148. Food & Drug Administration. Early Alzheimer's Disease: Developing Drugs for Treatment: Guidance for Industry. https://www.fda.gov/media/110903/download (2018).

Acknowledgements

R.A.'s grant support includes National Institutes of Health (NIH) grants (AG062109, AG068753, AG072654 and AG063635). Additional support was provided by the American Heart Association (20SFRN35360180 and 20SFRN35490098), the Alzheimer's Drug Discovery Foundation (201902-2017835) and Gates Ventures. W.M.v.d.F received support from the Research of Alzheimer center Amsterdam, which is part of the neurodegeneration research program of Amsterdam Neuroscience. The chair of W.v.f.F is supported by the Pasman stichting. W.F. is a recipient of ABOARD, which is a public–private partnership receiving funding from ZonMW (73305095007) and Health~Holland, Topsector Life Sciences & Health (PPP allowance, LSHM20106). More than 30 partners participate in ABOARD. H.W. receives research grant from the National Brain Project funded by the Ministry of Science and Technology, China (2021ZD0201805). C.C. is supported by the National Medical Research Council of Singapore (MOH-000707-00, NMRC/OFLCG/2019, NMRC/CIRG/1485/2018 and NMRC/CSA-SI/0007/2016). The Gérontopôle (chair B.V.) has received research grant support from the European Commission as well as industries including Biogen, Green Valley Pharmaceuticals, Novo Nordisk, Pfizer, Pierre-Fabre, Roche, Lily and Eisai. J.C. is supported by NIGMS grant P20GM109025, NINDS grant U01NS093334, NIA grants R01AG053798, P20AG068053 and R35AG71476 and the Alzheimer's Disease Drug Discovery Foundation. A.S. receives support from multiple NIH grants (P30 AG010133, P30 AG072976, R01 AG019771, R01 AG057739, U01 AG024904, R01 LM013463, R01 AG068193, T32 AG071444, U01 AG068057 and U01 AG072177). The authors thank D. Henley for his contribution to the critical revision of the Perspective. Medical writing support was provided by L. O'Brien of CMC AFFINITY, McCann Health Medical Communications and was funded by Eisai.

Author contributions

H.H., A.V., S.D.S. and P.G. developed the initial concept and theoretical framework for this Perspective. All authors contributed to researching the literature and data, discussing the content, and writing, reviewing and/or editing of the Perspective.

Competing interests

H.H. is an employee of Eisai and serves as senior associate editor for the Journal Alzheimer's & Dementia and has not received any fees or honoraria since May 2019. H.H. is inventor of 11 patents and has received no royalties for: In Vitro Multiparameter Determination Method for The Diagnosis and Early Diagnosis of Neurodegenerative Disorders patent no. 8916388; In Vitro Procedure for Diagnosis and Early Diagnosis of Neurodegenerative Diseases patent no. 8298784; Neurodegenerative Markers for Psychiatric Conditions publication no. 20120196300; In Vitro Multiparameter Determination Method for The Diagnosis and Early Diagnosis of Neurodegenerative Disorders publication no. 20100062463; In Vitro Method for The Diagnosis and Early Diagnosis of Neurodegenerative Disorders publication no. 20100035286; In Vitro Procedure for Diagnosis and Early Diagnosis of Neurodegenerative Diseases publication no. 20090263822; In Vitro Method for The Diagnosis of Neurodegenerative Diseases patent no. 7547553; CSF Diagnostic in Vitro Method for Diagnosis of Dementias and Neuroinflammatory Diseases publication no. 20080206797; In Vitro Method for The Diagnosis of Neurodegenerative Diseases publication no. 20080199666; Neurodegenerative Markers for Psychiatric Conditions publication no. 20080131921; Method for diagnosis of dementias and neuroinflammatory diseases based on an increased level of procalcitonin in cerebrospinal fluid: US patent no. 10921330. R.A. is a scientific advisor to Signant Health and consultant to Biogen. S.M. serves on the board of directors of Senscio Systems and the scientific advisory board of AiCure Technologies, and Boston Millennia Partners, and has received consulting fees from AARP, Biogen, Biotronik, Bristol-Myers Squibb, C2N, Eisai and Roche. Research programs of W.M.v.d.F. have been funded by ZonMW, NWO, EU-FP7, EU-JPND, Alzheimer Nederland, CardioVascular Onderzoek Nederland, Health~Holland, Topsector Life Sciences & Health, stichting Dioraphte, Gieskes-Strijbis fonds, stichting Equilibrio, Pasman stichting, stichting Alzheimer & Neuropsychiatrie Foundation, Biogen MA, Boehringer Ingelheim, Life-MI, AVID, Roche BV, Fujifilm and Combinostics. W.F. holds the Pasman chair. W.F. is a recipient of ABOARD, which is a public–private partnership receiving funding from ZonMW (73305095007) and Health~Holland, Topsector Life Sciences & Health (PPP allowance, LSHM20106). W.F. has performed contract research for Biogen MA and Boehringer Ingelheim. W.F. has been an invited speaker at Boehringer Ingelheim, Biogen MA, Danone, Eisai, WebMD Neurology (Medscape) and Springer Healthcare. W.F. is consultant to Oxford Health Policy Forum CIC, Roche and Biogen MA. W.F. participated in advisory boards of Biogen MA and Roche. All funding is paid to the institution of W.F. W.F. was associate editor of Alzheimer, Research & Therapy in 2020/2021. W.F. is associate editor at Brain. P.A. reports research agreements with Janssen, Lilly and Eisai, grants from NIA, the Alzheimer's Association and FNIH and consulting fees from Biogen, Roche, Merck, Abbvie, Immunobrain Checkpoint, Rainbow Medical and Shionogi. L.A. has provided consultation to Eli Lilly, Biogen, Eisai, GE Healthcare and Two Labs. L.G.A. receives research support from NIA U01 AG057195, NIA R01 AG057739, NIA P30 AG010133, Alzheimer Association LEADS GENETICS 19-639372, Roche Diagnostics RD005665, AVID Pharmaceuticals and Life Molecular Imaging. L.G.A. received honoraria for participating in independent data safety monitoring boards and providing educational CME lectures and programs. L.G.A. has stock in Cassava Sciences and Semiring. C.C. receives research grants from the National Medical Research Council of Singapore. C.C. also receives research support from Moleac, Roche, Eisai and Lundbeck; and has participated in advisory boards for Cerecin and Eisai in the past 3 years. A.I. receives research grant from AMED (Japanese Agency for Medical Research), JSPS (Japan Society for Promotion of Science), Eisai, Daiichi Sankyo, Shionogi, Chugai-Roche and Kyowa Kirin. A.I. also receives consultant fees from Eisai, Biogen and Janssen Pharmaceuticals. A.I. also receives lecture fees from Eisai, Daiichi Sankyo, Otsuka, Ono Pharmaceutical and Fujirebio. A.S. received support from Avid Radiopharmaceuticals, a subsidiary of Eli Lilly (in kind contribution of PET tracer precursor), Bayer Oncology (Scientific Advisory Board), Eisai (Scientific Advisory Board), Siemens Medical Solutions USA (Dementia Advisory Board) and Springer Nature Publishing (Editorial Office Support as Editor-in-Chief, Brain Imaging and Behavior). S.T. has served on the advisory boards of Roche, Biogen, Eisai and Grifols within the last 3 years. B.V. has served as consultant/advisor to Eisai, Biogen, Lilly, Longeveron, Novo Nordisk, TauRx P and Roche in the past 3 years. A.V. declares no competing interests related to the present paper and the contribution of A.V. to this paper reflects entirely and only A.V.'s own academic expertise on the matter. A.V. was an employee of Eisai (November 2019–June 2021). A.V. did not receive any fees or honoraria since November 2019. Before November 2019, A.V. received lecture honoraria from Roche, MagQu and Servier. H.W. has provided consultation to Eisai, Lundbeck, Roche and Signant Health pharmaceutical and assessment companies. H.W. owns the copyright of the individualized management system of neuropsychiatric symptoms (NPSIMS) and the smartphone-based application of brief cognitive screening kit (shairenzhi). J.C. provided consultation to AB Science, Acadia, Alkahest, AlphaCognition, ALZPathFinder, Annovis, AriBio, Artery, Avanir, Biogen, Biosplice, Cassava, Cerevel, Clinilabs, Cortexyme, Diadem, EIP Pharma, Eisai, GatehouseBio, GemVax, Genentech, Green Valley, Grifols, Janssen, Karuna, Lexeo, Lilly, Lundbeck, LSP, Merck, NervGen, Novo Nordisk, Oligomerix, Ono, Otsuka, PharmacotrophiX, PRODEO, Prothena, ReMYND, Renew, Resverlogix, Roche, Signant Health, Suven, Unlearn AI, Vaxxinity, VigilNeuro pharmaceutical, assessment and investment companies. M.C., S.D.S., P.G. and R.K. are employees of Eisai.

Additional information

Correspondence should be addressed to Harald Hampel.

Peer review information *Nature Aging* thanks Niklas Mattsson-Carlgren and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Patient/site readiness for a potential new Alzheimer's disease treatment paradigm

Eva Županič, Milica Gregorič Kramberger

There were more than 34,000 people living with dementia in Slovenia in 2018 and this number is predicted to double by 2050. (1) Dementias represent a global health challenge and also incur high economic costs. In Slovenia, all dementia costs (medical, formal and informal home help, nursing home placements costs) are estimated at 377 million euros. (2) Reducing the dementia severity or even delaying the diagnosis would greatly reduce this burden; e.g. an intervention that would delay the onset of dementia by five years today could reduce costs by 36% in 2050. (3)

The majority of all dementia cases, Alzheimer's dementia (AD), is caused by a progressive accumulation of beta-amyloid protein plaques and neurofibrillary tangles, which damage synaptic connections and neurons and lead to the loss of cognitive abilities. In Europe, there are currently no disease modifying treatments (DMT) available and treatment of AD is symptomatic, limited to acetylcholinesterase inhibitors, memantine and other supportive care measures, which do not slow or stop the progression of the disease. However, after two decades of clinical trial failures, we finally received the long awaited positive news on a DMT for AD. On January 6, 2023, lecanemab, an anti-amyloid monoclonal antibody was approved under an accelerated pathway by the US Food and Drug Administration and is currently under review by the European Medicines Agency. (4) In an 18-month study involving participants with mild AD, lecanemab slowed the rate of cognitive decline by 27%. (5)

Are we prepared for potential lecanemab approval by European Medicines Agency (EMA) and Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP)?

With the potential approval of lecanemab we can expect huge demands from the general population for diagnosis and eventual treatment. Persons aged 65 years or older with MCI or mild AD (MMSE–Mini Mental State Examination > 21 points or MoCA–Montreal Cognitive Assessment > 16 points) and Alzheimer's disease positive biomarkers will be potential candidates for treatment. Alzheimer's disease biomarkers include positive amyloid-PET imaging or cerebrospinal fluid (CSF) biomarkers, and since amyloid-PET imaging is currently not available in Slovenia, CSF biomarker analyses are used instead. At the present time, there are no reliable blood based biomarker that could substitute the lumbar puncture. In that scenario, blood-based biomarkers combined with cognitive testing could be performed in a primary level setting, which may serve as a gatekeeping mechanism. However, this would call for additional capacities of the primary level, which is, even at present, critically understaffed.

Firstly, the site should have the diagnostic capacity to recognize potential candidates for treatment. Secondly, the site should be able to prepare the infusions, safely monitor patients (with clinical assessments and regular MRI scans) and deal with possible complications, thus requiring enough room, personnel, and other resources.

Since 2009, patients with cognitive complaints can be referred to the Centre for Cognitive Impairments at the Department of Neurology, Ljubljana University Medical Centre, Slovenia. At first visit, a detailed history is taken from all patients, who also undergo a general neurological examination, a screening cognitive assessment and are further referred for extensive laboratory testing and a structural brain scan. Additional examinations are indicated on a case-by-case basis. For selection of potential lecanemab candidates that would entail lumbar puncture with CSF analyses. In the past two years (2021-2022), there were 1,461 first visits, 3,133 control visits and 891 lumbar punctures performed in persons with a cognitive complaint. Pathological CSF biomarker profile was present in 257, however, only half (n = 126) were at the stage of MCI or mild AD and thus potential lecanemab candidates.

The cost to evaluate 891 patients with neurological assessment, MRI and lumbar puncture would be around €2.5 million, however, in reality, the costs were even higher since some patients also underwent FDG-PET or neuropsychological examination.

With dementia prevalence data for Slovenia (1) and an estimation of 7.7% of MCI due to Alzheimer's disease in persons aged 65 year or more, (6, 7) there are 44,278 potentially eligible candidates for

lecanemab treatment. With current annual lecanemab's price of approximately €24,000 and all eligible patients receiving the treatment, this would account to €1,06 billion, which is more than an annual cost for all medication in Slovenia (€743 million in 2022). (8) Diagnosing all candidates with a neurological assessment, MRI and lumbar puncture would account to almost €125 million. However, since 891 assessments were required to yield 126 potential candidates, one must realize that the introduction of lecanemab would greatly increase the direct medical costs in the healthcare system even for patients that would never be treated with the drug.

It is clearly unrealistic to recognize and treat all the potential candidates. Besides Centre for Cognitive Impairments in Ljubljana, only Maribor has subspecialized outpatient facilities for patients with cognitive impairment, which probably do not exceed Ljubljana's capabilities. The approval of lecanemab would increase the pressure on these two centres and increase the waiting times. Moreover, even if the drug receives regulatory approval, high cost might cause the national agency to limit the number of treated patients or even refuse reimbursement altogether. The Institute for Clinical and Economic Review (ICER), an independent non-profit research organization that assesses expected clinical benefits against potential side-effects and costs, concluded lecanemab's price would require a 66% to 19% discount to be considered cost-effective. (9) Therefore, at current capacity, the Slovenian healthcare system is unable to diagnose and select eligible patients for DMT in Alzheimer's disease. Substantial investments in personnel, infrastructure and medication alone will be required to provide timely diagnosis and enable treatment with lecanemab.

References:

1. Alzheimer Europe. Prevalence of dementia in Europe. [27.4.2023]. Available from: https://www.alzheimer-europe.org/dementia/prevalence-dementia-europe.

2. Županič E, Wimo A, Winblad B, Kramberger MG. Cost of Diagnosing and Treating Cognitive Complaints: One-year Cost-evaluation Study in a Patient Cohort from a Slovenian Memory Clinic. Zdravstveno varstvo. 2022;61(2):76-84 DOI: 10.2478/sjph-2022-0011.

3. Alzheimer's Research UK. The Power to Defeat Dementia [27.4.2023]. Available from: https://www.alzheimersresearchuk.org/wp-content/uploads/2015/01/Defeat-Dementia-policy-report.pdf.

4. Eisai. Marketing authorization application for lecanemab as treatment for early Alzheimer's disease accepted by European Medicines Agency. 2023 [27.4.2023]. Available from: https://www.eisai.com/news/2023/pdf/enews202311pdf.pdf.

5. Van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in early Alzheimer's disease. New England Journal of Medicine. 2023;388(1):9-21.

6. Overton MC. Assessment of cognition in ageing. Investigating internal validity, occurrence and reversion of Mild Cognitive Impairment. Data from the general population study "Good Aging in Skåne": Lund University; 2019.

7. Gustavsson A, Norton N, Fast T, Frölich L, Georges J, Holzapfel D, et al. Global estimates on the number of persons across the Alzheimer's disease continuum. Alzheimer's & Dementia. 2023;19(2):658-70.

8. EFPIA - European Federation of Pharmaceutical Industries and Associations. The Pharmaceutical Industry in Figures. Key data 2022. 2022. Available from: https://www.efpia.eu/media/637143/the-pharmaceutical-industry-in-figures-2022.pdf.

9. Grace Lin MDW, Abigail Wright, Foluso Agboola, Serina Herron-Smith, Steven D Pearson, David Rind. Antibodies for Early Alzheimer's Disease: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review. 2023 [27.4.2023]. Available from: https://icer.org/wp-content/uploads/2021/12/ICER_Alzheimers-Disease_Revised-Evidence-Report_03012023.pdf.

Functional brain networks in neurodegenerative disorders

Tomaž Rus

Abstract

Until recently, neurodegenerative disorders such as Alzheimer's and Parkinson's disease had no medication that could impact their progression. Many clinical trials may have failed due to a lack of understanding of the underlying pathophysiological mechanisms and poorly defined inclusion criteria. As a result, researchers have turned to identifying biomarkers that can reflect disease-specific pathological processes. One promising approach is studying disease-specific changes in functional brain networks. These networks can be detected in patients using various functional imaging methods, including [18F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) and resting-state functional magnetic resonance imaging (rs-fMRI). Both FDG PET and rs-fMRI can detect changes in functional brain networks in neurodegenerative disorders, providing insights into the interdependence or connectivity of various brain regions, forming a brain network.

Backgrounds

The increasing prevalence of neurodegenerative disorders worldwide has fueled scientific efforts to discover cures for these devastating conditions, which can present with dementia or parkinsonian syndromes (1). Despite tremendous investment and effort, only recently have promising disease-modifying drugs for Alzheimer's disease (AD) been released, with none currently available for Parkinson's disease (PD) (2).

The lack of understanding of the etiology and pathophysiological mechanisms of these disorders, as well as the absence of pathology-based inclusion criteria, has likely contributed to many failed clinical trials. These factors have motivated researchers to seek biomarkers that can reflect the disease-specific pathological processes. For instance, while biomarkers such as amyloid-beta, tau, and phosphorylated tau (p-tau) measured in cerebrospinal fluid (CSF) or captured by positron emission tomography (PET), together with structural neuroimaging (MRI), have been included in research criteria for AD (3), there is emerging evidence that different neurodegenerative disorders may be differentiated by studying topographical differences in functional brain networks (4). These networks can be detected in patients using various imaging methods, among which the most established are [18F]-fluorodeoxyglucose (FDG) PET and resting-state functional magnetic resonance imaging (rs-fMRI) (4). These networks allow us to gain insight into disease mechanisms in vivo and to accurately distinguish between similar syndromes. Both FDG PET and rs-fMRI have been shown to be useful tools for detecting changes in functional brain networks in neurodegenerative disorders.

Functional brain network mapping

Functional imaging techniques differ from structural imaging in that they indirectly measure dynamic metabolic processes or brain activity by assessing regional changes or activity of specific molecules or markers. In FDG PET images, the spatial distribution of radioactive FDG, which accumulates in brain tissue according to metabolic demands and correlates with neuronal activity, can be examined (5). By using simple univariate statistical methods, such as statistical parametric mapping (SPM), which compare individual voxels or regions between patients and healthy controls, we can identify the areas that significantly differ between the groups, thus improving image contrast (6). Advanced algorithms not only analyze

individual brain voxels or regions but also consider relationships between them, providing insights into the interdependence or connectivity of various brain regions, forming a brain network. Several analytical methods, such as principal component analysis (PCA) or graph theory, have been developed for this purpose and are commonly used (7,8).

PCA-based analytical methods have been used for several years to identify disease-specific metabolic brain networks in neurodegenerative disorders, which have been rigorously validated in diverse clinical populations worldwide. Recent advances in analytical models have enabled the use of similar methods in four-dimensional rs-fMRI images, using an alternative independent component analysis (ICA) approach (9). While FDG PET captures static metabolic images within a few minutes, rs-fMRI captures transient fluctuations in blood oxygenation in different brain regions, closely related to neural activity due to neurovascular coupling. Both modalities are complementary. However, while rs-fMRI is cheaper and more easily available, higher noise makes the image contrast less accurate in intermediate cases.

