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Preface

Milica G. KRAMBERGER, MD, PhD

Dear esteemed colleagues,

It is with genuine enthusiasm that I extend to you a collection of scholarly articles and abstracts curated for the upcoming 12th Cognitive Day international meeting.

Alzheimer's disease (AD) stands as a formidable challenge in the realm of neurodegenerative disorders, its pathogenesis woven from a tapestry of intricate factors. Marked by the accumulation of Aβ plaques and tau neurofibrillary tangles (NFTs), AD heralds neuronal loss and cognitive decline. The insidious nature of AD manifests through years of silent aggregation before clinical symptoms emerge, underscoring the urgent need for proactive interventions. Over the years, the landscape of AD research has witnessed remarkable strides towards early detection through in-vivo biomarkers and the pursuit of multimodal therapeutic approaches. Promising avenues, including therapies targeting amyloid accumulation and tau pathology, offer hope in the global effort to combat this relentless disease.

The significance of Cognitive Day international meetings transcends mere academic discourse; they serve as crucibles for ongoing education and refinement of clinical practices in managing patients grappling with cognitive impairments. We are honored by the enduring support extended to us, enabling the congregation of esteemed experts hailing from diverse disciplines and corners of the globe – psychiatry, geriatrics, neurology, psychology, and neuroradiology, among others. Central to our mission is the provision of dynamic education, empowering all stakeholders involved in the care of patients with neurodegenerative conditions. Through collaborative efforts, we strive to fortify the endeavors of multidisciplinary teams dedicated to addressing the needs of individuals navigating cognitive challenges.
Through this compendium and the collective wisdom it encapsulates, we aim to illuminate the latest breakthroughs in our shared field of inquiry. This anthology, designed to serve as both an enriching resource and a testament to higher education, promises to captivate medical students, trainee specialists, and seasoned practitioners alike. Its insights will undoubtedly enrich the practice of every member of the multidisciplinary team, fostering enhanced care for those entrusted to our collective stewardship.

Our heartfelt appreciation extends to all the esteemed lecturers and contributors whose unwavering dedication has enriched this endeavor beyond measure.

Program

08:30 - 09:00 **Registration**

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

RISK FACTORS

09:05 **Cardiovascular risk factors in older adults**
Andreja ŠPEH, Ljubljana, Slovenia

09:25 **Genetics and epigenetics of Alzheimer's disease**
Alja VIDETIČ PASKA, Ljubljana, Slovenia

09:45 **Late life depression - diagnostic and treatment strategies**
Polona RUS PRELOG, Ljubljana, Slovenia

10:05 **Discussion**

STRUCTURAL IMAGING BIOMARKERS

10:15 **Alzheimer's disease - imaging protocol, implementation and challenges**
Srečko DOBRECOVIĆ, Ljubljana, Slovenia

10:45 **ARIA-E, ARIA-H, and iatrogenic CAA-related inflammation. Time for reconsiderations?**
Fabrizio PIAZZA, Milan, Italy

11:15 **Discussion**

11:30 - 11:45 **Coffee Break**

FLUID BIOMARKERS

11:45 **Diagnostic performance of novel p tau biomarkers in clinical practice**
Andreja EMERŠIČ, Ljubljana, Slovenia

12:15 **Blood biomarkers for clinical diagnosis and anti-amyloid therapy monitoring: important factors to consider**
Thomas K. KARIKARI, Pittsburgh, USA

12:45 **Discussion**

13:00 - 14:00 **LUNCH**

THERAPY

14:00 **Alzheimer disease – future treatment strategies & challenges**
Bengt WINBLAD, Stockholm, Sweden

14:30 **Lecanemab - from mutation to a treatment for Alzheimer's disease**
Lars LANNFELT, Uppsala, Sweden

15:00 **Discussion**

15:15 **Closing remarks**

Cardiovascular health and cognition in older adults: Differences across screening strategies and European countries in the MOPEAD project

Andreja Špeh

BACKGROUND

The number of people with dementia is expected to increase in the future, yet the projected increases vary across different geographical regions. The smallest percentage changes in projected dementia cases are expected in high income Asia Pacific and western Europe, and the largest in north Africa and Middle East [1]. These regional variations stem from many factors including cultural disparities, policy variations, and economic disparities, all of which impact an individual's health and cognitive status, thus affecting dementia prevalence.

In dementia research, recruitment procedures for individuals with cognitive impairment vary, leading to study samples with different characteristics. Population-based sampling tend to include subjects who are older, less educated, and exhibit poorer cognitive performance, along with a less frequent family history of Alzheimer's disease (AD) [2, 3], while convenience samples show more pronounced rates of hippocampal volume decline [3].

Modifiable risk factors, such as hypertension, obesity, and physical inactivity account for 40 % of dementias, which could theoretically be prevented or delayed [4], emphasizing the potential for preventive interventions. Additionally, in the future of disease-modifying treatments for AD, early and efficient diagnostics gain importance, requiring an understanding of individual and environmental characteristics. The European Union Innovative Medicines Initiative project, Models of Patient Engagement for Alzheimer's Disease (MOPEAD), aimed to identify the most effective and cost-efficient screening method for detecting prodromal AD and mild AD dementia in different European countries [5]. Our aim was to examine differences in cardiovascular factors and cognitive function among five European countries and four screening strategies using MOPEAD data.