Functional Brain Network Alterations in Creutzfeldt-Jakob's Disease: A Model Neurodegenerative Disorder

Creutzfeldt-Jakob's disease (CJD) is often regarded as an in vivo model of neurodegeneration due to the well-known mechanism of prion protein spread throughout the brain. The prion hypothesis has been proposed as a possible explanation for the spread of neurodegeneration in the brain (10,11). Furthermore, although the final pathological diagnosis is often unknown in neurodegenerative diseases due to their long duration, the rapid progression of CJD and the legal obligation to conduct an autopsy allow for the collection of well-established and pathology-confirmed cases for study.

Our research group has recently identified a CJD-specific metabolic brain network using the SSM-PCA method and validated it on an independent cohort from a remote center (12). Despite the clinical heterogeneity of the disease early in its course, the pattern of the network was stable and coherent. Although pathological features differed somewhat among different molecular subtypes, metabolic features were consistent regardless of the molecular subtype and correlated with the relative disease duration, cognitive, functional, and neurological decline (13). This finding was somewhat unexpected but in line with some studies that showed consistent network disruption in other neurodegenerative disorders such as progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) regardless of the subtype (14).
We further investigated the internal network structure using a graph theory approach and found ineffective network reorganization with disconnection between vital network hubs. This may explain the severe cognitive decline in CJD despite preserved metabolism and relatively sparse histopathological findings in certain classical cognition-related brain areas (12).

Functional brain networks in Parkinson’s disease and related disorders

Parkinson's disease (PD) is characterized by stereotypical spread of pathological changes. Accumulation of α-synuclein begins in the brainstem and pons, followed by midbrain including the substantia nigra. In the advanced stages, the cortical regions are affected (15,16). The clinical features of PD correlate with both the pathological sequence and changes in functional neural networks. The motor network of PD (Parkinson’s Disease-Related Pattern; PDRP) correlates with bradykinesia and rigidity, while the cognitive network of PD (Parkinson’s Disease Cognitive Pattern; PDCP) correlates with cognitive decline (17). Both networks have been identified and validated in numerous cohorts worldwide, based on FDG PET and rs-fMRI brain imaging.

PDRP topographically includes increased activity (relative hypermetabolism) in the basal ganglia, thalamus, and cerebellum, along with decreased activity (relative hypometabolism) in premotor and posterior parietal areas. Its activity can be modulated by symptomatic treatment, which improves motor symptoms (18,19).

Changes in the cognitive network PDCP appear with a characteristic delay of a few years after the PDRP. PDCP topographically involves the ventral default mode network (DMN) with additional areas of the cerebral cortex, such as the dorsolateral prefrontal and medial parietal cortices (20,21). The temporal sequence of PDRP and PDCP expression is stereotypical and consistent with the aforementioned pathological sequence as proposed by Braak (17).

Symptomatic treatments for PD, such as dopaminergic medication or surgical techniques like deep brain stimulation, decrease the expression of PDRP (4). Detection of brain alterations on a network level holds potential in evaluating the effectiveness of novel disease-modifying treatments. Advanced analytical approaches like

graph theory not only allow for the study of network expression but also the examination of changes in network structure (22). By doing so, variations in information transmission within the network and other connectivity measures can be assessed. These methods have recently demonstrated particular modifications in network organization through genetic therapy for PD using AAV2-GAD application to the subthalamic nuclei and the impact of drugs that affect mitochondrial respiratory function.

Despite similar clinical presentation in early disease, atypical parkinsonian syndromes, such as MSA, PSP or corticobasal degeneration (CBD), have different pathophysiological mechanisms and sequences of pathological changes. These syndromes are characterized by different disease-specific networks: MSA-, PSP and CBD-related patterns (23,24).

An important feature of functional brain imaging network analysis using SSM-PCA/ICA approach is that multiple pathological networks can be prospectively calculated on a single FDG PET or rs-fMRI image. For example, in a patient with undefined parkinsonism expressions of several parkinsonian networks such as PDRP, MSARP and PSPRP can also be calculated. Based on the expression of multiple networks, computer algorithms (logistic, SVM, etc.) can calculate probability of individual disease and significantly improve the accuracy of early diagnosis (25,26).

Recent PD research has concentrated on the prodromal phase of the disease in order to develop early, or even preclinical, diagnostic methods. During this phase, individuals may experience non-specific symptoms such as olfactory disturbances, constipation, depression, and REM Sleep Behavior Disorder (RBD). Patients with RBD typically go on to develop PD or another α-synucleinopathy, such as MSA or dementia with Lewy bodies (DLB). Functional brain imaging studies have demonstrated that PDRP is already present during the prodromal phase (27,28). PDRP and other related networks are being studied as potential presymptomatic biomarkers for PD.

Functional brain networks in cognitive disorders

As in parkinsonian disorders, specific metabolic brain patterns characterizing pathological functional brain networks have been identified in several neurodegenerative disorders primarily affecting cognition such as AD, DLB and behavioral variant of frontotemporal dementia (bvFTD), so called ADRP, DLBRP and bvFTDRP (29–31). Specific distribution of interconnected metabolic changes enables differentiation from each other in a specific topographic arrangement of changes in brain activity. As the AD is the most prevalent neurodegenerative disease, ADRP is most studied network validated by many groups and characterized by relatively decreased activity in the temporoparietal cortex, posterior cingulate, and precuneus, and relatively increased activity in the cerebellum (29). It's expression correlates with cognitive decline and may be used to predict conversion from mild cognitive impairment to dementia making it a reliable biomarker of disease progression.

According to the clinical presentation, DLBRP is topographically characterized by hypometabolism in occipital lobe while the bvFTDRP by frontotemporal hypometabolism (30,31). In case of the latter, the detailed analysis of internal network structure showed consistent disruption of functional connections between frontal and occipito-parietal hub (31).

Conclusion

The advancement of functional network research in neurodegenerative diseases in recent years has led to the development of robust biological markers that have been confirmed in various clinical populations using different imaging methods. These biomarkers can be used for diagnostic and prognostic purposes, monitoring disease progression, and tracking the effect of new drugs. The next challenge is to test these markers in real clinical settings and identify metabolic patterns from rs-fMRI images. However, progress in the field suggests that the use of functional brain networks in routine diagnostics and clinical research is within reach.

References

1. Feigin VL, Nichols E, Alam T, Bannick MS, Beghi E, Blake N, et al. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol [Internet]. 2019 May 1 [cited 2022 May 8];18(5):459. Available from: /pmc/articles/PMC6459001/
2. CH van D, CJ S, P A, RJ B, C C, M G, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med [Internet]. 2023 [cited 2023 May 4];388(1):142–3. Available from: https://pubmed.ncbi.nlm.nih.gov/36449413/
3. 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 & Dementia. 2018 Apr;14(4):535–62.
4. Perovnik M, Rus T, Schindlbeck KA, Eidelberg D. Functional brain networks in the evaluation of patients with neurodegenerative disorders. Nat Rev Neurol [Internet]. 2023 Feb 1 [cited 2023 Feb 19];19(2). Available from: https://pubmed.ncbi.nlm.nih.gov/36539533/
5. Guedj E, Varrone A, Boellaard R, Albert NL, Barthel H, van Berckel B, et al. EANM procedure guidelines for brain PET imaging using [18F]FDG, version 3. Eur J Nucl Med Mol Imaging [Internet]. 2022 Jan 1 [cited 2022 May 14];49(2):632. Available from: /pmc/articles/PMC8803744/
6. Friston K, Ashburner J, Kiebel S, Nichols T, Penny W, editors. Statistical Parametric Mapping: The Analysis of Functional Brain Images. London: Elsevier; 2007.
7. Spetsieris PG, Eidelberg D. Scaled subprofile modeling of resting state imaging data in Parkinson's disease: Methodological issues. Neuroimage [Internet]. 2011 Feb 14 [cited 2019 Aug 21];54(4):2899–914. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20969965
8. Ko JH, Spetsieris PG, Eidelberg D. Network Structure and Function in Parkinson's Disease. Cerebral Cortex. 2018 Oct;28(12):4121–35.
9. Vo A, Sako W, Fujita K, Peng S, Mattis PJ, Skidmore FM, et al. Parkinson's disease-related network topographies characterized with resting state functional MRI. Hum Brain Mapp. 2017;38(2):617–30.
10. Jan A, Gonçalves NP, Vaegter CB, Jensen PH, Ferreira N. The Prion-Like Spreading of Alpha-Synuclein in Parkinson's Disease: Update on Models and Hypotheses. Int J Mol Sci [Internet]. 2021 Aug 1 [cited 2022 Feb 2];22(15). Available from: https://pubmed.ncbi.nlm.nih.gov/34361100/
11. Duyckaerts C, Clavaguera F, Potier MC. The prion-like propagation hypothesis in Alzheimer's and Parkinson's disease. Curr Opin Neurol [Internet]. 2019 Apr 1 [cited 2022 Jun 27];32(2):266–71. Available from: https://pubmed.ncbi.nlm.nih.gov/30724769/
12. Rus T, Mlakar J, Ležaić L, Vo A, Nguyen N, Tang C, et al. Sporadic Creutzfeldt-Jakob disease is associated with reorganization of metabolic connectivity in a pathological brain network. Eur J Neurol [Internet]. 2022 [cited 2023 Feb 19]; Available from: https://pubmed.ncbi.nlm.nih.gov/36583625/
13. Rus T, Mlakar J, Kramberger M, Pirtošek Z, et al. Correlations between brain metabolism and neuropathology in sporadic Creutzfeldt-Jakob disease. In: Matkovič A, Bresjanec M, editors. SNC21 [Internet]. Ljubljana: SiNAPSA, Slovenian Neuroscience Association; 2021 [cited 2022 May 27]. p. 23–23. Available from: http://www.sinapsa.org/SNC21/program/128
14. Martí-Andrés G, van Bommel L, Meles SK, Riverol M, Valentí R, Kogan R V., et al. Multicenter Validation of Metabolic Abnormalities Related to PSP According to the MDS-PSP Criteria. Mov Disord [Internet]. 2020 Nov 1 [cited 2022 Feb 12];35(11):2009–18. Available from: https://pubmed.ncbi.nlm.nih.gov/32822512/
15. Braak H, Tredici K Del, Rüb U, de Vos RAI, Jansen Steur ENH, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003 Mar;24(2):197–211.
16. Hawkes CH, Del Tredici K, Braak H. A timeline for Parkinson's disease. Parkinsonism Relat Disord. 2010;16(2):79–84.
17. Rus T, Schindlbeck K, Tang C, Vo A, Dhawan V, Trošt M, et al. Stereotyped relationship between motor and cognitive metabolic networks in Parkinson's disease. Movement Disorders. 2022;
18. Ma Y, Tang C, Spetsieris PG, Dhawan V, Eidelberg D. Abnormal metabolic network activity in Parkinson's disease: test-retest reproducibility. Journal of Cerebral Blood Flow & Metabolism. 2007;27(3):597–605.
19. Tomše P, Jensterle L, Grmek M, Zaletel K, Pirtošek Z, Dhawan V, et al. Abnormal metabolic brain network associated with Parkinson's disease: replication on a new European sample. Neuroradiology. 2017;59(5):507–15.
20. Meles SK, Tang CC, Teune LK, Dierckx RA, Dhawan V, Mattis PJ, et al. Abnormal metabolic pattern associated with cognitive impairment in Parkinson's disease: a validation study. J Cereb Blood Flow Metab [Internet]. 2015 Sep [cited 2019 Feb 3];35(9):1478–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26058693
21. Huang C, Mattis P, Tang C, Perrine K, Carbon M, Eidelberg D. Metabolic brain networks associated with cognitive function in Parkinson's disease. Neuroimage [Internet]. 2007 Jan 15 [cited 2018 May 17];34(2):714–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17113310
22. Niethammer M, Tang CC, LeWitt PA, Rezai AR, Leehey MA, Ojemann SG, et al. Long-term follow-up of a randomized AAV2-GAD gene therapy trial for Parkinson's disease. JCI Insight. 2017;2(7):e90133.
23. Eckert T, Tang C, Ma Y, Brown N, Lin T, Frucht S, et al. Abnormal metabolic networks in atypical parkinsonism. Movement Disorders. 2008;23(5):727–33.
24. Niethammer M, Tang CC, Feigin A, Allen PJ, Heinen L, Hellwig S, et al. A disease-specific metabolic brain network associated with corticobasal degeneration. Brain [Internet]. 2014 Nov [cited 2018 Mar 8];137(11):3036–46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25208922
25. Tang CC, Poston KL, Eckert T, Feigin A, Frucht S, Gudesblatt M, et al. Differential diagnosis of parkinsonism: a metabolic imaging study using pattern analysis. Lancet Neurol [Internet]. 2010 [cited 2018 Mar 8];9(2):149–58. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4617666/pdf/nihms728459.pdf

26. Rus T, Tomše P, Jensterle L, Grmek M, Pirtošek Z, Eidelberg D, et al. Differential diagnosis of parkinsonian syndromes: a comparison of clinical and automated - metabolic brain patterns' based approach. Eur J Nucl Med Mol Imaging [Internet]. 2020 Apr 27 [cited 2020 Apr 27];1–10. Available from: http://link.springer.com/10.1007/s00259-020-04785-z
27. Holtbernd F, Gagnon JF, Postuma RB, Ma Y, Tang CC, Feigin A, et al. Abnormal metabolic network activity in REM sleep behavior disorder. Neurology [Internet]. 2014 Feb 18 [cited 2019 Jan 21];82(7):620–7. Available from: https://pubmed.ncbi.nlm.nih.gov/24453082/
28. Meles SK, Renken RJ, Janzen A, Vadasz D, Pagani M, Arnaldi D, et al. The Metabolic Pattern of Idiopathic REM Sleep Behavior Disorder Reflects Early-Stage Parkinson Disease. Journal of Nuclear Medicine [Internet]. 2018 Sep [cited 2019 Jan 21];59(9):1437–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29476004
29. Perovnik M, Tomše P, Jamšek J, Emeršič A, Tang C, Eidelberg D, et al. Identification and validation of Alzheimer's disease-related metabolic brain pattern in biomarker confirmed Alzheimer's dementia patients. Sci Rep. 2022 Dec;12(1):11752.
30. Perovnik M, Tomše P, Jamšek J, Tang C, Eidelberg D, Trošt M. Metabolic brain pattern in dementia with Lewy bodies: Relationship to Alzheimer's disease topography. Neuroimage Clin [Internet]. 2022 [cited 2022 Jun 24];35(March):103080. Available from: https://pubmed.ncbi.nlm.nih.gov/35709556/
31. Rus T, Perovnik M, Vo A, Nguyen N, Tang C, Jamšek J, et al. Disease specific and nonspecific metabolic brain networks in behavioral variant of frontotemporal dementia. Hum Brain Mapp [Internet]. 2022 Nov 5 [cited 2022 Nov 8]; Available from: https://pubmed.ncbi.nlm.nih.gov/36334269/

Review article

EUROPEAN STROKE JOURNAL

European Stroke Journal
2021, Vol. 6(1) 5–17

DOI: 10.1177/23969873211000258
journals.sagepub.com/home/eso
SAGE

Cognitive impairment in patients with cerebrovascular disease: A white paper from the links between stroke ESO Dementia Committee

Ana Verdelho[1], Joanna Wardlaw[2], Aleksandra Pavlovic[3], Leonardo Pantoni[4], Olivier Godefroy[5], Marco Duering[6,7], Andreas Charidimou[8,9], Hugues Chabriat[10] and Geert Jan Biessels[11]

Abstract

Purpose: Many daily-life clinical decisions in patients with cerebrovascular disease and cognitive impairment are complex. Evidence-based information sustaining these decisions is frequently lacking. The aim of this paper is to propose a practical clinical approach to cognitive impairments in patients with known cerebrovascular disease.

Methods: The document was produced by the Dementia Committee of the European Stroke Organisation (ESO), based on evidence from the literature where available and on the clinical experience of the Committee members. This paper was endorsed by the ESO.

Findings: Many patients with stroke or other cerebrovascular disease have cognitive impairment, but this is often not recognized. With improvement in acute stroke care, and with the ageing of populations, it is expected that more stroke survivors and more patients with cerebrovascular disease will need adequate management of cognitive impairment of vascular etiology. This document was conceived for the use of *strokologists* and for those clinicians involved in cerebrovascular disease, with specific and practical hints concerning diagnostic tools, cognitive impairment management and decision on some therapeutic options.

Discussion and conclusions: It is essential to consider a possible cognitive deterioration in every patient who experiences a stroke. Neuropsychological evaluation should be adapted to the clinical status. Brain imaging is the most informative biomarker concerning prognosis. Treatment should always include adequate secondary prevention.

Keywords

Stroke, small vessel disease, cerebrovascular disease, cognitive impairment, dementia

Date received: 1 February 2021; accepted: 4 February 2021

[1]Department of Neurosciences and Mental Health, CHLN-Hospital de Santa Maria, Instituto de Medicina Molecular – IMM e Instituto de Saúde Ambiental –ISAMB, Faculdade de Medicina, University of Lisbon, Lisbon, Portugal
[2]Centre for Clinical Brain Sciences, UK Dementia Research Institute, University of Edinburgh, Edinburgh, UK
[3]Faculty for Special Education and Rehabilitation, University of Belgrade, Belgrade, Serbia
[4]Stroke and Dementia Lab, "Luigi Sacco" Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy
[5]Department of Neurology, Amiens University Hospital, Laboratory of Functional Neurosciences1,6 (UR UPJV 4559), Jules Verne Picardy University, Amiens, France
[6]Institute for Stroke and Dementia Research, University Hospital, LMU Munich, Germany
[7]Department of Biomedical Engineering, University of Basel, Basel, Switzerland
[8]Hemorrhagic Stroke Research Program, J. Philip Kistler Stroke Research Center, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[9]Department of Neurology, Boston Medical Center, Boston University School of Medicine, Boston, MA, USA
[10]Department of Neurology, FHU NeuroVasc, Hôpital Lariboisiere, University of Paris, Paris, France
[11]Department of Neurology, UMC Utrecht Brain Center, University Medical Center Utrecht, the Netherlands

Corresponding author:
Ana Verdelho, Department of Neurosciences, Hospital de Santa Maria, University of Lisbon, Av Prof. Egas Moniz, Lisbon, Portugal.
Email: averdelho@medicina.ulisboa.pt

Introduction

Vascular risk factors are recognized as one of the main determinants of cognitive impairment associated with ageing.[1,2] Cognitive impairment (CI) due to cerebrovascular disease (CVD) can exist after stroke or in the context of chronic CVD without previous stroke, representing a leading concern of patients and caregivers.[3] Although acute stroke care has evolved substantially over the last decades, post-stroke cognitive impairment (PSCI) remains frequently underdiagnosed as it may be overlooked in the presence of other distressing signs (for instance motor or visual symptoms). Consequently, cognitive impact of acute stroke is often underestimated. Moreover, subtle and progressive decline might also be caused by vascular lesions (e.g. either lesions related to small vessel disease (SVD), repetitive minor injuries, or vascular consequences of systemic failure as for instance cardiac insufficiency). Stroke clinicians are well trained in the identification of stroke, but do not always recognize the myriad of cognitive and behavioural symptoms that accompany stroke in the acute and chronic phases.

Methods

This paper is a result of an effort of the ESO Dementia Committee (2018-2020), under the approval of the ESO Executive Committee, aiming to produce some practical clinical suggestions on the identification, diagnosis and management of CI for clinicians involved in the management of patients with stroke. Its use is not only for *strokologists*, but also for others professionals involved in the management of patients with CI due to vascular pathology. Several comprehensive and updated reviews are available on the topic, acknowledged throughout this paper, and we did not aim to do an exhaustive or systematic review or to cover all current evidence. We tried to incorporate differences of approach and access to ancillary investigations, keeping in mind the standard usual best practice.

Concerning CI in the context of CVD, different terminologies exist,[4–6] and consensus is missing, although those terms refer broadly to the same or quite similar entities. In order to be practical, for the purpose of this paper, we will use vascular dementia (VD),[4] major vascular cognitive impairment/disorder[5] and the more recent major vascular neurocognitive disorder (NCD)[6] interchangeably, and where less severely affected, we use mild cognitive impairment/disorder or mild NCD.[5,6] Post-stroke dementia (PSD) or post-stroke cognitive impairment (PSCI) will be used when it refers to stroke patients, irrespectively of the time elapsed since stroke.

Findings

How to recognize cognitive complaints/impairment

Cognitive impairment due to CVD can occur in different settings: after a stroke (PSCI), in the acute stage, in the recovery stage (while other stroke symptoms improve), or delayed until months/years after stroke. When CI due to CVD follows repetitive or chronic vascular lesions, identification of those symptoms may be difficult as they might be quite subtle and misleading. Characteristically, and apart from focal cognitive symptoms due to stroke itself (such as aphasia and hemineglect), the initial symptoms may be hard to identify. These symptoms might include reduced initiative for usual tasks, slowness, and higher latency to start an answer/action. Patients may accept undertaking actions if externally motivated and initiated and more time may be needed. Because attention is impaired, patients are easily distracted even by irrelevant stimuli. Multi-tasking can be difficult, not only due to attention shifting difficulties, but also to difficulty in alternating between different tasks and patients may have difficulties in making decisions. Sometimes, behaviour is predominantly affected and proxies/families acknowledge some "personality" changes. Behaviour changes can co-exist or even be the only initial manifestation, such as more inflexible behaviour, with reduced tolerance to changes of routine activities and repetition of the same mistakes (as patients may not be able to correct themselves). Control of inhibition may be disturbed, loss of control of emotional expression, as well as socially inappropriate manifestations (even sexually inappropriate behaviour), although these latter are usually less frequent and occur in more advanced stages. Patients may be labelled as "depressed" although usually do not complain of sadness, and other key aspects of depression are not present. As a result of the symptoms above, patients reduce their level of social interaction, quit usual hobbies and sometimes relatives/caregivers takeover tasks intuitively. The keystone for considering the above symptoms as a manifestation of CVD is that they represent a change from a previous way of functioning, implicate an adaptation in daily-life, and finally, CVD is the presumed etiology. Evolution might be stepwise, progressive, or fluctuant. If only the patient is interviewed, it is possible to miss the picture. Interview of a proxy(ies) may be necessary, but beware of the patient who always looks to the partner to answer and the obliging partner who provides all the responses. Separate interview of the informant/relatives should be considered whenever interview of both patient and relative becomes a sensitive point, as relatives/caregivers might be uncomfortable giving some information or describing some details in the presence

of the patient. This separate interview should, nevertheless, follow usual good practice approaches.

Criteria for CI and for CI due to CVD

Several sets of criteria for CI due to CVD have been proposed,[4,5] most of them requiring to demonstrate the presence of CI, the presence of cerebral vascular lesions and a relationship between them. The VASCOG criteria[5] have the advantage to define criteria for both mild and major CI (based on the DSM-V)[6] and for both patients with stroke and those without stroke. This is especially important considering studies showing that a large proportion of patients with CI related to a cerebrovascular lesion did not have a clinically-evident stroke.[7]

The criterion of CI is operationalized in the diagnostic criteria of CI due to CVD,[4,5] although this operationalization still lacks consensus. Diagnosis of mild CI frequently uses the 1.5 standard deviation threshold on cognitive testing following criteria of Winblad et al.[8] two thresholds have been proposed in the DSM-V (1 and 2 standard deviations for mild CI and major CI, respectively).[6] In addition, some teams and studies applied these thresholds to each performance score or to each domain summary scores. Moreover, different results can be due to the chosen operationalized criteria[9] since normative data depend on selection of the controls (volunteers, community or not community, with or without brain imaging), which can, *per se*, limit interpretation of findings. A strict and explicit harmonization is needed as the use of different procedures deeply influences the interpretation (at least in patients with mild impairment) and the false positive rate.[10,11] The use of a global cognitive score summarizing all domains and the fifth percentile threshold has been shown to improve sensitivity while controlling for specificity [i.e. false positive rate].[10] Whatever the chosen procedure, it is essential to ensure that it provides an optimal sensitivity and controls specificity adequately. In addition, the selection (volunteers vs general population), demographic characteristics (representation of older and low education subjects) and size sample of normative population influence the determination of cognitive test cutoff scores.

The characteristics of vascular lesions in the brain are detailed in the subsection 'Predictors of CI and dementia'. The relationship between CI and cerebrovascular lesions is typically operationalized by its temporal course (i.e., onset within 3 months of diagnosed stroke, abrupt onset, or stepwise progression).[4,5] However, abrupt onset is rare in the absence of a stroke, and stepwise progression is infrequent owing to better prevention of stroke recurrence. This excludes patients with non-acute CI due to vascular lesion without clinical stroke, a situation which is especially encountered in small vessel disease (SVD). Purposefully the VASCOG criteria[5] included this situation and consider the diagnosis of CI due to CVD when deficits in executive functions and/or action speed are prominent and associated with at least one out of three features (gait disturbances, urinary control disorders or mood changes).

How to evaluate the neuropsychological status in stroke patients

Regarding stroke patients, we will focus on the post-acute phase, i.e., 3 to 6 months post-stroke. Cognitive assessment at the acute stroke onset should be performed as part of the neurological examination and contributes to the diagnosis of the acute condition in the emergency room; in the stroke unit it usually consists of clinical assessment and screening tests with, when needed, language or hemineglect tests to manage early rehabilitation.[12] More detailed information is already published.[12] Although most post-stroke assessments are now performed within 3-6 months, timing of neuropsychological assessment may influence the profile of CI: marked improvement in speed and attention, frontal executive functions, perceptual and nominal skills can occur over time, compared to stable findings in verbal and visual memory.[13,14]

We propose that the initial full neuropsychological evaluation should only be conducted after some stabilization was achieved (possibly as late as 6 months after a severe stroke), unless specific cognitive training could be advised earlier (for instance cognitive intervention for neglect). We do not advise to test and re-test repeatedly, unless specific questions arise (search for associated degenerative disease, driven ability or other legal reason, or working difficulties and need for retirement evaluation, for instance). In case re-test is needed for clinical clarification, an ideal interval of 12 months should be considered to avoid learning bias between evaluations.

PSCI is observed in about 50% of stroke survivors, two thirds of them corresponding to mild CI, and one third to major CI according to present CI criteria (see previous section).[11,15,16] PSCI has a marked effect on functional prognosis, risk of institutionalization[15,17,18] and risk of recurrence of a major vascular event.[19,20]

Optimal diagnosis of PSCI should be based on comprehensive cognitive assessment in patients at risk of CI. Although this is always a clinical indication, and should, in the end, based on the individual level, some cues can be given: this objective can be achieved using a recently explored strategy based on risk factors of PSCI (Table 1 provided in supplementary material, and "Predictors" section).[21] Several factors have been

Table 1. Diagnostic evaluation of patients with CI-CVD.

Step	Aim of investigation
Risk factor assessment	Stroke subtype • Increased risk associated with haemorrhagic (comparing to ischemic strokes) • Increased risk in cardioembolic etiology and large artery atherosclerosis
Clinical assessment	Detection of CI and other manifestations (depression, apathy). Functional status assessment
Brain imaging (MRI, if contraindications: CT)	MRI preferred mode of examination Differential diagnosis to other conditions causing CI. Identification of CVD type, location, and extent of CVD
Laboratory investigations (blood, CSF)	Risk factor identification Differential diagnosis to other conditions

CI – cognitive impairment; CVD – cerebrovascular disease; CSF - cerebrospinal fluid; MRI- Magnetic resonance imaging; CT- computerized tomography.

found to be associated with PSCI, major CI, in particular.[10,16,22] A recent study has identified a minimal set of factors for selecting patients at risk of full-spectrum PSCI.[21] The Rankin score represents an important step provided it is graded with a reliable informant, using a structured interview (including difficulties in instrumental activities of daily living).[23] Except in specific situations (e.g. return to a complex occupation), a comprehensive assessment might be considered to be futile in patients having regained all pre-stroke activities without any concerns (i.e., Rankin score=0), and in bedridden patients (i.e., Rankin score=5). In the same vein, comprehensive assessment is usually unnecessary for diagnosis in patients with substantial impairment on screening tests.

The administration of a comprehensive neuropsychological battery is the gold standard for the diagnosis of CI but may be complex to perform and not feasible in all stroke survivors and requires suitable quiet and uninterrupted settings. Hence, the first line of cognitive assessment usually relies on clinical examination and screening tests such as Informant Questionnaire on Cognitive Decline in the Elderly (mainly used to identify pre-stroke CI),[24] MiniMental Status Examination (MMSE)[25] and Montréal Cognitive Assessment (MoCA).[26] These instruments are a first step and may identify different severities of CI. We must acknowledge that MMSE and MoCA do not have interchangeable results. MoCA tests included more nonverbal and non-memory items (namely visuospatial/executive functions and attention) compared to MMSE. A recent systematic review indicated good to excellent accuracy, good internal consistency and good reliability of MoCA in differentiating between both mild CI and major CI patients from controls.[27] Nevertheless, despite the mildly higher sensitivity of MoCA as compared to MMSE,[27] a low specificity[28,29] still limits its use and both tests have only moderate to good sensitivity for the diagnosis of PSCI.[28–31] Thus, both tests underestimate the impairment in a significant proportion of affected patients, i.e. they miss about one fifth of cognitively impaired patients, a proportion which increases in mild PSCI. In addition, their specificity is also lower than 100%,[28,30,32] indicating that mildly decreased scores might be observed in subjects with normal comprehensive assessment. Score interpretation needs to take into account the first language, education level (for both tests) and age (for MoCA)[28,33]; their scores might also be influenced by sensorymotor deficit, deficits in language and perception (hemi-neglect). Hence, it important to highlight that screening tests scores need always to be integrated in the clinical context and in the whole condition of the patient, in order not to over value results of the screening tests.

Assessment of cognitive abilities is difficult in patients with severe aphasia. In such cases diagnosis of PSCI is usually made on the basis of an aphasia battery and screening test. Further assessment might be necessary to determine the cognitive profile (i.e. associated memory disturbances, executive dysfunction and action slowing). When comprehension abilities allow the use of cognitive tests, further cognitive assessment is usually based in non-verbal tests including visual recognition tests (such as the Doors test, for more details Table 2 in supplementary material), reasoning on visual material (such as Progressive Matrices), visual-motor tests assessing attention and processing speed (such as cancellation test, digit symbol modalities subtest).

Which tests should be used in patients with suspected CI due to CVD?

Considering the profile of vascular CI, a comprehensive test/battery should assess attention, action speed (also called psychomotor speed or processing speed), cognitive and behavioural executive functions, episodic

Table 2. MRI sequences in CI due to CVD should include:[59,80]

Sequence	Provides information on:
T1-weighted	Brain morphology, focal or diffuse atrophy
T2-weighted or fluid-attenuated inversion recovery (FLAIR)	White-matter hyperintensities, old vascular lesions
Diffusion-weighted imaging (DWI)	Number, size and location of most recent ischemic lesions
Susceptibility-weighted imaging (SWI)/GRE-T2*	Microbleeds, cortical superficial siderosis

memory, language, and visuo-constructive abilities as well as depressive symptoms. When needed, this first line of tests should be followed by optional tests assessing aphasia, hemi-neglect, agnosia, etc. Cognitive testing should anyway be adapted for the age and sociocultural context, beyond specific stroke deficits. The battery of tests is now standardized owing to the Harmonization Standards protocol battery.[34] This battery has been adapted into multiple languages and cultures and interestingly it provides similar cognitive profiles across countries, which sustains evidence for the robustness and generalizability of the included tests (detailed tests and references provided in Table 2 of supplemental material). Other studies have used neuropsychological assessment, albeit different, that permitted pooled analysis, including the main cognitive domains identified by harmonization standards protocol.[35]

Difficulties in activities of daily living (ADL) should be assessed using scales that can distinguish those difficulties due to CI (as needed for a diagnosis of major CI) from those due to sensory-motor deficit and less frequently, to psychiatric disorders,[4,5] as physical impairment can be a confounder for diagnosis.[10] As this distinction (critical for the diagnosis of major CI) may be challenging, some studies have used an adaptation of instrumental activities of daily living assessment, with additional questions and examination that identify the mechanism (sensory-motor, cognitive or psychiatric depressive) accounting for the decline of each activity.[10] This poorly investigated area still requires additional validation studies.

Predictors of CI

Several factors have been identified as predictive of future mild or major CI in patients with CVD disease. These factors can be informative for clinicians regarding counselling of patients and relatives as well as selection of patients for more intensive follow-up and for clinical trials.

Neuroimaging predictors of cognitive impairment in small vessel disease. In patients with cerebral SVD (but not necessarily with history of stroke), clinical status and brain magnetic resonance imaging (MRI) aid in predicting cognitive deterioration. While age and initial clinical status (cognitive and functional assessments) already predict future cognitive decline and incident dementia to a large extent, brain MRI has added value.[36] Although volumetric measures, such as total brain volume, white matter volume and hippocampal volume, emerged as the most consistent imaging predictors,[37,38] their practical use in non-specialized clinical settings is scarce. Baseline white matter hyperintensities (WMH) and lacunes (cavitated lesions) have also been identified as independent predictors.[37,39] More novel markers, such as diffusion (tensor) imaging and structural network analysis, show potential,[40,41] but still need further development and simplification to be applicable in clinical routine care.

Neuroimaging predictors of post-stroke cognitive impairment. Specific MRI markers as post-ischemic event predictors have been summarized in a recent review.[42] The most consistent neuroimaging predictors of PSCI, in addition to clinical predictors, were global and medial temporal lobe atrophy.[42,43] These data suggest that it might be beneficial to use brain imaging (computerized tomography - CT- or MRI) to identify stroke patients with these atrophy patterns. Volume and location of the infarct (including lacunes) and strategically-located infarcts were also found to be major predictors.[43] Interestingly, data from the large STRIDE study suggests that imaging predictors for PSCI may differ depending on the time point of CI symptom onset.[44] While early PSCI showed the strongest association with infarct features (mostly size and location), delayed PSCI was strongly associated with (pre-existing) SVD on MRI,[45] although these findings await replication in other studies. PSCI risk may differ according to stroke subtype, with an increased risk of CI for cardioembolic etiology and large artery atherosclerosis,[46,47] while others reported no differences after adjustment for other factors such as stroke severity and premorbid status,[48] or noted a significant progressive trend of CI among patients with small vessel disease and lacunes up to 5 years after stroke[47] (Table 1).

Pre-stroke brain pathology may contribute to cognitive decline after stroke by increasing the susceptibility to CI. Because of their high prevalence in the elderly, SVD and neurodegenerative pathology, in particular of the Alzheimer's disease (AD) type, are the most obvious candidate predictors. An association between pre-existing AD pathology detected by amyloid positron emission tomography (PET) and PSD early after stroke has indeed been shown.[49] However, several studies do not support a prominent role of amyloid pathology in delayed PSCI[50] or PSD,[45,51] i.e., CI occurring months to years after stroke.

MRI markers of SVD, such as WMH, lacunes, and cerebral microbleeds should be assessed since these all increase the risk of PSCI.[52] A large comprehensive systematic review and meta-analysis clearly demonstrates a strong association between increasing severity of WMH (on MRI or CT) and several adverse outcomes including subsequent dementia.[52] Nevertheless, this association becomes less strong with aging, when degenerative pathology (AD type) probably superimposed on the impact of WMH.[53] However, many studies did not account for factors such as premorbid cognitive ability or resilience/reserve (discussed below), which may partly account for the apparent 'looseness' of the association between WMH burden and cognition.[54] Given these results, the effect of some other predictors of delayed PSCI, such as diabetes, might at least in part be mediated by cerebral SVD, and is potentially modifiable through better risk factor control. The fact that delayed CI occurs months to years after the initial stroke might open a time window for therapeutic interventions, again emphasizing the importance of risk factor treatment after the acute event.

From a practical point of view, infarct volume and location, in combination with WMH, microbleeds and atrophy (globally and medial temporal lobe), may be the most important neuroimaging predictors of PSCI,[51] providing added value on top of clinical variables.

Finally, it should be mentioned that predictors of minor and major CI after ischemic stroke and after intracerebral haemorrhage appear to be largely similar,[22] with haemorrhagic stroke associated with an increased risk of PSCI compared with ischemic stroke.[48,55]

Clinical predictors. Predictors are of particular interest in the context of PSCI, to identify patients at high-risk for CI promptly identified after the acute event. Multiple studies on PSCI identified predictors related to the concept of brain resilience or reserve.[44] This concept addresses the phenomenon that the same level of brain pathology leads to different levels of CI depending on the premorbid condition of the brain and presumably its ability to actively compensate for the damage.[56] Or. in other words, lower resilience leads to a greater susceptibility for PSCI. Predictive factors attributable to the concept of resilience or reserve are level of education, early-life intelligence (also reflected in type of job), leisure activities, as well as employment and relationship status pre-stroke.[10,57–60]

The Oxford Vascular Study[22] is at present the largest prospective incidence study for PSD. Stroke severity as measured by the National Health Institutes Stroke Scale (NIHSS)[61] score was one of the strongest predictors of PSD. Other factors were age, previous stroke, recurrent stroke, dysphasia, baseline cognition, low education, pre-morbid dependency, leukoaraiosis - on brain imaging-, and diabetes. The latter is of particular interest for clinicians, since it was the only vascular risk factor associated with PSD. This suggests that intensified risk factor management post-stroke might be most effective in the case of diabetes, or reflect that hypertension and hyperlipidaemia are already now well managed. Recent data from the same study found that APOE e4 homozygosity was associated with PSD, reinforcing the conviction of the influence of a previous neurodegenerative pathology.[62]

Still concerning stroke survivors, a combined cognitive risk score based on four easily documented factors (severity of neurological deficit, presence of multiple strokes, multiple deep WMH corresponding to Fazekas score ≥ 2 and a mild decrease of MMSE score, i.e., adjusted MMSE score from 21 to 27) provided a very good screening strategy[21] but remains to be tested independently and more widely in other cohorts before adoption into practice.

A last word considering age. Although age is an important predictor, PSCI, both acute and delayed, is not infrequent in young stroke survivors, and considering relative risk (although not absolute risk), the dementia risk is greater in younger populations.[16,22] Inspite of that, predictors of post-stroke cognitive status in this subpopulation are largely understudied.[63,64]

Complementary investigations not to be missed

The large clinical and neuroimaging heterogeneity of CI due to CVD explains the difficulty of developing a standardized medical evaluation in the clinical setting for all types of CI due to CVD.[65,66]

It should go without saying that all patients who are seen in a CVD clinic have a comprehensive evidence-based vascular risk factors assessment[67,68] and a work-up for determining the stroke subtype and potential underlying mechanism.[69–71] The underlying source of vascular brain damage should be pursued in all CI due to CVD patients[72] in order to prevent subsequent/recurrent strokes.

Clinical assessment of patients with CI due to CVD should include the analysis of typical cognitive changes (described above) but also the recognition of non-

cognitive manifestations of CVD such as depression, apathy, motor disability, gait difficulties, balance problems, sensorimotor deficit(s), sphincter control dysfunction, parkinsonism, pseudobulbar palsy and all their possible functional consequences in daily life (Table 1).

While functional outcome in patients surviving acute stroke is well-established, comprising measures of disability (modified Rankin scale score)[73] and functional independence (Barthel Index),[74] other aspects of activities and functional disturbances in daily living are multifaceted, nuanced, difficult to delineate and not well assessed using specific tools.[65,66,75–77] Cognitive impairment and executive dysfunction, in particular, as well as depression and apathy, may all have a significant impact on patients' functional abilities and independence.[78] One practical way to assess this impact is using the interview, with a relative/caregiver. The interview should include aspects mentioned before in "how to recognize cognitive impairment/complaints" such as abandonment of leisure activities, change of habits.