RESULTS

We analysed data from 414 individuals aged 65-85 (M = 71.9, SD = 5.0) years with a positive screening result indicating high risk of prodromal or mild AD. Four different screening strategies were used: a web-based screening tool, an open house initiative (OHI), a primary care-based protocol for early detection of cognitive decline, and a tertiary care-based screening at diabetologist clinics. Participants from Germany, Spain, the Netherlands, Sweden, and Slovenia were included. Our findings revealed significant differences in cardiovascular health and cognition among five European countries and four screening strategies using data from the MOPEAD project.

Cross-country differences

Significant differences were observed between included countries in physical activity, high blood pressure, dyslipidaemia, and all cognitive outcomes. Participants from Sweden exhibited the highest levels of physical activity and the lowest prevalence of dyslipidaemia, whereas individuals from Spain demonstrated the opposite trend. While Swedish participants have been previously documented as highly active [6], individuals from Spain displayed notably higher rates of negative health outcomes, including hypertension (67.2 %), hyperlipidaemia (65.7 %), physical inactivity (61.9 %), and smoking (5.2 %). Despite the Mediterranean region's reputation for healthy living, Spanish adults appear comparatively less active than their European counterparts [7] [8]. Additionally, studies focusing on diet report than the adherence to the Mediterranean diet among Spanish older individuals has declined [9–11], reflecting a shift towards more westernized eating habits characterised by increased consumption of commercial pastries, sweetened beverages, and red or processed meats.

In terms of cognition, similar trends emerged among participants. Individuals from Germany and the Netherlands achieved the highest scores on cognition, whereas Spanish participants had the lowest scores across most of cognitive domains. The cognitive performance of Spanish participants could be explained with their poorer cardiovascular health. Interestingly, previous studies on European participants have often highlighted Scandinavians as exhibiting the

highest cognitive performance [12, 13]. However, Formanek et al. reported that Scandinavians experienced an annual cognitive decline at approximately twice the rate compared to other European regions, a phenomenon attributed to their high cognitive reserve [13]. It is plausible that this process of cognitive decline has already compensated for their earlier cognitive performance, potentially explaining why Scandinavians may not stand out as prominently in our comparisons.

Screening differences

Participants recruited via diabetologist clinics had worse cardiovascular health, poorer performance on cognitive tests, and the highest proportion of individuals diagnosed with MCI and dementia. Considering the frequently present concurrent risk factors in diabetes, this finding did not come as a surprise. However, it represents a significant weakness in relation to (early) diagnosis of cognitive disorders.

Individuals enrolled via web-based testing demonstrated the most favourable outcomes, with the highest levels of physical activity, lowest incidence of diabetes and heart disease, and best cognitive performance on the domains of global cognition, immediate memory, visuo-spatial/constructional abilities, attention, and delayed memory. Virtually recruited samples tend to be slightly younger and more geographically diverse [17].

Diverse recruitment methods yield study samples with different characteristics. While memory clinic settings provide the most cost-effective context to study the phenomenology of subjective cognitive decline (SCD) to AD and eventually recruit patients for secondary prevention trials, population-based samples seem to be less biased and probably more suitable for the study of memory complaints [20]. Our findings underscore the importance of considering diverse recruitment methods in assessing and managing cardiovascular health and cognitive function. The high proportion of under detected dementia cases in community and residential settings [21] further supports the importance of implementing effective screening programs to identify individuals at risk and provide timely interventions. Recognizing potential problems early in their course offers many advantages, prompting a demand for quick and effective identification methods. We believe that the OHI emerges as a promising strategy for capturing a diverse range of participants, which could be especially relevant for early diagnostics in the context of future disease-modifying treatments. This approach facilitates broader community engagement, enabling clinicians to reach individuals from various backgrounds and demographics who may not typically seek clinical evaluation.

CONCLUSIONS

Our study unveils significant disparities in cardiovascular health and cognition among five European countries participating in the MOPEAD project, as well as across four distinct screening strategies. Emphasizing the importance of recruitment methods, the OHI shows promise in capturing a more representative sample. Future research should focus on formulating tailored recommendations for reducing risk factors considering the specific characteristics of different populations.

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Genetics and epigenetics of Alzheimer's disease

Alja Videtič Paska

Alzheimer's disease (AD) is a complex and multifactorial disorder that is influenced by the interplay of genetic background and environmental factors. Development of AD has long prodromal phase in which early prevention strategies could importantly contribute to slower progression of the disease. Currently, the significant biomarkers of AD are senile extracellular plaques of amyloid- and intracellular neurofibrillary tangles of hyperphosphorylated tau protein in the brain, but these are determined when the characteristic symptoms of the disease already appear [1]. For better prognosis and timely treatment interventions additional biomarkers of AD would be necessary.

More than 95% of AD cases are sporadic or late-onset AD (LOAD) and the etiology is heavily influenced by interconnected genetic and environmental risk factors [2,3]. The search for genetic biomarkers, including extensive genome-wide association studies, revealed more than 20 genes that could affect the risk of developing AD. The strongest association with AD showed the apolipoprotein E (ApoE) gene. The most common alleles are Apo E4, E3 and E2 in heterozygous or homozygous states. The strongest genetic risk factor for AD is the allele ApoE E4 that causes earlier disease onset and accelerates symptoms. The ApoE has been implicated in atherosclerosis, as well as hypertension, and it is of much interest due to its relation to the amyloid- pathology [3].

The AD-related genetic variants of ApoE are composed of two single nucleotide polymorphisms (SNPs): rs429358 and rs7412. With the combination of these SNPs the distinct allelic variants ApoE-ε2, ApoE-ε3, and ApoE-ε4 are formed. The most common variant is ApoE-ε3, while ApoE-ε4 is the AD susceptibility variant. The ApoE-ε4 homozygotes have a 25-fold increased risk for developing AD compared to ApoE-ε3 homozygotes [4].