Laboratory analysis in CI due to CVD

No specific laboratory analysis or biomarker in the blood or cerebrospinal fluid (CSF) is available yet for determining the exact vascular injury responsible for CI due to CVD.[67] However, blood laboratory tests can help identify and monitor vascular risk factors.

In patients with SVD, CSF studies may help in differential diagnosis of inflammatory myelin disorders or to exclude vasculitis.[79] CSF protein examination can provide evidence of blood-brain barrier disruption (increased $albumin_{CSF}$ to $albumin_{blood\ ratio}$).[60,79]

Analysis of CSF markers of cortical neuronal degeneration and amyloid pathology may help in detecting mixed etiologies (namely with AD -reduced amyloid β1-42 - also detected in amyloid angiopathy - associated with increased phosphorylated-tau).[79] Other multiple markers are so far of limited value in clinical practice,[80–83] such as serum and CSF inflammatory markers, markers of extracellular matrix breakdown (matrix metalloproteinases) or of neuroaxonal damage (serum neurofilament light chain), markers of hypercoagulable state, oxidative stress as well as other metabolic markers (e.g., homocysteine).

Neuroimaging in CI due to CVD

Neuroimaging will have been performed in most patients in the acute setting to assess the stroke subtype, and to plan the secondary prevention strategy at individual level (Table 3 in supplementary material).[66,72,84,85] This imaging can also support the evaluation of the likely cause of CI. In this context, the best imaging tool is brain MRI, which can be considered as the gold standard for diagnosis of CI due to CVD,[65] although CT scanning is the most widely available method and provides relevant information on stroke type and pre-stroke brain changes including leukoaraiosis and atrophy. MRI examination should include sequences shown in Table 2.

MRI can also show suggestive patterns of lesions in favor of specific underlying disorders; Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is often associated with temporal pole T2 hyperintensities; cerebral amyloid angiopathy (CAA) often leads to lobar macro- and microbleeds and cortical superficial siderosis.[86,87] Diffusion tensor imaging that can probe the microstructure of white matter (even in otherwise normal appearing brain tissue), as well various refined MRI modalities (high-resolution MRI systems, proton NMR spectroscopy and dynamic contrast-enhanced MRI) can provide information about the tissue status but are not used in daily clinical practice.[40,79,88] Neuroimaging acquisition, interpretation and reporting of cerebral SVD are now better standardized, and the Standards for ReportIng Vascular changes in nEuroimaging (STRIVE) criteria have been proposed to better define MRI lesions.[89] In patients with MRI contraindications, CT scans can depict atrophy, intracranial haemorrhage, acute and old infarcts, and, to a lesser degree, lacunes and extensive WMH.[67] The use of fluorodeoxyglucose -PET is not helpful for differentiating AD from patients with vascular pathology.[90] In a recent meta-analysis, PET amyloid positivity (a classical feature in presence of CAA or AD) has been reported in elderly APOE ε4 carriers meeting the criteria of VD, and a further increase may be observed in PSD subjects,[50,67,91] suggesting a contribution from AD pathology, and a mixed etiology in older patients with PSD.

Integration of diagnostic information and diagnostic labels

Complementary investigations may be needed for the differential diagnosis of MRI-identified lesions (e.g. vascular versus demyelinating lesions in younger patients, or differential diagnosis of white matter lesions at different ages)[92,93] or for identifying associated disorders, particularly neurodegenerative conditions that develop with aging.[79] In hereditary forms of CI due to CVD, the patient should be referred to a comprehensive center enabling diagnosis of genetic diseases which can help to reduce unnecessary diagnostic procedures and implement treatment strategies.

Treatment to improve cognition in patients with CI due to CVD

Currently, there is no specifically approved treatment for CI due to CVD. A systematic review of cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and N-methyl-d-aspartate receptor antagonists (memantine) suggested that these drugs improved cognition in CI due to CVD, but did not improve behaviour or functional status.[94,95] It should be noted, however, that due to the limitations of inclusion and diagnostic criteria, the vascular origin of cognitive impairment could not be determined in all participants in any of the trials. More dropouts and adverse events (anorexia, nausea, vomiting, diarrhea, and insomnia) occurred with cholinesterase inhibitors compared with memantine. In CADASIL, a pure form of VD,[96] the use of donepezil was also found to improve some executive performances but without improving activities of daily living.[97] Hence, these drugs are not recommended when CI or dementia is of purely vascular origin. However, they can be considered at individual level when the vascular component of dementia is associated with a degenerative disease such as AD, which might be the case in many patients seen in daily practice, particularly older patients.

No significant effect was detected on CI due to CVD using nimodipine, piracetam, huperzine A, cytidine diphosphocholine and vinpocetine. Other molecules have shown a limited benefit in patients with CI due to CVD (dl-3-n-butylphthalide, gingko biloba extract, cerebrolysin, actogevin).[72,98] The results were obtained in small samples or only in subgroups of individuals and were not replicated at large scale. Therefore, we see no evidence to recommend these drugs in patients with CI due to CVD.

In conclusion, the use of cholinesterase inhibitors and memantine might be considered in patients with CI due to CVD only very cautiously and on a case-by-case basis where AD is thought to contribute, depending on the authorization available in the country, the individual tolerance of the treatment and the perceived benefit during follow-up.

Prevention in patients with CI due to CVD

In patients with CI due to CVD or at risk of developing CI of vascular origin, it is obviously crucial to prevent the occurrence of any new stroke event or incident cerebrovascular lesion. The assessment of the underlying CVD and all measures to reduce its progression should be undertaken in all patients.

Control of vascular risk factors and lifestyle changes have limited effects at cognitive level, with exception of hypertension (with suggestions of some benefit from randomized studies),[99] but globally, multi-domain interventions, including non-pharmacologic and lifestyle modifications showed no consistent benefit in cognition in stroke survivors.[100–103]

Patients with CI due to CVD should be treated as usually recommended after the occurrence of an acute ischemic or haemorrhagic stroke.[104] In patients with a past history of ischemic stroke, there is accumulating evidence suggesting that the number of microbleeds on MRI imaging should no longer be considered as a contra-indication to antithrombotic drugs.[105] Recent data support that in the vast majority of cases, the absolute risk of ischemic events largely exceeds that of haemorrhages. Only the presence of lobar haemorrhage in probable CAA, anticoagulant should be thoroughly discussed dependent on the level of risk of ischemic events.

Particular attention must be paid to patients with CI due to CVD when cognitive deficits are severe, to assess the risk related to therapeutic compliance, including errors or misunderstanding regarding the use of antithrombotic treatments.[106] In some individuals, a caregiver may be needed to control the treatment administration. When in doubt, treatments that expose a high risk of complications might be avoided.

Reperfusion therapies in presence of CI

There is no study examining specifically the potential of thrombolysis or thrombectomy to treat acute ischemic stroke in patients with CI due to CVD. However, the risk of death and haemorrhage is not increased in persons suffering from dementia[107] and there is some evidence that persons with dementia may benefit as do other acute stroke patients from intravenous rt-PA.[108] Therefore, thrombolysis or thrombectomy should be considered in all acute stroke patients including those with CI due to CVD. However, the premorbid level of function, quality of life, social support and life expectancy should be weighted whenever possible before deciding to treat as they can be major determining factors in outcome.[107]

Hence, the use of cerebral reperfusion therapies should not be ruled out in patients with CI. Individual decisions of not to treat maybe taken, namely in situations where autonomy is already severely affected and when large lesions cannot be significantly reduced by the treatment.

Discussion and conclusion

Additional investigations are needed to improve the management of cognitive disorders due to cerebrovascular pathology. The development of innovative preventive therapies in stroke patients that can further

reduce the risk of vascular brain damage will remain the best guarantee for decreasing the risk of cognitive decline. Any progress in the management of all types of CVD will be essential in this context.

Since the benefit of some specific pharmacologic agents may vary depending on the distribution and severity of cerebral damage, importance of brain and cognitive reserve, but also on age, gender, metabolic or genetic factors, new strategies that could better integrate complex parameters at individual level should be considered in future clinical trials for developing a personalized approach to management.

The potential of various types of neuroprotective agents for reducing cerebral tissue damage in CVD needs further investigations. eHealth interventions for improving prevention, clinical follow-up and treatment will need specific studies. This approach might be also used in the near future to enable innovative numeric rehabilitation and regular counselling via internet platforms.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Olivier Godefroy during the last five years has served on scientific advisory boards and speaker (Biogen, Astra Zeneca, Novartis) and received funding for travel and meetings from Bristol-Myers Squibb, Roche, Biogen, Teva-santé, Boehringer-Ingelheim, Covidien, Ipsen. The remaining authors declare that there are no conflict of interest concerning the paper.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Informed consent for patient information to be published in this article was not obtained because this was an audit.

Guarantor

AV.

Contributorship

All authors contributed equally to conceive the manuscript, the structure of paper, literature research and writing of the manuscript. All authors contributed to the different stages of the manuscript, reviewed and edited and finally approved the final version of the manuscript.

Acknowledgements

We thank Professor Franz Fazekas from the Medical University of Graz, Austria for his contribution on this paper and we thank the European Stroke Organization for supporting and for the endorsing this initiative.

ORCID iDs

Ana Verdelho https://orcid.org/0000-0003-4945-4946
Joanna Wardlaw https://orcid.org/0000-0002-9812-6642
Leonardo Pantoni https://orcid.org/0000-0001-7357-8530

References

1. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet* 2017; 390: 2673–2734.
2. METACOHORTS Consortium. METACOHORTS for the study of vascular disease and its contribution to cognitive decline and neurodegeneration: an initiative of the Joint Programme for Neurodegenerative Disease Research. *Alzheimers Dement* 2016; 12: 1235–1249.
3. Pollock A, St George B, Fenton M, et al. Top 10 research priorities relating to life after stroke–consensus from stroke survivors, caregivers, and health professionals. *Int J Stroke* 2014; 9: 313–320.
4. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993; 43: 250–260.
5. Sachdev P, Kalaria R, O'Brien J, et al. International society for vascular behavioral and cognitive disorders. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer Dis Assoc Disord* 2014; 28: 206–218.
6. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. Arlington: American Psychiatric Association, 2013.
7. Vermeer S E, Prins ND, den Heijer T, et al. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med* 2003; 348: 1215–1222.
8. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment–beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment. *J Intern Med* 2004; 256: 240–246.
9. Pendlebury ST, Mariz J, Bull L, et al. Impact of different operational definitions on mild cognitive impairment rate and MMSE and MoCA performance in transient ischaemic attack and stroke. *Cerebrovasc Dis* 2013; 36: 355–362.
10. Barbay M, Taillia H, Nédélec-Ciceri C, et al. Prevalence of post-stroke neurocognitive disorders using NINDS-CSN, VASCOG criteria and optimized criteria of cognitive deficit. *Stroke* 2018b; 49; 1141–1147.
11. Barbay M, Diouf M, Roussel M, et al, on behalf of the GRECOG-VASC study group. Prevalence of mild and major post-stroke neurocognitive disorders in hospital-based studies: a systematic review and meta-analysis. *Dementia Ger Cogn Dis* 2018a; 46: 322–334.
12. Godefroy O, Leclercq C and Roussel M. Vascular cognitive impairment in the stroke unit and after the acute stage. In: Godefroy O (ed) *Behavioral and cognitive neurology of stroke*. 2nd ed. Cambridge: Cambridge University Press, 2013, pp. 22–31.
13. Hurford R, Charidimou A, Fox Z, et al. Domain-specific trends in cognitive impairment after acute ischaemic stroke. *J Neurol* 2013; 260: 237–241.
14. Nijsse B, Visser-Meily JM, Van Mierlo ML, et al. Temporal evolution of poststroke cognitive impairment using the Montreal Cognitive Assessment. *Stroke* 2017; 48: 98–104.
15. Tatemichi TK, Desmond DW, Stern Y, et al. Cognitive impairment after stroke: frequency, patterns, and relationship to functional abilities. *J Neurol Neurosurg Psychiatry* 1994; 57: 202–207.
16. Pendlebury ST and Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol* 2009; 8: 1006–1018.
17. Pasquini M, Leys D, Rousseaux M, et al. Influence of cognitive impairment on the institutionalization rate 3 years after a stroke. *J Neurol Neurosurg Psychiatry* 2007; 78: 56–59.
18. Saposnik G, Cote R, Rochon PA, et al. Registry of the Canadian Stroke Network; Stroke Outcome Research Canada (SORCan) Working Group. Care and outcomes in patients with ischemic stroke with and without preexisting dementia. *Neurology* 2011; 77: 1664–1673.
19. Moroney JT, Bagiella E, Tatemichi TK, et al. Dementia after stroke increases the risk of long-term stroke recurrence. *Neurology* 1997; 48: 1317–1325.
20. Lee M, Saver JL, Hong KS, et al. Cognitive impairment and risk of future stroke: a systematic review and meta-analysis. *Can Med Assoc J* 2014; 186: E536–E546.
21. Godefroy O, Yaiche H, Taillia H, et al. Who should undergo a comprehensive cognitive assessment after a stroke? A cognitive risk score. *Neurology* 2018; 91: e1979–e1987.
22. Pendlebury ST and Rothwell PM. Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based Oxford Vascular Study. *Lancet Neurol* 2019; 18: 248–258.
23. Godefroy O, Just A, Ghitu A, et al. Rankin scale with revised structured interview. *Int J Stroke* 2012; 7: 183–184.
24. Jorm AF. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation. *Psychol Med* 1994; 24: 145–153.
25. Folstein MF, Folstein SE and McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189–198.
26. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005; 53: 695–699.
27. Ghafar MZAA, Miptah HN and O'Caoimh R. Cognitive screening instruments to identify vascular cognitive impairment: a systematic review. *Int J Geriatr Psychiatry* 2019; 34: 1114–1127.
28. Godefroy O, Fickl A, Roussel M, et al. Is the Montreal Cognitive Assessment superior to the mini-mental state examination to detect post-stroke cognitive impairment? A study with neuropsychological evaluation. *Stroke* 2011; 42: 1712–1716.
29. Chan E, Khan S, Oliver R, et al. Underestimation of cognitive impairments by the Montreal Cognitive Assessment (MoCA) in an acute stroke unit population. *J Neurol Sci* 2014; 343: 176–179.
30. Lees R, Selvarajah J, Fenton C, et al. Test accuracy of cognitive screening tests for diagnosis of dementia and multidomain cognitive impairment in stroke. *Stroke* 2014; 45: 3008–3018.
31. McGovern A, Pendlebury ST, Mishra NK, et al. Test accuracy of informant-based cognitive screening tests for diagnosis of dementia and multidomain cognitive impairment in stroke. *Stroke* 2016; 47: 329–335.
32. Rodrigues JC, Becker N, Beckenkamp CL, et al. Psychometric properties of cognitive screening for patients with cerebrovascular diseases: a systematic review. *Dement Neuropsychol* 2019; 13: 31–43.
33. Rossetti HC, Lacritz LH, Cullum CM, Weiner MF. Normative data for the Montreal Cognitive Assessment (MoCA) in a population-based sample. *Neurology* 2011; 77:1272–1275.
34. Hachinski V, Iadecola C, Petersen RC, et al. National institute of neurological disorders and stroke-Canadian stroke network vascular cognitive impairment harmonization standards. *Stroke* 2006; 37: 2220–2224.
35. Sachdev PS, Lo JW, Crawford JD, 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. *Alzheimers Dement (Amst)* 2016; 7: 11–23.
36. Chabriat H, Herve D, Duering M, et al. Predictors of clinical worsening in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: prospective cohort study. *Stroke* 2016; 47: 4–11.
37. Jouvent E, Duchesnay E, Hadj-Selem F, et al. Prediction of 3-year clinical course in CADASIL. *Neurology* 2016; 87: 1787–1795.
38. van Uden IW, van der Holst HM, Tuladhar AM, et al. White matter and hippocampal volume predict the risk of dementia in patients with cerebral small vessel disease: the RUN DMC study. *J Alzheimers Dis* 2016; 49: 863–873.
39. Pavlovic AM, Pekmezovic T, Tomic G, et al. Baseline predictors of cognitive decline in patients with cerebral small vessel disease. *J Alzheimers Dis* 2014; 42: S37–S43.
40. Baykara E, Gesierich B, Adam R, et al. A novel imaging marker for small vessel disease based on skeletonization of white matter tracts and diffusion histograms. *Ann Neurol* 2016; 80: 581–592.
41. Tuladhar AM, van Uden IW, Rutten-Jacobs LC, et al. Structural network efficiency predicts conversion to dementia. *Neurology* 2016; 86: 1112–1119.