The aim of our study was to identify the frequency of ApoE alleles in the Slovene memory clinic population of patients with cognitive impairment. The cohort included almost 700 patients with dementia and healthy volunteer controls for which classical AD biomarker tests like amyloid- and tau protein and also ApoE genotypes were determined. Genotyping revealed that ApoE ε 3/ ε 3 is the most common genotype in Slovenian population. The ApoE ε 4/ ε 4 genotype that was not identified in controls and showed gradual increase in frequency from controls, through subjective cognitive decline and mild cognitive impairment to AD patients, supporting ApoE as significant clinical biomarker also in Slovenian population. We can conclude that genotyping for ApoE alleles could be used also in clinical setting when the genotype information is crucial in decisions regarding administration of novel drugs, such as lacenemab.

The AD pathology is complex and is, beside genetics, the AD initiation, age of onset, and disease progression, driven also by lifestyle and environmental factors [3]. The interplay of these factors could be explained by epigenetics – the mechanisms that do not change the DNA sequence, but affect the gene expression. Among the most studied and understood epigenetic mechanisms is DNA methylation. It affects cognitive functions through maintenance of basic cellular processes and synaptic plasticity in the central nervous system. Recent advances in sequencing technologies and bioinformatics analysis enabled DNA methylation studies in larger scale. Several candidate genes, like APOE, brain-derived neurotrophic factor (BDNF), ankyrin 1 (ANK1), and others were studied, but so far no clear conclusion can be drawn. Namely, studies reported both increased and decreased levels of DNA methylation, which could be partially explained by different tissue samples used [5]. In our study DNA methylation status of BDNF and catechol-o-methyltransferase (COMT) were interrogated. BDNF is an important nervous growth factor that promotes neuronal survival, development and function. It plays an important role in modulating cognition, learning and memory. COMT is involved in catecholamine metabolism through dopamine degradation, and its COMT genetic variants have been shown to influence cognitive functions. Our results revealed higher expression levels of BDNF in mild cognitive impairment (MCI) subjects compared to individuals diagnosed with AD. Analysis of DNA methylation showed difference in DNA methylation between AD and MCI subjects. The results of this study suggest BDNF as potential biomarker that could help distinguish between MCI and AD patients. On the other hand, no difference in the COMT gene expression or DNA methylation was detected between two groups of subjects [6].

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Late-life depression: diagnostic and treatment strategies

Polona Rus Prelog

Late-life depression (LLD) is an umbrella term for major depressive disorder in the elderly, irrespective of when the initial depressive episode occurred. It includes both early-onset cases, often linked to genetic predispositions and adverse childhood experiences, as well as late-onset cases, more frequently associated with life stressors characteristic of advancing age and physical decline. The risk factors for developing LLD are multidimensional, including biological elements like subcortical cerebrovascular disease, cognitive impairment, frailty, sleep disturbances, and other coexisting medical conditions, particularly cardiovascular diseases and chronic illnesses (1). Psychological and psychiatric symptoms, often present in LLD, such as anxiety, neuroticism (observed through personality assessments), dysthymia, loneliness and substance misuse disorders, are significant contributors to the disease burden and presentation. Moreover, the social environment, including factors like grief, a role of caregiving, other family and relational stressors and diminished social support are critical in the manifestation of LLD. LLD differs from depression in younger individuals in various aspects, including risk and protective factors, clinical presentation, cognitive impairment, and co-occurring physical symptoms.

LLD is increasingly recognized as both a mood and cognitive disorder due to the intricate link between affective symptoms and cognitive decline, traditionally presenting as a triad of executive dysfunctions (e.g., planning, sequencing, multitasking), attentional deficits, and a general slowing in cognitive processing. However, recent studies indicate that memory impairment should also be considered in the assessment of LLD, as a factor complicating the cognitive profile associated with depression in the elderly. The efficacy of antidepressants in potentially ameliorating cognitive deficits as part of the treatment for LLD has yet to be clearly established.

Research suggests that depression, while treatable, presents a significant risk factor for dementia, and its elimination could potentially decrease the incidence of dementia on a population level by 4%, surpassing even the impact of reducing other risk factors such as hypertension, diabetes, obesity, and physical inactivity (2). The interconnection between depression, cognitive decline, and dementia is complex and remains not fully elucidated. Research evidence shows that depression is a potential causal factor for dementia, especially Alzheimer's disease (AD), with studies indicating a two-fold increase in the risk of dementia associated with depression. Additionally, the severity of depressive symptoms and the frequency of depressive episodes have been linked to a higher risk of all-cause dementia, suggesting that depression might also present a prodromal phase of dementia (3). The association was found for various dementia types, including AD and vascular dementia. Furthermore, depression has been recognized as an accelerating factor in cognitive decline. Irrespective of the viewpoint, the potential of depression as a modifiable factor in the development of dementia suggests that treatment strategies for depression could delay the progression of dementia.

LLD correlates with an array of detrimental long-term outcomes, including growing disability, functional and cognitive decline, an increased risk of dementia, and higher mortality due to medical conditions or suicide (4). Despite the well-developed treatment protocols, it is estimated that approximately half of the elderly individuals with LLD do not respond sufficiently to first-line antidepressant therapies (5). This leads to an increased risk of relapse, treatment non-adherence for concurrent physical conditions, and an increased likelihood of early mortality, which may include death by suicide. Barriers to accessing care remain significant, with less than half of the elderly with mental health and substance use issues receiving appropriate care.

Current treatments for LLD, comprising pharmacotherapy, neuromodulation, psychotherapy, and a suite of non-pharmacological interventions, demonstrate efficacy (6). Psychotherapeutic interventions for LLD have been examined through several systematic reviews and network meta-analyses, comparing the effectiveness and acceptability of various therapies including cognitive-behavioral therapy, life review therapy, and mindfulness, among others (7). The evidence suggests no significant differences in effectiveness among these therapies, with life review therapy ranking high in terms of effectiveness and acceptability. Despite limitations in the quality of evidence, psychotherapy approaches appear effective for LLD.

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Alzheimer‘s disease imaging protocol, implementation, and challenges

Srečko Dobrecović

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that affects millions of individuals worldwide. Imaging techniques play a crucial role in the diagnostic pathway, diagnosis and monitoring of AD progression. There are several objectives that imaging aims to asses. Detecting disease in preclinical stage when symptoms are diminutive, as mild cognitive impairment or in the early stages of AD. More than half of cases of AD remain undetected in the early stages. Imaging techniques play a crucial role in the diagnosis and management of AD. Magnetic resonance imaging (MRI) is commonly used to assess abnormalities in specific brain regions associated with AD, such as the hippocampus and entorhinal cortex. MRI provides detailed structural information of the brain, allowing for the detection of atrophy and changes in brain volume associated with the disease. Structural MRI is sensitive to presymptomatic disease and can be used as a biomarker. Therefore, standardized methods that produce stable results across scanners and over time are required. MRI protocol should approach a wide variety of disorders, typically slowly progressive, with variable gradual neurologic dysfunction. As is the case with most MRI protocols, there is no such thing as a universally agreed upon MRI protocol to image an individual with a suspected neurodegenerative condition. What is essential is that good quality three plane imaging (sagittal, coronal and axial) is obtained which includes T1, T2, FLAIR, DWI and SWI sequences.

A standard protocol should include: T1 sequence, volumetric gradient-echo e.g. MPRAGE, preferably isometric e.g. 0.9 mm reformatted in three planes. Anatomical, best for assessing regional volume loss and may be used for automated brain morphometry. T2 sequence: fast spin echo, whole-brain, e.g. 3 mm. Purpose: signal intensity of basal ganglia, and posterior fossa structures (often less well seen on FLAIR due to flow artefact) FLAIR sequence: whole-brain axial or or volumetric. Purpose: white matter signal abnormalities such as small vessel ischemia resulting in multi-infarct dementia and abnormal sulcal signal in leptomeningeal processes (e.g. leptomeningeal carcinomatosis). DWI/ADC Purpose: cortical or deep grey matter restricted diffusion in Creutzfeldt Jakob disease (CJD) and restriction in demyelination of infarction (e.g. cerebral vasculitis). SWI sequence (if not option T2*): SWI including phase and magnitude images. Purpose: microhemorrhages (e.g. cerebral amyloid angiopathy (CAA), hypertensive encephalopathy). Mineral deposition in the cortex (e.g. AD, amyotrophic lateral sclerosis (ALS)). Loss of low signal in substantia nigra (Parkinson disease). Additionally, functional imaging techniques such as positron emission tomography (PET) can provide valuable information on brain metabolism and amyloid deposition in Alzheimer's disease.

The implementation of imaging protocols in Alzheimer's disease involves standardized procedures for image acquisition, processing, and interpretation. These protocols aim to ensure consistency and reproducibility in imaging studies, allowing for accurate diagnosis and monitoring of disease progression. Collaboration between radiologists, neurologists, and other healthcare professionals is essential for the successful implementation of imaging protocols in AD.

Despite the advancements in imaging technology, several challenges remain in the imaging of AD. These challenges include the variability in imaging findings among patients, the interpretation of imaging results in the context of clinical symptoms, and the need for longitudinal imaging studies to track disease progression over time. Additionally, the cost and availability of imaging techniques can pose barriers to widespread implementation in clinical practice. In conclusion, imaging plays a crucial role in the diagnosis and management of AD. Standardized imaging protocols, collaboration among healthcare professionals, and addressing challenges in imaging interpretation are essential for improving the accuracy and utility of imaging in AD.

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ARIA-E, ARIA-H, and iatrogenic CAA-related inflammation. Time for reconsiderations?

Fabrizio Piazza

ARIA-E/H (amyloid-related imaging abnormalities-edema/hemorrhage) is an umbrella term coined to define the radiographic appearance of MRI images abnormality during treatments with Aβ-lowering monoclonal antibodies (mAbs) for Alzheimer's disease immunotherapy.

Today, it is well recognized that ARIA-E events can also occur spontaneously in patients with cerebral amyloid angiopathy-related inflammation (CAA-ri), a rare autoimmune encephalopathy associated with raised cerebrospinal fluid (CSF) concentrations of spontaneous auto-antibodies against Aβ (aAbs).

In this framework, the last years of research and experience of the iCAB international Network generated an increased consensus that therapy-induced ARIA is the iatrogenic manifestation of CAA-ri. Indeed, the natural history of CAA-ri, the response-to-corticosteroid therapy outcomes, the regional and temporal co-localization of radiographic ARIA-E with microglial activation (both on neuropathology and in vivo with TSPO-PET), and the downstream negative effects on the Aβ-clearance pathways and related risks on the subsequent occurrence of an ARIA-H event, all provide remarkable supportive evidence that ARIA-E associated with mAbs therapy is iatrogenic CAA-ri.