42. Casolla B, Caparros F, Cordonnier C, et al. Biological and imaging predictors of cognitive impairment after stroke: a systematic review. *J Neurol* 2018.
43. Puy L, Barbay M, Roussel M, et al. Neuroimaging determinants of poststroke cognitive performance. *Stroke* 2018; 49: 2666–2673.
44. Mok VC, Lam BY, Wong A, et al. Early-onset and delayed-onset poststroke dementia—revisiting the mechanisms. *Nat Rev Neurol* 2017; 13: 148–159.
45. Mok VCT, Lam BYK, Wang Z, et al. Delayed-onset dementia after stroke or transient ischemic attack. *Alzheimers Dement* 2016; 12: 1167–1176.
46. Levine DA, Wadley VG, Langa KM, et al. Risk factors for poststroke cognitive decline: the REGARDS study (reasons for geographic and racial differences in stroke). *Stroke* 2018; 49: 987–994.
47. Douiri A, Rudd AG, Wolfe CDA. Prevalence of poststroke cognitive impairment: South London Stroke Register 1995-2010. *Stroke* 2013; 44: 138–145.
48. Aam S, Einstad MS, Munthe-Kaas R, et al. Post-stroke cognitive impairment-impact of follow-up time and stroke subtype on severity and cognitive profile: the nor-COAST study. *Front Neurol* 2020; 11: 699.
49. Yang J, Wong A, Wang Z, et al. Risk factors for incident dementia after stroke and transient ischemic attack. *Alzheimers Dement* 2015; 11: 16–23.
50. Wollenweber FA, Darr S, Muller C, et al. Prevalence of amyloid positron emission tomographic positivity in poststroke mild cognitive impairment. *Stroke* 2016; 47: 2645–2648.
51. Allan LM, Rowan EN, Firbank MJ, et al. Long term incidence of dementia, predictors of mortality and pathological diagnosis in older stroke survivors. *Brain* 2011; 134: 3716–3727.
52. Georgakis MK, Duering M, Wardlaw JM, et al. WMH and long-term outcomes in ischemic stroke: a systematic review and meta-analysis. *Neurology* 2019; 92: e1298–e1308.
53. Zamboni G, Griffanti L, Jenkinson M, et al. White matter imaging correlates of early cognitive impairment detected by the Montreal Cognitive Assessment after transient ischemic attack and minor stroke. *Stroke* 2017; 48: 1539–1547.
54. Ritchie SJ, Bates TC and Deary IJ. Is education associated with improvements in general cognitive ability, or in specific skills? *Dev Psychol* 2015; 51: 573–582.
55. Corraini P, Henderson VW, Ording AG, et al. Long-term risk of dementia among survivors of ischemic or hemorrhagic stroke. *Stroke* 2017; 48: 180–186.
56. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol* 2012; 11: 1006–1012.
57. Chen X, Duan L, Han Y, et al. Predictors for vascular cognitive impairment in stroke patients. *BMC Neurol* 2016; 16: 115.
58. Mahon S, Parmar P, Barker-Collo S, et al. Determinants, prevalence, and trajectory of long-term post-stroke cognitive impairment: results from a 4-year follow-up of the ARCOS-IV study. *Neuroepidemiology* 2017; 49: 129–134.
59. Wong A, Lau AY, Lo E, et al. Relations between recent past leisure activities with risks of dementia and cognitive functions after stroke. *PLoS One* 2016; 11: e0159952.
60. Makin SD, Doubal FN, Shuler K, et al. The impact of early-life intelligence quotient on post stroke cognitive impairment. *European Stroke Journal* 2018; 3: 145–156.
61. Lyden P, Brott T, Tilley B, et al. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. *Stroke* 1994; 25: 2220.
62. Pendlebury ST, Poole D, Burgess A, et al. APOE-ε4 genotype and dementia before and after transient ischemic attack and stroke: population-based cohort study. *Stroke* 2020; 51: 751–758.
63. Schaapsmeerders P, Maaijwee NA, van Dijk EJ, et al. Long-term cognitive impairment after first-ever ischemic stroke in young adults. *Stroke* 2013; 44: 1621–1628.
64. Synhaeve NE, Schaapsmeerders P, Arntz RM, et al. Cognitive performance and poor long-term functional outcome after young stroke. *Neurology* 2015; 85: 776–782.
65. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011; 42: 2672–2713.
66. Jaul E and Meiron O. Systemic and disease-specific risk factors in vascular dementia: diagnosis and prevention. *Front Aging Neurosci* 2017; 9: 333.
67. Van der Flier WM, Skoog I, Schneider JA, et al. Vascular cognitive impairment. *Nat Rev Dis Primers* 2018; 4: 18003.
68. Biessels GJ. Diagnosis and treatment of vascular damage in dementia. *Biochim Biophys Acta* 2016; 1862: 869–877.
69. Amarenco P, Bogousslavsky J, Caplan LR, et al. The ASCOD phenotyping of ischemic stroke (updated ASCO phenotyping). *Cerebrovasc Dis* 2013; 36: 1–5.
70. Sirimarco G, Lavallée PC, Labreuche J, et al. Overlap of diseases underlying ischemic stroke: the ASCOD phenotyping. *Stroke* 2013; 44: 2427–2433.
71. Graff-Radford J. Vascular cognitive impairment. *Continuum (Minneap Minn)* 2019; 25: 147–164.
72. Amarenco P, Bogousslavsky J, Caplan LR, et al. New approach to stroke subtyping: the A-S-C-O (phenotypic) classification of stroke. *Cerebrovasc Dis* 2009; 27: 502–508.
73. Wilson J, Harendran A, Grant M, et al. Improving the assessment of outcomes in stroke: use off a structured interview to assign grades on the modified rankin scale. *Stroke* 2002; 33: 2243–2246.
74. Mahoney RI and Barthel DW. Functional evaluation: the Barthel Index. *Md Sate Mod J* 1965; 14: 61–65.
75. Sheehan B. Assessment scales in dementia. *Ther Adv Neurol Disord* 2012; 5: 349–358.
76. Inzitari D, Pracucci G, Poggesi A, et al. Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort. *Br Med J* 2009; 339: b2477.
77. Pantoni L, Fierini F, Poggesi A, et al. Impact of cerebral white matter changes on functionality in older adults: an overview of the LADIS Study results and future directions. *Geriatr Gerontol Int* 2015; 15: 10–16.
78. van Wanrooij LL, Borsboom D, Moll van Charante EP, et al. A network approach on the relation between apathy and depression symptoms with dementia and functional disability. *Int Psychogeriatr* 2019; 31: 1655–1663.
79. Rosenberg GA, Wallin A, Wardlaw JM, et al. Consensus statement for diagnosis of subcortical small vessel disease. *J Cereb Blood Flow Metab* 2016; 36: 6–25.
80. Wallin A, Kapaki E, Boban M, et al. Biochemical markers in vascular cognitive impairment associated with subcortical small vessel disease – a consensus report. *BMC Neurol* 2017; 17: 102.
81. Wallin A, Román GC, Esiri M, et al. Update on vascular cognitive impairment associated with subcortical small-vessel disease. *J Alzheimers Dis* 2018; 62: 1417–1441.
82. McCleery J, Abraham RP, Denton DA, et al. Vitamin and mineral supplementation for preventing dementia or delaying cognitive decline in people with mild cognitive impairment. *Cochrane Database Syst Rev* 2018; 11: CD011905.
83. Duering M, Konieczny MJ, Tiedt S, et al. Serum neurofilament light chain levels are related to small vessel disease burden. *J Stroke* 2018; 20: 228–238.
84. Skrobot OA, O'Brien J, Black S, et al. The vascular impairment of cognition classification consensus study. *Alzheimers Dement* 2017; 13: 624–633
85. Haeusler KG, Wilson D, Fiebach JB, et al. Brain MRI to personalise atrial fibrillation therapy: current evidence and perspectives. *Heart* 2014; 100: 1408–1413.
86. Greenberg SM and Charidimou A. Diagnosis of cerebral amyloid angiopathy: evolution of the Boston criteria. *Stroke* 2018; 49: 491–497.
87. Chabriat H, Joutel A, Dichgans M, et al. CADASIL. *Lancet Neurol* 2009; 8: 643–653.
88. van Veluw SJ, Shih AY, Smith EE, et al. Detection, risk factors, and functional consequences of cerebral microinfarcts. *Lancet Neurol* 2017; 16: 730–740.
89. Wardlaw JM, Smith EE, Biessels GJ, et al; STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013; 12: 822–838.
90. Nestor PJ, Altomare D, Festari C, et al. Clinical utility of FDG-PET for the differential diagnosis among the main forms of dementia. *Eur J Nucl Med Mol Imaging* 2018; 45: 1509–1525.
91. Ossenkoppele R, Jansen WJ, Rabinovici GD, et al. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. *J Am Med Assoc* 2015; 313: 1939–1949.
92. O'Brien JT and Thomas A. Vascular dementia. *Lancet* 2015; 386: 1698–1706.
93. Sarbu N, Shih RY, Jones RV, et al. White matter diseases with radiologic-pathologic correlation. *Radiographics* 2016; 36: 1426–1447.
94. Kavirajan H and Schneider LS. Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomized controlled trials. *Lancet Neurol* 2007; 6: 782–792.
95. McShane R, Westby MJ, Roberts E, et al. Memantine for dementia. *Cochrane Database Syst Rev* 2019; 3: CD003154.
96. Salloway S, Dichgans M, Markus H, et al. Efficacy of donepezil in CADASIL: a model of subcortical vascular cognitive impairment. *Neurology* 2008; 71: 155.
97. Dichgans M, Markus HS, Salloway S, et al. Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. *Lancet Neurol* 2008; 7: 310–318.
98. Paradise MB and Sachdev PS. Vascular cognitive disorder. *Semin Neurol* 2019; 39: 241–250.
99. Van Dalen, Willem J, Moll EP, et al. Effect of long-term vascular care on progression of cerebrovascular lesions: magnetic resonance imaging substudy of the PreDIVA trial (prevention of dementia by intensive vascular care). *Stroke* 2017; 48: 1842–1848.
100. Brainin M, Matz K, Nemec M, et al. Prevention of poststroke cognitive decline: ASPIS – a multicenter, randomized, observer-blind, parallel group clinical trial to evaluate multiple lifestyle interventions–study design and baseline characteristics. *Int J Stroke* 2015; 10: 627–635.
101. Matz K, Teuschl Y, Firlinger B et al. Multidomain lifestyle interventions for the prevention of cognitive decline after ischemic stroke: randomized trial. *Stroke* 2015; 46: 2874–2880.
102. Teuschl Y, Ihle-Hansen H, Matz K, et al. Multidomain intervention for the prevention of cognitive decline after stroke – a pooled patient-level data analysis. *Eur J Neurol* 2018; 25: 1182–1188.
103. Teuschl Y, Matz K, Firlinger B, et al. Preventive effects of multiple domain interventions on lifestyle and risk factor changes in stroke survivors: evidence from a two-year randomized trial. *Int J Stroke* 2017; 12: 976–984.
104. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014; 45: 2160–2236.

105. Wilson D, Ambler G, Lee KJ, et al. Cerebral microbleeds and stroke risk after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies. *Lancet Neurol* 2019; 18: 653–665.
106. El-Saifi N, Moyle W, Jones C, et al. Medication adherence in older patients with dementia: a systematic literature review. *J Pharm Pract* 2018; 31: 322–334.
107. Alshekhlee A, Li CC, Chuang SY, et al. Does dementia increase risk of thrombolysis?: a case-control study. *Neurology* 2011; 76: 1575–1580.
108. Paciaroni M, Pantoni L. Thrombolysis in dementia patients with acute stroke: is it justified? *Neurol Sci* 2017; 38: 27–31.

Review

EUROPEAN STROKE JOURNAL

European Stroke Journal
2021, Vol. 6(2) 111–119

DOI: 10.1177/2396987321994294
journals.sagepub.com/home/eso
SAGE

Cerebrovascular disease in patients with cognitive impairment: A white paper from the ESO dementia committee – A practical point of view with suggestions for the management of cerebrovascular diseases in memory clinics

Ana Verdelho[1], Geert Jan Biessels[2], Hugues Chabriat[3], Andreas Charidimou[4,5], Marco Duering[6,7], Olivier Godefroy[8], Leonardo Pantoni[9], Aleksandra Pavlovic[10] and Joanna Wardlaw[11]

Abstract

Purpose: Practical suggestions on clinical decisions about vascular disease management in patients with cognitive impairment are proposed.

Methods: The document was produced by the Dementia Committee of the European Stroke Organisation (ESO) based on the evidence from the literature where available and on the clinical experience of the Committee members. This paper was endorsed by the ESO.

Findings: Vascular risk factors and cerebrovascular disease are frequent in patients with cognitive impairment. While acute stroke treatment has evolved substantially in last decades, evidence of management of cerebrovascular pathology beyond stroke in patients with cognitive impairment and dementia is quite limited. Additionally, trials to test some daily-life clinical decisions are likely to be complex, difficult to undertake and take many years to provide sufficient evidence to produce recommendations. This document was conceived to provide some suggestions until data from field trials are available. It was conceived for the use of clinicians from memory clinics or involved specifically in cognitive disorders, addressing practical aspects on diagnostic tools, vascular risk management and suggestions on some therapeutic options.

Discussion and conclusions: The authors did not aim to do an exhaustive or systematic review or to cover all current evidence. The document approach in a very practical way frequent issues concerning cerebrovascular disease in patients with known cognitive impairment.

[1]Department of Neurosciences and Mental Health, CHLN-Hospital de Santa Maria, Instituto de Medicina Molecular – IMM e Instituto de Saude Ambiental-ISAMB, Faculdade de Medicina. University of Lisbon, Lisbon, Portugal
[2]Department of Neurology, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, the Netherlands
[3]Department of Neurology, FHU NeuroVasc, Hôpital Lariboisiere, University of Paris and INSERM U1141, Paris, France
[4]Hemorrhagic Stroke Research Program, J. Philip Kistler Stroke Research Center, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[5]Department of Neurology, Boston Medical Center, Boston University School of Medicine, Boston, MA, USA
[6]Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Germany
[7]Medical Image Analysis Center (MIAC AG) and qbig, Department of Biomedical Engineering, University of Basel, Basel, Switzerland
[8]Departments of Neurology, Amiens University Hospital, and Laboratory of Functional Neurosciences1,6 (UR UPJV 4559), Jules Verne Picardy University, Amiens, France
[9]Stroke and Dementia Lab, "Luigi Sacco" Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy
[10]Faculty for Special Education and Rehabilitation, University of Belgrade, Belgrade, Serbia
[11]Centre for Clinical Brain Sciences, UK Dementia Research Institute, University of Edinburgh, Edinburgh, UK

Corresponding author:
Ana Verdelho, Department of Neurosciences, Hospital de Santa Maria, University of Lisbon, Av Prof. Egas Moniz, Lisbon, Portugal.
Email: averdelho@medicina.ulisboa.pt

Keywords
Cerebrovascular disease, cognitive impairment, dementia, small vessel disease, stroke

Date received: 9 October 2020; accepted: 19 January 2021

Introduction

Dementia and stroke share several modifiable vascular risk factors and are risk factors for each other.[1–3] Hence, patients with cognitive impairment (CI) who are seen at memory clinics frequently present with vascular risk factors and cerebrovascular disease. Furthermore, cerebrovascular disease contributes to clinical symptoms that may aggravate or anticipate the clinical expression of underlying degenerative brain pathology There is a lack of evidence on the treatment of cerebrovascular disease in patients with CI.[4,5] Uncertainty about management of vascular risk factors and cerebrovascular disease in people affected by CI might lead to heterogeneity in the treatment of those patients. In addition, professionals from memory clinics may have less experience in the recognition and in the appropriate management of cerebrovascular disease. The aim of this paper is to help reducing this potential knowledge gap, while waiting for appropriate field trials.

Methods

This document is a white paper produced by the Dementia Committee members, and endorsed by the European Stroke Organization, aiming to give practical clinical suggestions for the management and treatment of cerebrovascular disease in patients with cognitive disorders. It was meant for the use of professionals involved in the management of patients with CI, including medical specialists, general practitioners, but also non-medical professionals interested in CI and dementia, in order to help clinical decisions. Content is not a result of a systematic review, but rather based on relevant literature and on the clinical experience of the authors

In this paper an effort was made to incorporate differences of approach and access to ancillary investigations, keeping in mind the standard usual best practice from a cerebrovascular disease perspective. For a practical use, cognitive impairment (CI) include patients with objective cognitive impairment regardless of having or not criteria for dementia. Subjective cognitive impairment refers to subjective complaints of decline in cognition without confirmation of decline on objective cognitive assessment.

Findings

Clinical expression of cerebrovascular contribution in CI

Cognitive and behavioral manifestations. Once a patient is seen in a memory clinic and the diagnosis of CI has been confirmed, the possible presence, coexistence, or relevance of a cerebrovascular component in the etiology of CI should be considered. Identification of cerebrovascular disease through neuroimaging is quite straightforward (see below). However, identification of symptoms and signs of cerebrovascular disease on clinical grounds might be less obvious. A synthetic approach is given in Text Box 1. Over the last years, there has been much discussion about the potential role of neuropsychology in order to differentiate the vascular from the degenerative component of CI.[6] Although there is consensus that compromise of some cognitive domains (such as memory) may be more prominent in Alzheimer disease (AD) than in cerebrovascular diseases,[7] and executive dysfunctions are thought to be more typical of cerebrovascular pathology, in fact all major cognitive domains are affected in small vessel disease[8] and neuropsychological testing cannot *per se* differentiate between vascular CI and AD at the

Text Box 1. Clinical symptoms/signs which should raise possibility of concomitant cerebrovascular disease

Cognitive symptoms	Slowness of processing speed Attention deficits Reasoning problems Decision-making difficulties Apathy
Behavioral and psychological symptoms	Mood changes (namely depressive symptoms) Emotional control problems Lack of initiative Apparent change in personality Informant report of cognitive decline and behavioral changes
Motor and other non-cognitive/ behavioral symptoms	Gait changes Urinary problems Finger tapping changes

individual level,[9] nor clearly outline the presence of a vascular contribution in patients with CI of degenerative origin.[10] Nevertheless, the combination of the information driven by neuropsychological testing (and remaining clinical evaluation) with brain imaging is the best clue to support a likely cerebrovascular contribution.

Behavioral and psychological symptoms are highly frequent among cerebrovascular disease manifestations[11,12] and might be different according to the nature of cerebrovascular lesions.[13] Those symptoms might be undervalued by relatives (and interpreted for instance as due to ageing) or overlooked due to other concomitant cognitive symptoms. Depressive symptoms, lack of emotion expression control and emotionalism, apathy and lack of initiative and change in personality traits are among those symptoms. There is no ideal short battery for the identification of deficits in patients with cerebrovascular disease. We should keep in mind that less exhaustive neuropsychological study might fail to put in evidence few cognitive deficits and behavioral changes[14]

Evolution over time. Apart from detailed evaluation of cognitive testing, there might be other clinical hints that suggest the presence of a vascular component in a patient with CI.

Historically, one clinical tool to differentiate the vascular component of the cognitive decline is to apply the so-called ischemic score published by Hachinski and co-authors, aiming to differentiate AD from multi-infarct dementia.[15] The score is today considered partly out-of-date and is more rarely used than in the past; however, it may serve to outline and discuss some aspects. According to the original paper, a few characteristics of the clinical course of the cognitive deterioration may indicate the presence of a vascular component (or cause); these are the abrupt onset, the stepwise deterioration, and a fluctuating course. However, it should be kept in mind that the original paper was referring to patients with multiple strokes. Today, we know that a good proportion of patients whose CI recognizes a vascular cause - or at least a vascular component of it -, have small vessel disease (SVD),[16] and the course of their cognitive decline is not usually stepwise but rather progressive and with insidious onset. Other items of the original scale, given the current knowledge, appear of limited utility as they are scarcely discriminative and are also a risk factor for AD (more information concerning Hachinski's score is provided in supplementary material).

Motor and non-motor manifestations. More relevant in this sense are the history of strokes and the presence of focal neurological symptoms and signs. These latter should be always searched for, systematically, as they are highly indicative of a cerebrovascular contribution.

CI phenotype usually reflects more than one pathological mechanism. Biomarkers (namely imaging for vascular pathology) are able to put in evidence cerebrovascular disease. The knowledge of the clinical expression of vascular pathology leads to the possibility of addressing better the specific trigger for CI in a specific person. Some neurological signs may help in the identification of the etiology of the clinical picture. One relevant aspect to be outlined is the possibility to suspect a vascular component of CI by assessing physical performance with simple and clinically friendly tools.[17] Patients with cerebrovascular disease have frequently gait disturbances with balance difficulties, small steps, and bradykinesia. Besides those affected by the sequelae of previous stroke such as hemiparesis, patients with SVD have typically a slowed, short-stepped, wide-based gait. These patients also have an increased rate of falls. More sophisticated tools for assessing gait performance maybe better but also difficult to implement in memory clinics on a large scale.[18]

Finally, there have been data supporting that changes in other non-cognitive symptoms (as for instance urinary troubles early in the course of the disease) since these are common in patients with vascular contributions to CI and have an adverse effect on their daily lives. Cerebral SVD is associated with urinary problems[19] and also with abnormalities on neurological examination, such as slowness of finger tapping.[20] Despite the possibility that these features might direct the attention of the treating physician towards the presence of a vascular contribution, other degenerative pathologies may present with similar findings[21,22] . It might be reasonable however to search for all these aspects in each patient arriving at a memory clinic.

Subjective cognitive impairment. One last word concerning subjective CI, that usually is associated with higher risk of dementia, usually of the Alzheimer type (and not with SVD).[12] However, among community cohorts, may represent an increase in the relative risk risk for, particularly, CI of vascular origin.[23] Clinicians should keep in mind that patients with subjective complaints living in the community are an opportunity to identify vascular risk factors in people otherwise well, and reinforce preventive actions concerning those vascular risk factors.

What investigation/complementary investigation(s) are important?

Patients presenting to memory clinics should have brain imaging that includes assessment for vascular and neurodegenerative or other brain lesions. They should be assessed for common modifiable vascular and lifestyle risk factors to minimize their impact on brain and general health (Table 1).