In this talk, we will present and critically discuss the emerging new data supporting the potential of the assay for anti-Aβ (auto)antibody CSF testing as a companion diagnostic and early biomarker for CAA-ri and ARIA in real-world clinical practice and immunotherapy trials. In this framework, we will also present the recently launched "ARIAis-CAAri" Biomarkers Research study; an international, prospective, longitudinal cohort Registry and Biobank of patients with ARIA and CAA-ri from the real-world clinical practice aimed at fostering a precision medicine approach and improving research collaborations between the AD and CAA community.

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Diagnostic performance of novel P-tau biomarkers in clinical practice

Andreja Emeršič

Introduction

Alzheimer's disease (AD) is characterized by extracellular amyloid plaques made of aggregated amyloid-β (Aβ) peptides and neurofibrillary tangles of hyperphosphorylated tau (p-tau) protein that accumulate within neurons. Although underlying pathology can only be confirmed by postmortem examination, cerebrospinal fluid (CSF) and neuroimaging biomarkers are considered valid indicators of neuropathological hallmarks and have greatly improved the diagnostic accuracy for AD during life.1,2 However, the long-awaited approval of disease-modifying therapies might challenge clinical pathways in the future, as identifying potential candidates for treatment early in the disease course and monitoring drug activity with easily accessible and cost-effective tools will become crucial.2,3 Because established CSF and PET biomarkers require specialized facilities and costly or relatively invasive diagnostic procedures, they are less convenient for widespread application or frequent assessments of therapeutic response. Recent progress in the field of blood-based biomarkers of AD is well-timed and offers the possibility of broader community-based screening that is not limited to specialist care hospitals.3,4 Particularly promising are plasma p-tau biomarkers, demonstrating similar performances to detect AD pathology as their CSF counterparts.3–5

Tau phosphorylation and truncation

Tau is a more complex and heterogeneous biomarker than first thought. Aside from six tau isoforms, resulting from alternative splicing of the mRNA in the adult brain, tau can undergo several posttranslational modifications and proteolytic cleavage (truncation), which diversly affect protein function.6,7 Furthermore, the so-called big tau isoform is abundant in peripheral nervous system neurons and contributes up to 80% to the tau protein measured in plasma.8,9 The role of tau in microtubule assembly and stability is regulated primarily by the phosphorylation of amino acid residues in the microtubule-binding region, effectively modulating the binding affinity of tau for tubulin.10 Frequent cycles of phosphorylation and dephosphorylation (detachment from and binding of tau to microtubules) are fundamental to maintaining normal axonal transport, however, hyperphosphorylation can lead to tau misfolding and aggregation.7,10 Neurofibrillary tangles from AD brain have been shown to contain tau phosphorylated at more than 40 residues out of 85 potential phosphorylation sites (serine (S), threonine (T), and tyrosine residues), whereas only about 20 phosphorylated sites have been identified in tau extracted from healthy brains.7,11 Interestingly, tau is transiently hyperphosphorylated during brain development, hypothermia, and hibernation in hibernating mammals, so the process itself is not detrimental as long as it is reversible.12,13

Despite the overlaps between sites that have been found to undergo phosphorylation in AD and healthy brains,13 several p-tau biomarkers have proven useful for AD diagnosis. Antibody against tau phosphorylated at S202/T205 is commonly used in immunohistochemistry to reveal neurofibrillary tangles at postmortem examination14 while in CSF, p-tau181 is an established biomarker currently being used in clinical practice.3,15 Additionally, new assays targeting p-tau181, 217, 212, 231, and 235 have been shown to differentiate AD from non-AD neurodegenerative disorders, including other tauopathies, which are also associated with pathological aggregates of hyperphosphorylated tau protein.16–24 The finding that CSF (plasma) p-tau is not consistently increased in primary tauopathies could indicate different rates of p-tau secretion into the extracellular space, site-specific phosphorylation, or alternative proteolytic processing of tau in these diseases, resulting in protein concentrations or epitopes that are not detected by present immunoassays.25,26 Indeed, elevated CSF tau can arise from the passive release of tau from dying neurons, thereby reflecting the intensity of neurodegeneration or acute brain injury (total tau), but growing evidence suggests that tau is also actively secreted from AD-affected neurons.3,6,27 Because truncated C-terminal fragments are retained in the neurofibrillary tangles in the brain, CSF tau was shown to consist of mid-region and N-terminal tau fragments. The pool of soluble tau forms released into the blood is likely further reduced to contain mostly N-terminal tau species.27 A better understanding of tau processing has led to the development of

several blood p-tau biomarkers, with the best performance achieved by assays that quantify N-terminal p-tau.3,27

Novel p-tau biomarkers in the cerebrospinal fluid

Biomarkers of Aβ pathology are considered the earliest detectable change in AD as reduced CSF Aβ42 (Aβ42/40 ratio) is observed 10-20 years before the onset of dementia.1,28–30 The established CSF p-tau181 targeting mid-region parts of the protein becomes abnormal later, during mild cognitive impairment (MCI) or dementia stage, with the evolution of the following cognitive symptoms largely depending on the presence of other comorbidities, AD risk factors, and individual differences in cognitive reserve.1,28,30,31 Nevertheless, some p-tau forms seem to increase earlier in the disease course, in parallel with subtle changes in Aβ deposition.18,32,33 CSF mid-region p-tau231, N-terminal p-tau181, and N-terminal p-tau217 have been shown to increase before the mid-region p-tau181 in cognitively unimpaired individuals in preclinical stage of the AD continuum.18 Accordingly, these biomarkers differentiated better between Aβ positive and Aβ negative individuals (determined by CSF Aβ42/40 < 0.071, Aβ-PET positive visual read or Aβ-PET centiloid >12) than the established p-tau181.18 We obtained similar results when comparing the diagnostic performance of N-terminal p-tau217 and p-tau181 with mid-region p-tau181 in two memory clinic cohorts; both N-terminal p-tau biomarkers distinguished early AD MCI from non-AD MCI more accurately than the standard p-tau181.33 In line with the previous mass spectrometry study34, p-tau217 displayed the highest fold changes in our AD patients, indicating greater dynamic ranges compared to p-tau181 biomarkers.33 In participants across the AD continuum who had undergone Aβ and tau PET,32 increases in CSF p-tau231 were found to be associated with regional Aβ deposition in the medial orbitofrontal, precuneus, and posterior cingulate cortices even before global Aβ-PET positivity was reached.32 Compared to p-tau181, N-terminal p-tau231 also had a greater capacity to detect concomitant AD in our autopsy-verified Creutzfeldt-Jakob disease cases.35 Furthermore, novel p-tau235 has been suggested as a potential staging biomarker, since increased CSF concentrations were observed mostly in AD patients with preceding tau phosphorylation at threonine-231.21 Collectively, CSF studies have demonstrated several p-tau biomarkers can separate AD dementia from Aβ negative individuals with high accuracy, however, p-tau231 and p-tau217 show superior performances in preclinical AD and early MCI.

Diagnostic performances of plasma p-tau biomarkers

The diagnostic potential of plasma p-tau181, 217, and 231 has been extensively studied and validated compared to the established CSF and PET biomarkers and against the postmortem examination.3,4,20,23,36–38 Plasma p-tau181 and p-tau217 were found to increase already in presymptomatic stages in both sporadic and familial AD, up to 20 years before the estimated onset of MCI among the PSEN1 mutation carriers.22,39 Blood p-tau concentrations correlate with cognitive assessments and predict future decline and progression to AD MCI or dementia.16,22,24,40,41 Same as the corresponding CSF biomarkers, plasma p-tau231, and p-tau217 have demonstrated earlier and stronger associations with Aβ and tau pathologies than the p-tau181.20,23 Due to the observed associations with disease severity and increases along the AD continuum plasma p-tau biomarkers could become accessible tools to detect underlying AD pathology and provide insights into disease progression in different clinical and research settings.3,4 For example, pre-screening with plasma p-tau181 in the Alzheimer's disease neuroimaging initiative would presumably save almost 60% of the costs compared with the Aβ-PET screening alone.3 A two-step approach based on plasma p-tau217 has been proposed to risk stratify MCI patients for Aβ positivity, which could reduce the number of confirmatory CSF Aβ42/40 tests by >80% and thereby offer a cost-effective strategy to detect AD in memory clinic settings.42 In the clinical trial with donanemab pre-screening with plasma p-tau181 enriched the study population for Aβ and tau-PET positivity, which was confirmed in 63% of candidates who screened positive for p-tau181 compared to 37% of positive PET scans among those without pre-screening.4 Similarly, plasma p-tau181 was in agreement with CSF Aβ positivity in 51% of cases within our Precision Medicine Interventions in Alzheimer's Disease (PMI-AD) project.43 Applying p-tau217 to pre-screen individuals in this community-based cohort would increase recommended confirmatory CSF testing by 18%; among the participants who actually underwent lumbar puncture, 62% of those with plasma p-tau217 above the screening threshold had decreased CSF Aβ42/40 ratio (unpublished data).

Outstanding challenges

At present, methods that quantify novel p-tau biomarkers are research-grade assays, developed in independent academic or pharmaceutical research laboratories and validated mostly in well-characterized cohorts. Although commercial assays have become available, further standardization efforts are needed before they can be classified as in vitro diagnostic medical devices (IVD) to be used for clinical purposes.3,4 Few head-to-head comparison studies published so far have reported high accuracy for AD diagnosis for most of the investigated p-tau

biomarkers, however, significantly lower performances and only modest correlations with CSF measurements have been found for some of the existing plasma p-tau assays.3,5 Real-world data on p-tau performance in memory clinic cohorts with greater heterogeneity and diverse clinical presentations is still scarce but will importantly guide decisions on the appropriate use of plasma p-tau biomarkers in daily practice.3,44 Finally, to ensure the correct interpretation of the results, it will be essential to understand and address various factors that may influence p-tau measurements in the blood.3,45

Conclusions

We have witnessed tremendous progress in the field of blood-based biomarkers of AD. Recent studies have demonstrated plasma p-tau is a promising biomarker of underlying AD pathology with imminent diagnostic application. While some clinical trials have already adopted plasma p-tau to pre-screen eligible participants, outstanding challenges remain before we can implement these blood biomarkers into clinical practice.

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Blood biomarkers for clinical diagnosis and anti-amyloid therapy monitoring: Important factors to consider

Thomas K. Karikari

Plasma biomarkers have shown tremendous potential to support timely and accurate prognosis and diagnosis of Alzheimer's disease (AD), as well as its differential diagnosis versus other neurodegenerative causes of cognitive impairment. These performances, replicated across cohorts, centers and countries, have led to the inclusion of plasma biomarkers in several clinical and therapeutic trial programs. Furthermore, plasma biomarkers, particularly plasma p-tau217 and p-tau181, have demonstrated utility as potential surrogate markers for brain amyloid-beta (Aβ) plaques since their levels in blood decrease proportionally to the reduction of brain Aβ in anti-amyloid programs in the same individuals.