Neuroimaging

General considerations. On neuroimaging, vascular lesions include cortical or subcortical infarcts or old haemorrhages, signs of SVD including white matter hyperintensities (WMH), lacunes and microbleeds, and cortical superficial siderosis (cSS).[24] Perivascular spaces are common in cerebrovascular disease, but their clinical relevance is currently less clear.[25,26] Brain atrophy occurs in the common neurodegenerative dementias including AD (particularly of medial temporal lobes), fronto-temporal dementia (of frontal and temporal lobes), dementia with Lewy Bodies (of parietal lobes), but also occurs diffusely in SVD[27] and focally after infarcts and haemorrhages. The pattern of atrophy may provide clues of the dementia type, but many patients have global brain atrophy, so in practice, atrophy patterns may have limited specificity.

MRI and CT scan applications. Brain imaging can be performed with computerized tomography (CT) scanning or magnetic resonance imaging (MRI). MRI might not always be available, or not applicable for every patient, so clear knowledge about limitations and advantages of each technique is needed. Moreover, CT is of quick realization, which is quite relevant for instance in patients with behavioral changes, fear of closed environments or with MRI contraindications (pacemaker or some prostheses, for instance). CT is equally accurate as MRI for pathologies such as brain tumours, subdural haematomas, many larger infarcts, acute haemorrhages, and can show brain atrophy, moderate to severe white matter lesions (leukoaraiosis), and lacunes.[28] Nevertheless, differentiation of old haemorrhages from old infarcts, identification of microbleeds and cSS and some small acute infarcts is not reliable on CT. MRI is much more

Table 1. Investigations to avoid missing modifiable vascular risk factors.

Measure	To detect	
Modifiable vascular risk factors		
Blood pressure	Hypertension	May need multiple measures, or ambulatory monitoring
Blood glucose	Diabetes	
Blood lipids	Hyperlipidaemia	
Body mass index	Overweight and obesity	
Lifestyle history	Excessive alcohol intake, smoking, poor diet, inadequate exercise and sedentary habit	
Other proxy-risk factors, as obstructive sleep apnea, homocysteine levels	Different factors associated with higher vascular risk	If not actively searched be a missed opportunity to be identified
Sources of emboli and evidence of ischaemic cardiovascular disease:		
ECG	Cardiac arrhythmias, particularly atrial fibrillation; ischaemic heart disease	May need ambulatory monitoring, to detect paroxysmal arrhythmias or even an ECG-T (cardiac event recorder)
Echocardiogram	Heart valve disease, atrial septal defects (ASDs) Aortic cross atheroma	Transoesophageal echo with iv echo-contrast is more sensitive to ASDs than transthoracic
Doppler Ultrasound, CT or MR angiography	Carotid or vertebral artery extra- or intracranial stenosis	CT or MR angiography for suspected intracranial stenosis
Evidence of cerebrovascular disease		
MR or CT brain imaging[a]	Acute or old cortical infarcts; Acute or old subcortical infarcts; acute or old brain haemorrhage; WMH, lacunes, microbleeds, cortical siderosis; brain atrophy including regional distribution	T1-weighted, T2-weighted, FLAIR, SWI and DWI sequences are all essential to assess for the range of cerebrovascular disease lesions.

[a]MRI preferred, as more sensitive for detecting vascular changes. CT will detect non vascular causes and brain atrophy, many infarcts, acute haemorrhage, and moderate to severe WMH and lacunes, but not microbleeds, differentiate old infarct from haemorrhage, and is much less sensitive to SVD lesions than is MRI. CT possibilities discriminated in main text.

WMH: white matter hyperintensities; FLAIR: fluid attenuated inversion recovery; SWI: susceptibility-weighted imaging; DWI: diffusion-weighted imaging or diffusion imaging.

sensitive to vascular lesions, particularly WMH, microbleeds and cSS. MRI is also better for detecting and differentiating sporadic vascular lesions from multiple sclerosis, vasculitis, some infections and familial genetic causes of dementia and cerebrovascular disease such as CADASIL. However, when using MRI, the correct MRI sequences are required to identify key vascular pathologies. Many memory clinics use MRI protocols including 3 D T1 and T2, which detect brain atrophy, some cortical infarcts, lacunes and can exclude tumours and subdural haematomas, for instance. However, to detect key vascular lesions, a fluid attenuated inversion recovery (FLAIR) sequence is required for WMH and small cortical infarcts, a susceptibility-weighted imaging (SWI or Gradient Echo or T2*) sequence is essential to detect microbleeds, cSS, and old macrohaemorrhages, and diffusion-weighted imaging (DWI) is important to detect small acute infarcts.

Specific hints from neuroimaging. WMH, lacunes, microbleeds and atrophy all increase with age.[24,25] However, a higher than expected burden of WMH for age, and any lacunes or microbleeds, should trigger a search for modifiable risk factors.[29] Smith et al. provided a practical schema of WMH severities according to age groups, based on MRI, in a recent publication (see Figure 7 in).[29] Large numbers of WMH and lacunes in a young patient should raise the possibility of a monogenic SVD such as CADASIL. Multiple cortical infarcts especially in multiple arterial territories, should trigger a search for proximal embolic sources. Microbleeds are associated with hypertension, where they typically occur mainly in deep grey and white matter, and commonly found in patients with cerebral amyloid angiopathy (CAA) where they typically have a lobar distribution and are seen at the cortical-subcortical junction, although mixed distributions of microbleeds are common. Microbleeds plus cSS are likely to indicate CAA.[30]

Vascular risk management

Vascular risk factors assessment. The main modifiable vascular risk factors are hypertension, hyperlipidemia, diabetes, and sources of emboli or altered cerebral perfusion such as atrial fibrillation or other cardiac arrhythmias, heart valve disease, and atheromatous internal carotid artery stenosis. Modifiable lifestyle risk factors include tobacco smoking, lack of regular physical exercise and poor diet including excess dietary sodium and alcohol.

All patients attending memory clinics should have their blood pressure measured using an approved and well maintained sphygmomanometer device. Blood pressure should be assessed sitting after at least five minutes of rest, and in both arms to avoid falsely low reading due to a subclavian artery stenosis. More detailed repeated measures of BP in clinic or home monitoring may be required but this is out of scope for this paper. Loss of adherence to hypertension treatment should be prevented (namely patients might stop medication when values get normal due to treatment), hence, any attendance at a clinic is a good opportunity to check that vascular risk management is under control. Patients should also have their blood glucose and blood lipids (cholesterol, LDL, HDL) measured if these have not been performed recently elsewhere, and appropriate management implemented whenever necessary.[31]

Ancillary investigations concerning vascular risk factors. As cholinesterase inhibitors may delay atrial-ventricular conduction, an electrocardiogram (ECG) is usually requested in memory clinics. When there is evidence of cerebrovascular disease, an ECG will be helpful to identify arrhythmias, and signs of ischaemic heart disease or left or right chamber hypertrophy. Special attention must be given to patients with recent focal neurological symptoms or evidence of cerebrovascular lesions on scanning, especially if in multiple vascular territories: in those patients, ambulatory monitoring may be required to detect paroxysmal arrhythmias and further investigations such as echocardiography, and neck or intracranial artery imaging e.g. with Doppler ultrasound, CT or MR angiography[32] may be needed. Patients with more complex cerebrovascular disease as recurrent strokes despite adequate management and adequate secondary prevention, rare causes of stroke (as genetic diseases as CADASIL) and patients with recent acute stroke or suspected TIA should be considered for referral to a stroke clinic.

Other life-style and global measures. Tobacco smoking[33] and excess alcohol consumption damage the brain,[34] so cessation of those habits should be suggested. Exercise helps to maintain brain vascular health,[35] and a well-balanced diet including recommended amounts of fruit and vegetables,[36] avoiding excess sodium[37] and processed meats, is advisable. Lifestyle advice encourages patient awareness of their vascular risk and is part of comprehensive risk management.

A synopsis of suggested investigations is given in Table 1, and a summary of relevant suggestions in Text Box 2.

Treatment

Primary and secondary prevention of stroke. Prevention of new vascular events in people with symptomatic cardiovascular disease is one of the real success stories of

Text Box 2. Summary of suggestions for the management of cerebrovascular disease in patients with CI.

- Clinical appointments due to CI should be considered as an opportunity to check and better control of vascular risk factors
- Brain imaging (made in the context of CI) should be reviewed to verify existence of cerebrovascular disease
- In the case of cerebrovascular component highly suspected/not clear after CT, an MRI should be considered (namely if doubt about hemorrhagic component including microbleeds and cSS, small acute lesions, specific profiles as familiar -e.g.CADASIL, or extension of WMC and SVD)
- Specific investigations should be considered in acute lesions, recurrent and multiple strokes (namely neck and intracranial artery imaging and cardiac study)

preventive medicine. In patients who experienced a ischaemic stroke, or transient ischaemic attack, the risk of future vascular events can be reduced by 30–50% through guideline-based treatments and lifestyle recommendations.[38] Of note, the evidence on which these guidelines are built is largely derived from studies on atherosclerotic (large artery) disease. By comparison, the available evidence specifically concerning treatment of cerebral SVD, the commonest form of vascular brain injury encountered in people with CI, is quite limited.[29,39]

There clearly is an important potential for vascular prevention strategies in patients with CI. Yet, physicians should be careful to apply guidelines for secondary prevention after stroke to people with CI and so-called "silent cerebrovascular disease". In this setting, some treatments that are cornerstones in secondary prevention, in particular antithrombotic agents, may be ineffective, or sometimes even harmful. Although some recommendations are published,[29] we try to summarize few practical points in the next lines.

In all patients with CI and vascular brain injury, guidelines for primary prevention of cardiovascular disease apply.[40] This includes lifestyle recommendations, and encouraging cessation of smoking, if applicable, as mentioned above. To determine if additional treatment is needed, or existing treatments should be modified, a pragmatic approach is the following:

First, determine if the patient had a previous ischaemic vascular event or other ischemic vascular disease elsewhere in the body. If this is the case, this previous cardiovascular disease generally determines the choice of antithrombotic agents and blood pressure and cholesterol targets, according to available guidelines.[38,40] Nevertheless, the memory clinic visit should be taken as an opportunity to double check if this treatment is appropriately installed.

Next, determine the nature of the vascular brain injury. Asses the different lesion types and burden as indicators of risk of future vascular injury. Of note, lesions that are typically considered to be ischemic, such as WMH and lacunes, not only convey an increased risk of future ischemic stroke, but also of intracerebral haemorrhage (ICH).[41] Similarly, lesions that are typically considered to be haemorrhagic, in particular, microbleeds, also convey an increased risk of ischaemic stroke. For example, in patients who previously experienced a TIA or ischaemic stroke it has been established that presence of multiple microbleeds is associated with a much higher relative hazard ratio for future ICH than for ischaemic stroke.[42] Yet, because the overall rate of ischaemic stroke in these patients is several fold higher than that of ICH, even in patients with multiple microbleeds the absolute risk of ischaemic stroke is higher than that of ICH.[42] These observations illustrate how difficult it can be to base indications for antithrombotic agents on patients with these lesions. Practical hints are given in Text Box 3.

Specific issues in the use of antithrombotic therapy. It is also important to consider if the vascular brain injury, as seen on the scan, provides an indication to initiate or modify antithrombotic therapy. As a general principle "silent" ischemic lesions, in particular WMH, do not provide a clear indication for prescription of antithrombotic agents.[29] By contrast, it is also questionable if presence of a few microbleeds should be a reason to withhold antithrombotic agents in patients in whom such agents are otherwise indicated for presence of symptomatic ischaemic vascular disease. An exception may be people with high (e.g. >10) numbers of microbleeds and also people with cSS, particularly if disseminated (detected in more than 3 sulci). cSS is an indicator of CAA and conveys an absolute risk of future ICH of 11% per year when disseminated.[43,44]

In all cases, particularly for prescribing or discontinuing antithrombotic agents, an individualized approach is needed. Where possible this should be based on weighing the patients estimated absolute risk (and not relative risk which might often be misleading) of both future ischaemic and haemorrhagic events. The challenge is that such estimates are still imprecise and are largely derived from studies that did not specifically include patients from memory clinics. This clearly is an area for further study.

Text Box 3. Practical suggestions concerning treatment of cerebrovascular disease in patients with CI.

- Implement primary and secondary prevention of stroke; primary prevention applies to all patients. Patients who experienced a stroke should be treated according to secondary prevention guidelines.
- No evidence base to support application of secondary stroke prevention treatment strategies for WMH alone.
- Individualized approach to initiate or modify antithrombotic agents based on weighing the individual patients estimated absolute risk of future ischaemic or haemorrhagic events.

Conclusion and suggestions for future research

The interplay between vascular and neurodegenerative pathologies in patients with CI and dementia remains an active area of research. In recent years, the notion of potentially significant vascular contributions to CI and dementia in different patient settings is becoming better appreciated by clinicians. However, the mechanisms of how cerebrovascular pathophysiology reciprocally interacts with neurodegeneration in producing or contributing to cognitive symptoms and decline are complex and currently elusive. For example, there are many strong epidemiological links between traditional vascular risk factors and CI, and also a plethora of theoretical pathophysiologic crosstalk mechanisms between brain vessels pathologies and β-amyloid, a hallmark of neurodegeneration pathobiology. Often, age-related CI and dementia represent really a mix of neurodegenerative and vascular pathologies. Despite the details and trajectories being largely unknown, this realization gives a reason for hope, in that more contributions to CI in patients translates to more targets and opportunities to intervene. Such targets might include protection of the endothelium, the blood-brain barrier, other components of the neurovascular unit, or targeting CAA. It will also be of interest to assess the independent benefit on cognition of commonly used medications for primary and secondary stroke prevention, including antithrombotics in different stroke patient cohorts.

Ongoing and future research should focus on human- and animal-based studies of these interactions and on multidisciplinary consortia exploring potential biomarkers and clinical targets for intervention. Another relevant issue is the need to learn how to best evaluate and qualify cognitive performance as to outline cognitive components that are more specific of the vascular contribution[45] and whether this approach would be clinically meaningful. In the meanwhile, it is reasonable for all patients being assessed or managed for CI, to also be assessed for vascular brain injury and risk for it, and follow relevant published guidelines for primary or secondary prevention of cardiocerebrovascular disease as applicable.

Acknowledgements

We thank Professor Franz Fazekas, from the Medical University of Graz, Austria, for his contribution on this paper and we thank the European Stroke Organisation for supporting and for endorsing this initiative.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Olivier Godefroy during the last five years has served on scientific advisory boards and speaker (Biogen, Astra Zeneca, Novartis) and received funding for travel and meetings from Bristol-Myers Squibb, Roche, Biogen, Teva-santé, Boehringer-Ingelheim, Covidien, Ipsen. The remaining authors declare that there are no conflict of interest concerning the paper.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Informed consent is not applicable to this manuscript.

Ethical approval

Ethical approval is not applicable for this manuscript.

Guarantor

AV.

Contributorship

All authors contributed equally to conceive the manuscript, the structure of paper, literature research and writing of the manuscript. All authors contributed to the different stages of the manuscript, reviewed and edited and finally approved the final version of the manuscript.

ORCID iDs

Ana Verdelho https://orcid.org/0000-0003-4945-4946
Leonardo Pantoni https://orcid.org/0000-0001-7357-8530
Joanna Wardlaw https://orcid.org/0000-0002-9812-6642

Supplemental material

Supplementary material for this article is available online.

References

1. Rostamian S, Mahinrad S, Stijnen T, et al. Cognitive impairment and risk of stroke: a systematic review and meta-analysis of prospective cohort studies. *Stroke* 2014; 45: 1342–1134.
2. Pendlebury S, Rothwell P and Study OV. Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based oxford vascular study. *Lancet Neurol* 2019; 18: 248–258.
3. Hachinski V. Stoop to conquer: preventing stroke and dementia together. *Lancet* 2017; 389: 1518.
4. Deschaintre Y, Richard F, Leys D, et al. Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. *Neurology* 2009; 73: 674–680.
5. Frederiksen KS, Cooper C, Frisoni GB, et al. A European academy of neurology guideline on medical management issues in dementia. *Eur J Neurol* 2020; 27: 1805–1820.
6. Salvadori E and Pantoni L; on behalf of the Società Italiana di NeuroGeriatria (SINEG). The role of the neuropsychologist in memory clinics. *Neurol Sci* 2020; 41: 1483–1488.
7. Lamar M, Price CC, Giovannetti T, et al. The dysexecutive syndrome associated with ischaemic vascular disease and related subcortical neuropathology: a Boston process approach. *Behav Neurol* 2010; 22: 53–62.
8. Hamilton O, Kl Blackhouse EV, Janssen E, et al. Cognitive impairment in sporadic cerebral small vessel disease: a systematic review and meta-analysis. *Alzheimers Dement*. Epub ahead of print 13 November 2020. DOI: 10.1002/alz.12221.
9. Andriuta D, Roussel M, Barbay M, et al. Differentiating between Alzheimer's disease and vascular cognitive impairment: is the "memory versus executive function" contrast still relevant? *J Alzheimers Dis* 2018; 63: 625–633.
10. Mathias JL and Burke J. Cognitive functioning in Alzheimer's and vascular dementia: a meta-analysis. *Neuropsychology* 2009; 23: 411–423.
11. O'Brien J. Behavioral symptoms in vascular cognitive impairment and vascular dementia. *Int Psychogeriatr* 2003; 15 Suppl 1: 133–138.
12. Clancy U, Jochems ACC, Doubal FN, et al. Neuropsychiatric symptoms associate with cerebral small vessel disease: systematic review and Meta-analysis. *Lancet Psychiatry* (In press).
13. Tiel C, Sudo FK, Alves GS, et al. Neuropsychiatric symptoms in vascular cognitive impairment: a systematic review. *Dement Neuropsychol* 2015; 9: 230–236.
14. Salvadori E, Brambilla M, Cova I, et al. Cognitive evaluation in cerebral small vessel disease: towards an evidence-based identification of the reference standards. Part 1. A systematic review and qualitative data synthesis. *J Neurol*. Epub ahead of print 13 October 2020. DOI: 10.1007/s00415-020-10262-2. Epub ahead of print.
15. Hachinski VC, Iliff LD, Zilhka E, et al. Cerebral blood flow in dementia. *Arch Neurol* 1975; 32: 632–637.
16. Wardlaw JM, Smith C and Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol* 2019; 18: 684–696.
17. Verwer JH, Biessels GJ, Heinen R, et al.; Utrecht Vascular Cognitive Impairment (VCI) study group. Occurrence of impaired physical performance in memory clinic patients with cerebral small vessel disease. *Alzheimer Dis Assoc Disord* 2018; 32: 214–219.
18. Mc Ardle R, Morris R, Wilson J, et al. What can quantitative gait analysis tell us about dementia and its subtypes? A structured review. *J Alzheimers Dis* 2017; 60: 1295–1312.
19. Poggesi A, Pracucci G, Chabriat H, et al.; on behalf of the LADIS Study Group. Urinary complaints in nondisabled elderly people with age-related white matter changes: the leukoaraiosis and DISability (LADIS) study. *J Am Geriatr Soc* 2008; 56: 1638–1643.
20. Poggesi A, Gouw A, van der Flier W, et al. Cerebral white matter changes are associated with abnormalities on neurological examination in non-disabled elderly: the LADIS study. *J Neurol* 2014; 261: 1160–1169.
21. Jeppesen Kragh F, Bruun M, Budtz-Jørgensen E, et al. Quantitative measurements of motor function in Alzheimer's disease, frontotemporal dementia, and dementia with lewy bodies: a proof-of-concept study. *Dement Geriatr Cogn Disord* 2018; 46: 168–179.
22. Kim KJ, Jeong SJ and Kim JM. Neurogenic bladder in progressive supranuclear palsy: a comparison with Parkinson's disease and multiple system atrophy. *Neurourol Urodyn* 2018; 37: 1724–1730.
23. Slot RER, Sikkes SAM, Berkhof J, et al.; SCD-I Working Group. Subjective cognitive decline and rates of incident Alzheimer's disease and non-Alzheimer's disease dementia. *Alzheimers Dement* 2019; 15: 465–476.
24. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration: a united approach. *Lancet Neurol* 2013; 12: 822–838.
25. Debette S, Schilling S, Duperron M, et al. Clinical significance of magnetic resonance imaging markers of vascular brain injury: a systematic review and meta-analysis. *JAMA Neurol* 2019; 76: 81–94.
26. Francis F, Ballerini L and Wardlaw JM. Perivascular spaces and their associations with risk factors, clinical disorders and neuroimaging features: a systematic review and Meta-analysis. *Int J Stroke* 2019; 14: 359–371.
27. Ter Telgte A, van Leijsen EMC, Wiegertjes K, et al. Cerebral small vessel disease: from a focal to a global perspective. *Nat Rev Neurol* 2018; 14: 387–398.
28. Pasi M, Poggesi A and Pantoni L. The use of CT in dementia. *Int Psychogeriatr* 2011; 23 Suppl 2: S6–S12.
29. Smith EE, Saposnik G, Biessels GJ, et al.; American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Functional Genomics and Translational Biology; and Council on Hypertension. Prevention of stroke in patients with silent cerebrovascular disease: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2017; 48: e44–e71.
30. Wollenweber FA, Baykara E, Zedde M, et al. Cortical superficial siderosis in different types of cerebral small vessel disease. *Stroke* 2017; 48: 1404–1407.