For these reasons, plasma biomarkers are being considered for clinical use. However, several factors need to be considered ahead of time. For instance, which context of use would better suit these markers – primary care or specialist hospitals? Given the different rates of disease prevalence, should we expect the same performance in either context? Other factors include effects of common comorbidities of aging, and the generation and widespread validation of cutpoints to ensure external validity.

In this talk, we will discuss these points with lessons learned from recent research findings. Additionally, we will discuss the potential of plasma biomarkers to support patient eligibility determination for approved anti-Aβ therapies, prioritization of patients for these therapies based on who is at increased risk of future clinical decline, and monitoring adverse events in anti-Aβ therapy recipients.

Alzheimer Disease – therapies with focus on future

Bengt Winblad

The diagnosis of Alzheimer Disease (AD) is now put earlier and earlier. In addition to the clinical and neuropsychological evaluation, with the help of biomarkers (in CSF and blood), we can today make a definite diagnosis of MCI due to AD. Ongoing discussions indicate that biomarkers should be enough to diagnose even asymptomatic preclinical AD, which to me seem unlikely. Today, lecanemab is approved for treatment of MCI due to AD and mild dementia in the US, Japan and China (van Dyck CH et al, N Engl J Med 2023). Furthermore, donanemab (Sims JR et al, JAMA 2023) is under evaluation by FDA and EMA (authorities in the US and Europe). This is very promising as presently available pharma treatment are regarded as being only symptomatic, while lecanemab and donanemab affecting amyloid-beta aggregation are regarded as being disease-modifying (DMTs). Currently approved anticholinergic drugs and memantine are nowadays generics. A summary of all ongoing trials gives a very optimistic future view as currently 36 DMTs are in in phase 3 development (J Cummings et al, Alzheimer's Dementia 2023). Most immunotherapy studies have been passive.

The most promising therapy against tau is active immunotherapy and the tau vaccination (AADVac1) has passed phase 2 (Novak P et al, Lancet Neurol 2016; Novak P et al, Nature Aging 2021). To summarize, the AADVac1 data generated efficacy signals across biomarker and clinical modalities. The therapeutic effect was more pronounced in patients with higher antibody response (Novak et al, Nature Aging 2021).

Regarding the passive amyloid-related immunotherapies for AD, aducanumab is now back from Biogen to Neurimmune, and the Swiss company will test a subcutaneous formulation. Lecanemab has been approved in The US, Japan and China and is now under evaluation by EMA. Donanemab have also applied for EMA approval. Lecanemab is a humanized IgG2 monoclonal antibody that targets amyloid fibrils, especially protofibrils. Lecanemab was approved by FDA in January 2023. After a careful positive phase 2 study, the phase 3 study Clarity showed that lecanemab gave 27% slowing of decline on CDR-sb over 18 months. Lecanemab is now in phase 3 for subcutaneous administration. Donanemab has preliminary reported similar results as lecanemab. It is very difficult to compare the phase 3 studies with the DMTs lecanemab and donanemab, due to the use of different outcome scales and two different study populations.

With the so far observed results and the fact that AD is a multifactorial disorder, we believe that combination therapies will be necessary. One of the challenges with these new immunotherapy trials will certainly be related to a large number of patients requiring diagnosis and treatment. A lack of AD specialists leads to a long waiting list for cognitive testing and diagnosis. (Mattke S et al, J Prev Alzheimer Dis 2023.)

An important discussion will be the costing and reimbursement of the drugs. If a treatment is not demonstrated to be cost-effective, healthcare systems may not be willing to invest in diagnostic services (Jönsson L et al, Lancet Reg Health Europe 2023).

We are now approaching a new and optimistic time period with the first approved DMTs on the indication early AD treatment.

Lecanemab – from a mutation to a treatment for Alzheimer's disease

Lars Lannfelt

The symptomatic drugs currently on the market for Alzheimer's disease (AD) have no effect on disease progression, and this creates a large unmet medical need. The type of drug that has developed most rapidly in the last decade is immunotherapy, especially passive vaccination with monoclonal antibodies. Antibodies are attractive drugs as they can be made highly specific for their target.

Our detection of an Aβ precursor protein mutation that caused early-onset AD in a Swedish family (the Arctic mutation) by enhancing Aβ protofibril formation sharpened the focus on soluble Aβ aggregates (oligomers and protofibrils) as therapeutic targets. Initial studies tested a mouse monoclonal antibody (mAb158) with specific conformation-dependent binding to these soluble Aβ aggregates. Treatment with mAb158 reduced Aβ protofibrils in the brain and cerebrospinal fluid of a transgenic mouse model of AD. mAb158 had a 1,000-fold higher selectivity for protofibrils as compared with monomers of Aβ and had at least tenfold stronger binding to protofibrils compared to fibrils. A humanized version of mAb158, lecanemab, has been developed in a collaboration between BioArctic and Eisai.

We have characterized the binding properties of lecanemab and other Aβ antibodies to different Aβ species with inhibition ELISA, immunodepletion and surface plasmon resonance. Our results show different binding profiles of antibodies which may explain clinical results observed regarding both efficacy and side effects.

A phase 3, multicenter, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of lecanemab in 1795 patients with early AD. The participants received i.v. lecanemab (10 mg/kg every 2 weeks) or placebo. The primary efficacy end point was change in Clinical Dementia Rating–Sum of Boxes (CDR-SB) from baseline. The mean change in CDR-SB score was smaller in the lecanemab group by 27% over 18 months. Positive effects were also seen on secondary clinical endpoints and key biomarkers. However, longer-term follow-up is needed and an open-label extension study is ongoing.