31. Norrving B, Barrick J, Davalos A, et al. Action plan for stroke in Europe 2018–2030. *Eur Stroke J* 2018; 3: 309–336.
32. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2019; 50: e344–e418.
33. Karama S, Ducharme S, Corley J, et al. Cigarette smoking and thinning of the brain's cortex. *Mol Psychiatry* 2015; 20: 778–785.
34. Makin SD, Doubal FN, Shuler K, et al. The impact of early-life intelligence quotient on post stroke cognitive impairment. *Eur Stroke J* 2018; 3: 145–156.
35. Ngandu T, Lehtisalo J, Solomon A, 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* 2015; 385: 2255–2263.
36. Luciano M, Corley J, Cox SR, et al. Mediterranean-type diet and brain structural change from 73 to 76 years in a Scottish cohort. *Neurology* 2017; 88: 449–455.
37. Heye AK, Thrippleton MJ, Chappell FM, et al. Blood pressure and sodium: association with MRI markers in cerebral small vessel disease. *J Cereb Blood Flow Metab* 2016; 36: 264–274.
38. Kernan WN, Ovbiagele B, Black HR, et al.; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014; 45: 2160–2236.
39. Smith EE and Markus HS. New treatment approaches to modify the course of cerebral small vessel diseases. *Stroke* 2020; 51: 38–46.
40. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation* 2019; 140: e596–e646.
41. Kaffashian S, Tzourio C, Zhu YC, et al. Differential effect of white-matter lesions and covert brain infarcts on the risk of ischemic stroke and intracerebral hemorrhage. *Stroke* 2016; 47: 1923–1925.
42. Wilson D, Ambler G, Lee KJ, et al. Cerebral microbleeds and stroke risk after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies. *Lancet Neurol* 2019; 18: 653–665.
43. Charidimou A, Boulouis G, Greenberg SM, et al. Cortical superficial siderosis and bleeding risk in cerebral amyloid angiopathy: a meta-analysis. *Neurology* 2019; 93: e2192–e2202.
44. Wollenweber FA, Opherk C, Zedde M, et al. Prognostic relevance of cortical superficial siderosis in cerebral amyloid angiopathy. *Neurology* 2019; 92: e792–e801.
45. Salvadori E, Dieci F, Caffarra P, et al. Qualitative evaluation of the immediate copy of the Rey-Osterrieth complex figure: comparison between vascular and degenerative MCI patients. *Arch Clin Neuropsychol* 2019; 34: 14–23.

Cognition in Multiple Sclerosis: Evaluation, Treatment, and Brain Networks

Tom Fuchs

Multiple sclerosis is an immunological and neurodegenerative disease of the central nervous system. This disease, more prevalent in women in northern climates, is typically characterized by a “relapsing-remitting” phase followed by a more “progressive” phase where disability accrues more precipitously. The disease results in localized lesions in gray matter and white matter of the central nervous system. Locations of these lesions is non-random, e.g. around venules and more around the lateral ventricles, but locations vary widely from person to person. Because of this varied lesion locations, neurologic symptoms also vary widely. Notably though, cognitive dysfunction is common. Charcot, a 19th century French physician, provided broad but accurate descriptions of cognitive dysfunction in multiple sclerosis: “Marked enfeeblement of the memory" and "conceptions that formed slowly".

In the present age, cognitive impairment is observed in up to 80% of people with multiple sclerosis in later phases of the disease. However, because the location of damage can vary person to person, so too can the expected cognitive impairments and order of impairments. Nonetheless, there are some central expectations. The most commonly measured impairment in MS is slowed cognitive processing speed. We measure this using a test called the Symbol Digit Modalities Test. Tests of verbal and visuospatial learning and memory are also commonly applied ins MS. Although cognitive impairment in MS is specific to which brain networks are affected, we have investigated the most common order of impairment as the disease progresses. Slowing of processing speed is commonly the earliest cognitive dysfunction observed in MS. This is followed by impairment of short-term verbal and visuospatial memory and then by executive dysfunction. Other commonly addressed domains include auditory attention and verbal fluency. It is likely that we could find most any cognitive dysfunction in MS, depending on lesion locations of the patients observed and tests applied for assessment. For instance, emotional recognition and empathy is not widely tested in clinical environments, but dysfunction within these capacities have been repeatedly observed in small research cohorts.

Like physical disability in MS, cognition also worsens during relapses, followed by complete to almost complete recovery. It is not clear how much relapses contribute to decline overall. There are debates in our field about how often to test cognitive function. Practice effects could wash out our sensitivity to cognitive deterioration. Even once annual cognitive testing is likely to result in significant practice effects. In MS, we also must be vigilant of confounds specific to the disease. Physical and cognitive fatigue is the most commonly experienced symptom in MS and is often cited as a confound of cognitive performance. Symptomatic pharmacologic treatment of cognitive dysfunction in MS is not effective, though medications that control the disease appear to also reduce cognitive decline. Behavioral treatments are somewhat effective, though few long-term studies exist. Restorative rehabilitation techniques seem best suited in early stages of cognitive decline, whereas compensatory techniques, like story memory techniques, are likely better suited for later stages.

MRI can be applied to glean interesting insights about the relationship between the brain and cognition in MS. At the simplest level, we can measure central atrophy or the sum of lesion volume – and these correlate with cognitive performance. Lesions of the gray matter correlate more strongly but are difficult to view on clinical MRI. Gray matter atrophy also correlates strongly with cognitive dysfunction in MS and thalamic atrophy has proved to exhibit the strongest correlations with cognitive function. There are many potential explanations for this, including the closeness of the thalamus to CSF as well as its robust network connectivity – leaving it susceptible to damage as axons are affected throughout the bran. We can map the locations of lesions and the severity of their damage using diffusion-based techniques and identify how such lesions disrupt connections between brain hubs. This network-style approach helps us treat MS almost like an ablation model to better understand cognition, but from a network-oriented perspective rather than considering one brain region at a time. Dysfunction of memory affect networks involving hippocampal connections. Lesions affecting right-hemispheric parietal temporal connections relate with dysfunction in visuospatial memory, and lesions in frontal networks correlate with worsened ability to be goal-oriented and organized. Functional imaging has similarly allowed us to view how the brain adapts to network disruption. For instance, preservation of normal static functional connectivity, despite structural disruption, appears

to be paramount to preservation of cognitive functioning and this preservation of functional connectivity is moderated by cognitive reserve. Failures of usual functional dynamics, such as switching of functional network activation, is also associated with deterioration of cognitive function. Interestingly, higher-function functional networks appear to be most susceptible to change in relation to structural disruption, whereas primary sensory networks show less of a relationship between structural damage and deviation of functional connectivity.

Statins in patients with Alzheimer's dementia – a friend or a foe?

Bojana Petek

ABSTRACT

Several risk factors have been identified in the pathogenesis of Alzheimer's dementia (AD), including genetics, age, lifestyle factors, and certain medical conditions, reflecting a multifactorial backround. Among these factors, a disturbance of cholesterol homeostasis can be involved in the pathogenesis of AD. Therefore, possible cognitive effects of cholesterol-modulating medications have lead to an extensive amount of research, driven by a lack of effective treatment of AD. Statins are a class of cholesterol-lowering medications widely used to prevent and treat cardiovascular disease. In addition to their cholesterol-lowering effects, statins exhibit anti-inflammatory and neuroprotective properties that may be beneficial in the context of AD. Epidemiological evidence of potential cognitive benefit of statins have been inconclusive or controversial in the past two decades. In this presentation, we will review the current state of knowledge on the role of statins in the prevention and treatment of AD as well as potential risks. We will discuss the potential mechanisms underlying the effects of statins on cognition.

CHOLESTEROL HOMEOSTASIS AND MECHANISMS OF STATINS IN AD

Cholesterol is an essential component of cell membranes, involved in several cognitive processes, including neuronal function and signaling. About a quarter of the whole-body cholesterol content is stored in the brain and is metabolically separated from the peripheral cholesterol pool by a functional blood-brain barrier (1). Dysregulation of central cholesterol homeostasis has been proposed to be involved in the pathogenesis of AD through different mechanisms, including the effect on the amyloid pathway, vascular impairment or interaction with other metabolic pathways in the brain (2). Moreover, a genetic polymorphism of cholesterol transporter in the brain, ApoE4, represents a major risk factor for late-onset AD. On the other hand, a complex association between peripheral hypercholesterolemia and cognition has been recognized. Hypercholesterolemia in midlife has been linked to a higher risk of AD in late life (3). However, dyslipidemia in late life is thought to reflect a better overall health and is associated with a slower cognitive decline (4).

Statins are a group of medications widely used in the prevention of cardiovascular disease which act through a competitive reversible inhibition of enzyme HMG-CoA reductase. In addition to the inhibition of endogenous cholesterol production, they exhibit other pleotropic characteristics, such as anti-inflammatory, anti-oxidant and neuroprotective abilities (2). The brain penetration of an individual statin has been linked to several factors, such as their individual lipophilicity, size of the molecule and different transporters (5). Most biochemical studies divided statins into two groups regarding their lipophilicity: a group with a higher lipophilicity which facilitates the brain penetration (e.g. simvastatin, atorvastatin, fluvastatin) and a hydrophilic group of statins which enter the brain less easily (e.g. rosuvastatin, pravastatin). Epidemiological studies which compared lipophilic to hydrophilic statins were inconsistent and have reported no difference when comparing the cognitive decline in these groups (6), or a possible benefit of lipophilic statins (7).

The overall cognitive effects of statins on cognition have been linked to a complex interplay of several factors, such as brain penetration and function of the blood-brain barrier, the balance of the beneficial and harmful effects of statins on several processes in a neurovascular unit (8), lenght of treatment and dose of a medication (9), time of treatment in the course of AD pathogenesis (10), patients comorbidities and medication interactions, to name a few.

PREVIOUS RESEARCH ON STATINS AND AD

Since the promising results of first two observational studies almost two decades ago (11,12), an extensive amount of consecutive observational studies and clinical trials reported inconsistent findings. Moreover, a number of potential, usually mild and reversible short-term cognitive adverse effects of statins have been reported (13). Several well-designed large systematic reviews and meta-analyses did not confirm the adverse cognitive effects risk (14,15) and some suggested that use of statins may lower the risk of AD (16). Clinical trials generally reported a null effect (17,18) but were possibly underpowered or used less robust cognition-evaluation tools. More recent studies considered several epidemiological biases due to observational nature or a heterogeneous design of studies to be important cause of these discrepancies (10).

CONCLUSION

The cognitive effects of statins on cognition in patients with AD probably result from a complex interplay of several factors, linked to the medication (lipophilicity and brain penetration, the cholesterol-lowering and pleotropic effects, lenght of treatment and dose) and individual patient's characteristics (pathogenesis of AD, function of the blood-brain barrier, comorbidities and comedication). It is biologically plausible and consistent with epidemiological evidence that treating dyslipidemia in midlife diminishes the metabolic risk factor of hyperlipidemia on cognitive decline in late life. Most of the recent research does not suggest an overall harmful effect of statins on cognitive abilities. Moreover, statins may be beneficial to a subgroup of AD patients with central cholesterol homeostasis disturbance or early in the disease pathogenesis.

REFERENCES

1. Gamba P, Staurenghi E, Testa G, Giannelli S, Sottero B, Leonarduzzi G. A crosstalk between brain cholesterol oxidation and glucose metabolism in Alzheimer's disease. Front Neurosci. 2019;13(MAY).
2. Petek B, Villa-Lopez M, Loera-Valencia R, Gerenu G, Winblad B, Kramberger MG, et al. Connecting the brain cholesterol and renin–angiotensin systems: potential role of statins and RAS-modifying medications in dementia. J Intern Med. 2018;284(6):620–42.
3. Kivipelto M, Solomon A. Cholesterol as a risk factor for Alzheimer's disease - Epidemiological evidence. Acta Neurol Scand. 2006;114(SUPPL. 185):50–7.
4. Benito-León J, Vega-Quiroga S, Villarejo-Galende A, Bermejo-Pareja F. Hypercholesterolemia in elders is associated with slower cognitive decline: A prospective, population-based study (NEDICES). J Neurol Sci. 2015;350(1–2):69–74.
5. Sierra S, Ramos MC, Molina P, Esteo C, Vázquez JA, Burgos JS. Statins as neuroprotectants: A comparative in vitro study of lipophilicity, blood-brain-barrier penetration, lowering of brain cholesterol, and decrease of neuron cell death. J Alzheimer's Dis. 2011;23(2):307–18.
6. Haag MDM, Hofman A, Koudstaal PJ, Stricker BHC, Breteler MMB. Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. The Rotterdam Study. J Neurol Neurosurg Psychiatry. 2009;80(1):13–7.
7. Lin FC, Chuang YS, Hsieh HM, Lee TC, Chiu KF, Liu CK, et al. Early statin use and the progression of Alzheimer disease: A total population-based case-control study. Med (United States). 2015;
8. Mendoza-Oliva A, Zepeda A, Arias C. The Complex Actions of Statins in Brain and their Relevance for Alzheimer's Disease Treatment: an Analytical Review. Curr Alzheimer Res. 2014;
9. Olmastroni E, Molari G, De Beni N, Colpani O, Galimberti F, Gazzotti M, et al. Statin use and risk of dementia or Alzheimer's disease: a systematic review and meta-analysis of observational studies. Eur J Prev Cardiol. 2021 Dec 6;
10. Power MC, Weuve J, Sharrett AR, Blacker D, Gottesman RF. Statins, cognition, and dementia-systematic review and methodological commentary. Nat Rev Neurol. 2015;11(4):220–9.
11. Wolozin B, Kellman W, Ruosseau P, Celesia GG, Siegel G. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. Arch Neurol. 2000;57(10):1439–43.
12. Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. Lancet. 2000;356(9242):1627–31.
13. Wagstaff LR, Mitton MW, Arvik BML, Doraiswamy PM. Statin-associated memory loss: Analysis of 60 case reports and review of the literature. Vol. 23, Pharmacotherapy. 2003. p. 871–80.
14. Adhikari A, Tripathy S, Chuzi S, Peterson J, Stone NJ. Association between statin use and cognitive function: A systematic review of randomized clinical trials and observational studies. J Clin Lipidol. 2021 Jan 1;15(1):22-32.e12.

14. Adhikari A, Tripathy S, Chuzi S, Peterson J, Stone NJ. Association between statin use and cognitive function: A systematic review of randomized clinical trials and observational studies. J Clin Lipidol. 2021 Jan 1;15(1):22-32.e12.
15. Davis KAS, Bishara D, Perera G, Molokhia M, Rajendran L, Stewart RJ. Benefits and Harms of Statins in People with Dementia: A Systematic Review and Meta-Analysis. J Am Geriatr Soc. 2020 Mar 1;68(3):650–8.
16. Poly TN, Islam MM, Walther BA, Yang HC, Wu CC, Lin MC, et al. Association between Use of Statin and Risk of Dementia: A Meta-Analysis of Observational Studies. Neuroepidemiology. 2020 May 1;54(3):214–26.
17. Sano M, Bell KL, Galasko D, Galvin JE, Thomas RG, Van Dyck CH, et al. A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease. Neurology. 2011;77(6):556–63.
18. Feldman HH, Doody RS, Kivipelto M, Sparks DL, Waters DD, Jones RW, et al. Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease: LEADe. Neurology. 2010;74(12):956–64.

Association of blood pressure variability with delirium in critically ill

Nika Zorko Garbajs

DELIRIUM AND CRITICAL ILLNESS

Delirium, an acute fluctuating neurocognitive condition characterized by inattention, depressed awareness, and impaired cognition, is commonly found in critically ill patients (from 20% in non-intubated to 87% in the mechanically ventilated) 1, 2. The underlying causes for delirium are presumably multifactorial, including neuroinflammation, oxidative stress, neuroendocrine dysregulation, and disturbances of cerebral vascular regulation 3. Is it associated with numerous adverse outcomes of intensive care unit (ICU) treatment, including increased ICU and hospital mortality rates and lengths of stay, prolonged mechanical ventilation duration, increased risk of hospital readmissions, death after hospital discharge 4, 5, and just as importantly long-term cognitive impairment 6-8. The increased severity of these complications in patients with delirium led to the launching of various initiatives to detect and eliminate precipitating risk factors for delirium and to implement interventions for modifiable risk factors. To this end, bundle interventions, such as the ICU Liberation initiative 9, have been introduced to prevent delirium in patients admitted to an ICU; however, current bundle interventions do not include BPV as an intervention target 10.

BLOOD PRESSURE VARIABILITY AND MORBIDITY

Blood pressure variability (BPV) is a complex phenomenon defined as the magnitude and pattern of blood pressure (BP) fluctuations during a certain period of time 11. Increased short-term and long-term BPV is associated with the development and progression of cardiac, vascular, neurologic, and kidney disease, increased risk of cardiovascular events and death 12-17, and long-term cognitive decline in ambulatory populations 18, 19. Additionally, intraoperative BPV (and not only intraoperative hypotension) 20-22, has been identified as a risk factor for postoperative delirium 23-26. Disparity between mean BP and BPV can be attributed to the deleterious effects of BPV, which is independent of mean BP 27. The deleterious effects of BPV on cerebral function can be explained by microvascular and blood-brain barrier damage caused by enlarged pulsatile loads, which are inadequately buffered by impaired cerebral autoregulation during acute critical illness 28, 29.

ESTABLISHING AN ASSOCIATION BETWEEN BPV AND DELIRIUM IN CRITICALLY ILL

We performed two studies in which we aimed to analyze the association between BPV during the first 24 hours after ICU admission and the likelihood of acute delirium during ICU admissions in a large patient cohort. The first study included previously cognitively unimpaired older patients (> 50 years old), voluntary participants of the Mayo Clinic Study of Ageing, and analyzed the associations between BPV, delirium and long-term cognitive outcomes 30. The second analyzed the association of BPV with delirium in all adult ICU population 31. Both excluded patients with primary neurological diseases, as they can affect the reliability of delirium evaluation.

We evaluated delirium by Confusion Assessment Method of the Intensive Care Unit (CAM-ICU) score in non-sedated patients at least every 8-12 hours. Long-term cognitive outcome was evaluated through the changes in the slope of longitudinally assessed global cognitive scores associated with ICU admission (comparing pre-admission and post-admission assessments). Systolic and diastolic blood pressure, measured in 15-minute to 1-hour intervals during first 24 hours of ICU admission were recorded. The primary BPV measure for systolic and diastolic BP each was average real variability (ARV), representing the average of absolute differences between consecutive measures during the observed time, accounting for the number and order of consecutive measurements 32.