This represents a significant advance for patients with AD, although many challenges remain. In particular, it is now more important than ever to identify individuals who are vulnerable to AD, so that treatment can be initiated at an early stage in the disease process.

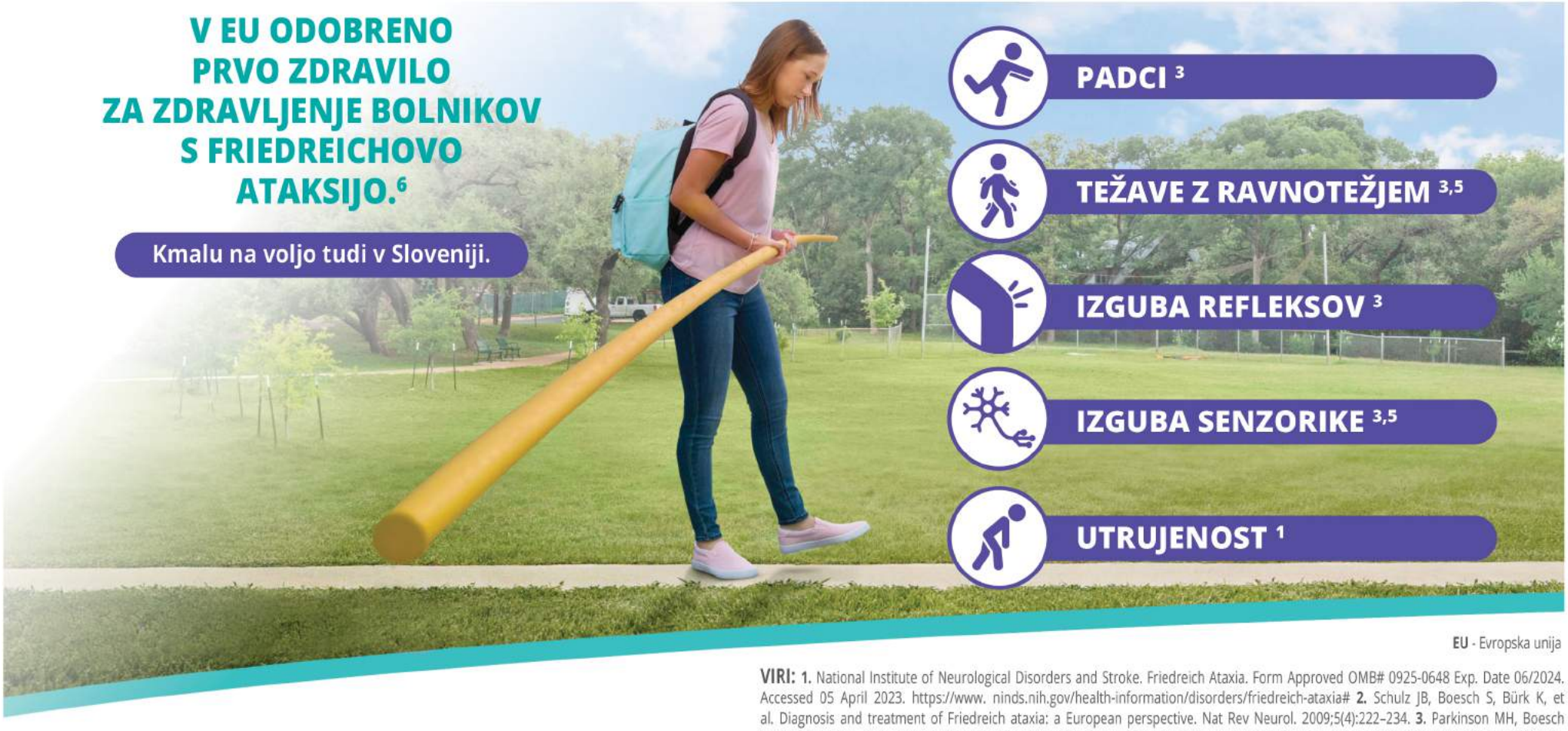
Prepoznava zgodnjih znakov

Friedreichove ataksije

skrajša čas do postavitve diganoze

Friedreichova ataksija (FA) je **najpogostejša dedna ataksija**.[1,2] Zgodnji znaki se navadno pojavijo že med 10. in 15. letom starosti in se lahko prekrivajo z znaki drugih bolezenskih stanj.[3,4]

Zato **NAJPREJ** pomislite na FA, ko pri bolniku vidite kombinacijo naslednjih znakov in simptomov:



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VIRI: 1. National Institute of Neurological Disorders and Stroke. Friedreich Ataxia. Form Approved OMB# 0925-0648 Exp. Date 06/2024. Accessed 05 April 2023. https://www. ninds.nih.gov/health-information/disorders/friedreich-ataxia# **2.** Schulz JB, Boesch S, Bürk K, et al. Diagnosis and treatment of Friedreich ataxia: a European perspective. Nat Rev Neurol. 2009;5(4):222–234. **3.** Parkinson MH, Boesch S, Nachbauer W, et al. Clinical features of Friedreich's ataxia: classical and atypical phenotypes. J Neurochem. 2013;126(suppl 1):103–117. **4.** Wallace SE, Bird TD. Molecular genetic testing for hereditary ataxia: what every neurologist should know. Neurol Clin Pract. 2018;8(1):27–32. **5.** Fogel BL, Perlman S. Clinical features and molecular genetics of autosomal recessive cerebellarataxias. Lancet Neurol. 2007;6(3):245–257. **6.** https://www.ema.europa.eu/en/medicines/human/EPAR/skyclarys

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