The first study included 794 patients with 1,130 ICU admissions. Of these admissions, 185 (16%) manifested with delirium. Compared to patients who did not experience cognitive disturbance in the ICU, participants who developed delirium were sicker and had a higher rate of mechanical ventilation during the first 24 hours. There was a dose-response relationship between 24-hour systolic and diastolic ARV and the development of delirium, meaning higher BPV was associated with an increased likelihood acute delirium during the first day of admission and after. For the assessment of the association of BPV with the change in long-term trajectory of cognition, 371

participants met criteria, with average follow up duration of 2.5 years pre- and post- first ICU admission. We found an accelerated global cognitive decline after ICU admission, that was steeper in patients experiencing delirium during admission (15 - 4.3%), but unaffected by measures of BPV 30.

In the second study 66,549 ICU admissions of 54,056 unique patients were included in our analysis. Delirium was documented in 13,427 (20.2%) ICU admissions. Increased BPV was associated with higher odds of delirium (P<.001) and an increased duration of delirium (P ≤.001). Specifically, a 5-mm Hg increase in systolic ARV was associated with a 34% increase in the odds of delirium (OR, 1.34; 95% CI, 1.29-1.40) 31.

CONCLUSION

Our studies are the first identifying a relationship between early BPV and delirium in the ICU, demonstrating higher BPV during the first 24 hours of ICU admission is associated with increased risk and duration of delirium in critically ill, regardless whether the patients in question were elderly or a general ICU population. However, our results do not prove causality. If our observations are confirmed in future prospective studies, new interventions may be developed and subsequently assessed in clinical trials to examine whether reducing BPV can decrease the burden of delirium in patients with critical illness.

References:

1. Van Rompaey B, Schuurmans MJ, Shortridge-Baggett LM, Truijen S, Elseviers M, Bossaert L. A comparison of the CAM-ICU and the NEECHAM Confusion Scale in intensive care delirium assessment: an observational study in non-intubated patients. Crit Care 2008;12:R16.
2. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001;29:1370-1379.
3. Maldonado JR. Acute Brain Failure: Pathophysiology, Diagnosis, Management, and Sequelae of Delirium. Crit Care Clin 2017;33:461-519.
4. Salluh JI, Wang H, Schneider EB, Nagaraja N, Yenokyan G, Damluji A, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ 2015;350:h2538.
5. Fiest KM, Soo A, Hee Lee C, Niven DJ, Ely EW, Doig CJ, et al. Long-Term Outcomes in ICU Patients with Delirium: A Population-based Cohort Study. Am J Respir Crit Care Med 2021;204:412-420.
6. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. N Engl J Med 2013;369:1306-1316.
7. Sakusic A, Gajic O, Singh TD, O'Horo JC, Jenkins G, Wilson GA, et al. Risk Factors for Persistent Cognitive Impairment After Critical Illness, Nested Case-Control Study. Crit Care Med 2018;46:1977-1984.
8. Bulic D, Bennett M, Georgousopoulou EN, Shehabi Y, Pham T, Looi JCL, et al. Cognitive and psychosocial outcomes of mechanically ventilated intensive care patients with and without delirium. Ann Intensive Care 2020;10:104.
9. Rose L, Burry L, Agar M, Campbell NL, Clarke M, Lee J, et al. A Core Outcome Set for Research Evaluating Interventions to Prevent and/or Treat Delirium in Critically Ill Adults: An International Consensus Study (Del-COrS). Crit Care Med 2021.
10. Ely EW. The ABCDEF Bundle: Science and Philosophy of How ICU Liberation Serves Patients and Families. Crit Care Med 2017;45:321-330.
11. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. Nat Rev Cardiol 2013;10:143-155.
12. Stevens SL, Wood S, Koshiaris C, Law K, Glasziou P, Stevens RJ, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. BMJ 2016;354:i4098.
13. Bennett AE, Wilder MJ, McNally JS, Wold JJ, Stoddard GJ, Majersik JJ, et al. Increased blood pressure variability after endovascular thrombectomy for acute stroke is associated with worse clinical outcome. J Neurointerv Surg 2018;10:823-827.
14. Lattanzi S, Cagnetti C, Provinciali L, Silvestrini M. Blood Pressure Variability and Clinical Outcome in Patients with Acute Intracerebral Hemorrhage. J Stroke Cerebrovasc Dis 2015;24:1493-1499.
15. Kirkness CJ, Burr RL, Mitchell PH. Intracranial and blood pressure variability and long-term outcome after aneurysmal sub-arachnoid hemorrhage. Am J Crit Care 2009;18:241-251.

16. Rossignol P, Girerd N, Gregory D, Massaro J, Konstam MA, Zannad F. Increased visit-to-visit blood pressure variability is associated with worse cardiovascular outcomes in low ejection fraction heart failure patients: Insights from the HEAAL study. Int J Cardiol 2015;187:183-189.
17. Saito K, Saito Y, Kitahara H, Nakayama T, Fujimoto Y, Kobayashi Y. In-Hospital Blood Pressure Variability: A Novel Prognostic Marker of Renal Function Decline and Cardiovascular Events in Patients with Coronary Artery Disease. Kidney Blood Press Res 2020;45:748-757.
18. Zhou TL, Kroon AA, van Sloten TT, van Boxtel MPJ, Verhey FRJ, Schram MT, et al. Greater Blood Pressure Variability Is Associated With Lower Cognitive Performance. Hypertension 2019;73:803-811.
19. Tadic M, Cuspidi C, Bombelli M, Facchetti R, Mancia G, Grassi G. Relationships between residual blood pressure variability and cognitive function in the general population of the PAMELA study. J Clin Hypertens (Greenwich) 2019;21:39-45.
20. Wachtendorf LJ, Azimaraghi O, Santer P, Linhardt FC, Blank M, Suleiman A, et al. Association Between Intraoperative Arterial Hypotension and Postoperative Delirium After Noncardiac Surgery: A Retrospective Multicenter Cohort Study. Anesth Analg 2022;134:822-833.
21. Williams-Russo P, Sharrock NE, Mattis S, Liguori GA, Mancuso C, Peterson MG, et al. Randomized trial of hypotensive epidural anesthesia in older adults. Anesthesiology 1999;91:926-935.
22. Langer T, Santini A, Zadek F, Chiodi M, Pugni P, Cordolcini V, et al. Intraoperative hypotension is not associated with postoperative cognitive dysfunction in elderly patients undergoing general anesthesia for surgery: results of a randomized controlled pilot trial. J Clin Anesth 2019;52:111-118.
23. Lizano-Diez I, Poteet S, Burniol-Garcia A, Cerezales M. The burden of perioperative hypertension/hypotension: A systematic review. PLoS One 2022;17:e0263737.
24. Radinovic K, Markovic Denic L, Milan Z, Cirkovic A, Baralic M, Bumbasirevic V. Impact of intraoperative blood pressure, blood pressure fluctuation, and pulse pressure on postoperative delirium in elderly patients with hip fracture: A prospective cohort study. Injury 2019;50:1558-1564.
25. Wang NY, Hirao A, Sieber F. Association between intraoperative blood pressure and postoperative delirium in elderly hip fracture patients. PLoS One 2015;10:e0123892.
26. Hirsch J, DePalma G, Tsai TT, Sands LP, Leung JM. Impact of intraoperative hypotension and blood pressure fluctuations on early postoperative delirium after non-cardiac surgery. Br J Anaesth 2015;115:418-426.
27. de Havenon A, Anadani M, Prabhakaran S, Wong KH, Yaghi S, Rost N. Increased Blood Pressure Variability and the Risk of Probable Dementia or Mild Cognitive Impairment: A Post Hoc Analysis of the SPRINT MIND Trial. J Am Heart Assoc 2021;10:e022206.
28. Rickards CA, Tzeng YC. Arterial pressure and cerebral blood flow variability: friend or foe? A review. Front Physiol 2014;5:120.
29. Goodson CM, Rosenblatt K, Rivera-Lara L, Nyquist P, Hogue CW. Cerebral Blood Flow Autoregulation in Sepsis for the Intensivist: Why Its Monitoring May Be the Future of Individualized Care. J Intensive Care Med 2018;33:63-73.
30. Garbajs NZ, Singh TD, Valencia Morales DJ, Herasevich V, Warner DO, Martin DP, et al. Association of blood pressure variability with short- and long-term cognitive outcomes in patients with critical illness. Journal of Critical Care 2022;71.
31. Zorko Garbajs N, Valencia Morales DJ, Singh TD, Herasevich V, Hanson AC, Schroeder DR, et al. Association of Blood Pressure Variability with Delirium in Patients with Critical Illness. Neurocritical Care 2022.
32. Mena LJ, Felix VG, Melgarejo JD, Maestre GE. 24-Hour Blood Pressure Variability Assessed by Average Real Variability: A Systematic Review and Meta-Analysis. J Am Heart Assoc 2017;6.

Pregabalin Krka

trde kapsule, 25 mg, 50 mg, 75 mg, 150 mg, 300 mg *pregabalin*

Smernice za zdravljenje **nevropatske bolečine** priporočajo **pregabalin** kot **prvo izbiro zdravljenja**. (1)

Več jakosti za več možnosti zdravljenja

Sestava Ena trda kapsula vsebuje 25 mg, 50 mg, 75 mg, 150 mg ali 300 mg pregabalina. **Terapevtske indikacije** *Nevropatska bolečina* Zdravljenje periferne in centralne nevropatske bolečine pri odraslih. *Epilepsija* Dodatno zdravljenje pri odraslih s parcialnimi napadi, sekundarno generalizacijo ali brez nje. *Generalizirana anksiozna motnja pri odraslih* **Odmerjanje in način uporabe** Odmerjanje Razpon odmerjanja je od 150 do 600 mg na dan v 2 ali 3 odmerkih. *Nevropatska bolečina* Zdravljenje se lahko začne s 150 mg na dan v 2 ali 3 odmerkih. Glede na bolnikov odziv in prenašanje je mogoče čez 3 do 7 dni odmerek povečati na 300 mg na dan, in če je treba, čez nadaljnjih 7 dni na največji odmerek 600 mg na dan. *Epilepsija* Zdravljenje se lahko začne s 150 mg na dan v 2 ali 3 odmerkih. Glede na bolnikov odziv in prenašanje se odmerek čez 1 teden lahko poveča na 300 mg na dan. Po dodatnem tednu se lahko doseže največji odmerek, to je 600 mg na dan. *Generalizirana anksiozna motnja* Razpon odmerjanja je od 150 do 600 mg na dan v 2 ali 3 odmerkih. Potrebo po zdravljenju je treba redno ocenjevati. Zdravljenje s pregabalinom se lahko začne z odmerkom po 150 mg na dan. Glede na bolnikov odziv in prenašanje se lahko odmerek po 1 tednu poveča na 300 mg na dan. Še 1 teden zatem se lahko odmerek poveča na 450 mg na dan. Največji dovoljeni odmerek, ki se lahko doseže 1 teden pozneje, je 600 mg na dan. *Ukinitev pregabalina* Če je treba jemanje pregabalina prekiniti, ga je v skladu s klinično prakso, ne glede na indikacijo, priporočljivo zmanjševati postopoma, vsaj 1 teden. *Bolniki z ledvično okvaro* Očistek pregabalina je neposredno sorazmeren z očistkom kreatinina, zato je treba pri bolnikih z oslabljenim ledvičnim delovanjem odmerek individualno prilagoditi glede na očistek kreatinina. Pri bolnikih na hemodializi je treba dnevni odmerek pregabalina prilagoditi ledvičnemu delovanju. Poleg dnevnega odmerka morajo bolniki po vsaki 4-urni hemodializi takoj dobiti dodaten odmerek. *Bolniki z jetrno okvaro* Bolnikom z jetrno okvaro odmerka ni treba prilagajati. *Pediatrična populacija* Varnost in učinkovitost zdravila pri otrocih in mladostnikih nista bili dokazani. Na podlagi trenutno razpoložljivih podatkov ni mogoče dati priporočil o odmerjanju. *Starejši bolniki (po 65. letu)* Če je njihovo ledvično delovanje oslabljeno, je treba odmerek zmanjšati. Način uporabe Zdravilo se lahko jemlje s hrano ali brez nje. **Kontraindikacije** Preobčutljivost za učinkovino ali katerokoli pomožno snov v zdravilu. **Posebna opozorila in previdnostni ukrepi** V skladu s klinično prakso moramo nekaterim bolnikom s sladkorno boleznijo, pri katerih med zdravljenjem s pregabalinom pride do povečanja telesne mase, prilagoditi hipoglikemična zdravila. V obdobju trženja so poročali o preobčutljivostnih reakcijah, vključno z angioedemom. V povezavi z zdravljenjem s pregabalinom so redko poročali o hudih kožnih neželenih učinkih, vključno s Stevens-Johnsonovim sindromom (SJS) in toksično epidermalno nekrolizo (TEN), ki so lahko življenjsko nevarni ali smrtni. Zdravljenje s pregabalinom je bilo povezano z omotico in somnolenco, ki lahko pri starejših poveča pogostost nezgodnih poškodb (padcev). V obdobju trženja so poročali tudi o izgubi zavesti, zmedenosti in poslabšanju mentalnih sposobnosti, zato je treba bolnikom svetovati, naj bodo previdni, dokler ni znano, kako zdravilo učinkuje nanje. V obdobju trženja so poročali o neželenih učinkih na vid, vključno z izgubo vida, zamegljenostjo ali drugimi spremembami ostrine vida, ki so bile v večini primerov prehodnega značaja. Poročali so o primerih ledvične odpovedi; ob prekinitvi zdravljenja je bil ta neželeni učinek v nekaterih primerih reverzibilen. Za ukinitev sočasnega jemanja antiepileptičnih zdravil in prehod na monoterapijo s pregabalinom, ko je pri dodatnem zdravljenju s pregabalinom dosežen nadzor nad napadi, ni zadostnih podatkov. V obdobju trženja so pri nekaterih bolnikih, ki so jemali pregabalin, poročali o primerih kongestivnega srčnega popuščanja. Takšne reakcije so se večinoma pojavile pri starejših bolnikih s srčno-žilnimi boleznimi, ki so dobivali pregabalin za nevropatsko indikacijo. Pri zdravljenju bolnikov s centralno nevropatsko bolečino kot posledico poškodbe hrbtenjače se je povečala pogostost neželenih učinkov, povezanih z osrednjim živčevjem, posebno somnolence. Pri bolnikih, ki imajo zmanjšano respiratorno funkcijo, bolezen dihal ali živčevja, ledvično okvaro ali sočasno uporabljajo depresorje osrednjega živčevja, in pri starejših lahko obstaja večje tveganje za pojav hude depresije dihanja. Pri bolnikih, ki so se zaradi različnih indikacij zdravili z antiepileptiki, so poročali o samomorilnem razmišljanju in vedenju. Pri bolnikih, ki so dobivali pregabalin v obdobju trženja, so opazili povečano tveganje za pojav samomorilnega vedenja in smrti zaradi samomora. V obdobju trženja so ob sočasnem jemanju pregabalina in zdravil, ki lahko povzročijo zaprtje, kot so opioidni analgetiki, poročali o učinkih, povezanih z zmanjšanim delovanjem spodnjega gastrointestinalnega trakta (npr. o črevesni zapori, paralitičnem ileusu, zaprtju). Pri predpisovanju pregabalina sočasno z opioidi je potrebna previdnost zaradi tveganja za pojav depresije osrednjega živčevja. Poročali so tudi o primerih nepravilnega jemanja, zlorabe in odvisnosti. Po prekinitvi kratkotrajnega ali dolgotrajnega zdravljenja s pregabalinom so pri nekaterih bolnikih opazili odtegnitvene simptome. Med jemanjem pregabalina ali kmalu po prekinitvi se lahko pojavijo krči, vključno z epileptičnim statusom in generaliziranimi krči. Predvsem pri bolnikih z osnovnimi stanji, ki lahko izzovejo encefalopatijo, so poročali o primerih encefalopatije. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij** Pregabalin lahko stopnjuje učinke etanola in lorazepama. V obdobju trženja so poročali o primerih odpovedi pljuč in primerih kome pri bolnikih, ki so jemali pregabalin in druga zdravila, ki zavirajo delovanje osrednjega živčevja. Kaže, da pregabalin prispeva k okvari kognitivnega in grobega motoričnega delovanja, ki jo povzroča oksikodon. **Plodnost, nosečnost in dojenje** Ženske v rodni dobi morajo med zdravljenjem uporabljati učinkovito kontracepcijo. Jemanje pregabalina v prvem trimesečju nosečnosti lahko povzroči večje prirojene napake pri nerojenem otroku. Pregabalin Krka se ne sme jemati med nosečnostjo, razen če je nujno potrebno (če koristi za mater prevladajo nad možnim tveganjem za plod). Pregabalin se izloča v materino mleko. Učinek pregabalina na dojene novorojenčke/dojenčke ni znan. Odločiti se je treba med prenehanjem dojenja in prekinitvijo zdravljenja s pregabalinom, pri čemer je treba pretehtati prednosti dojenja za otroka in prednosti zdravljenja za mater. **Vpliv na sposobnost za vožnjo in upravljanje strojev** Zdravilo Pregabalin Krka lahko povzroči omotico in somnolenco in tako blago ali zmerno vpliva na sposobnost za vožnjo in upravljanje strojev. Bolnikom je treba svetovati, naj ne vozijo, ne upravljajo zapletenih strojev in ne opravljajo drugih potencialno nevarnih dejavnosti, dokler ni znano, ali to zdravilo vpliva na njihovo zmožnost opravljanja takšnih dejavnosti. **Neželeni učinki** Zelo pogosti neželeni učinki so omotica, somnolenca in glavobol. Pogosto se pojavijo nazofaringitis, povečanje apetita, evforično razpoloženje, zmedenost, razdražljivost, dezorientiranost, nespečnost, zmanjšanje libida, ataksija, poslabšana koordinacija, tremor, dizartrija, amnezija, okvara spomina, motnje pozornosti, parestezije, hipestezija, sedacija, motnje ravnotežja, letargija, zamegljen vid, diplopija, vrtoglavica, bruhanje, navzeja, zaprtje, driska, flatulenca, napetost trebušne stene, suha usta, mišični krči, artralgija, bolečine v hrbtu, bolečine v udih, krči v vratu, motnje erekcije, periferni edemi, edemi, nenormalna hoja, padec, občutek pijanosti, nenormalno počutje, utrujenost in povečanje telesne mase. Ostali neželeni učinki se pojavijo občasno, redko ali zelo redko. **Imetnik dovoljenja za promet z zdravili** Krka, d. d., Šmarješka cesta 6, 8501 Novo mesto, Slovenija. **Način izdajanja zdravila** Samo na zdravniški recept. **Oprema** 56 trdih kapsul po 25 mg, 50 mg, 75 mg, 150 mg ali 300 mg pregabalina. **Datum zadnje revizije besedila** 19. 2. 2023.

Slovenija, 5/2023, 395401-2023, TM.

1. Attal N, Cruccu G, Baron R et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. European Journal of Neurology 2010, 17: 1113-1-23.

Samo za strokovno javnost. Celoten povzetek glavnih značilnosti zdravila je objavljen na www.krka.si.

Krka, d. d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenija, www.krka.si

KRKA

The 11th COGNITIVE DAY meeting was made possible by

Main sponsor
Krka d.d.

Organisers
Center for Cognitive Impairments, Department of Neurology, University Medical Centre Ljubljana

Slovenian Neurological Association

Sponsors

ABBVIE d. o. o.

BIOGEN Pharma d. o. o.

LEK farmacevtska družba d. d.

MEDIS d. o. o.

NOVARTIS Pharma Services INC.

STADA d. o. o.