Advancements in the Early Identification and Treatment of Alzheimer's Disease

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THIS YEAR marked the 10th Congress of the European Academy of Neurology (EAN), hosted in Helsinki, Finland, from 29th June–2nd July 2024. The penultimate afternoon saw an insightful symposium that delved into the current advances in early identification of, and current anti-amyloid antibody therapies for, Alzheimer's disease (AD). With talks from Sebastiaan Engleborghs, University Hospital Belgium, Ghent, Belgium; Milica Kramberger, University of Ljubljana, Slovenia; and Youssuf Saleh, University of Oxford, UK, this session identified the pillars of AD diagnosis and how the advent of novel disease-modifying therapies could revolutionise the field of AD treatment research.

EARLY DIAGNOSIS: AN ETHICAL CONUNDRUM

Engleborghs explained that the current approach to AD identification focuses on the concept of timely diagnosis; however, the ability to screen for AD before symptom onset raises an ethical debate. Should screening protocols be introduced for early disease identification while AD remains an incurable disease? All three speakers discussed the importance of patients reserving the right to choose to remain unaware of whether they have AD. However, with the emergence of disease-modifying therapies (DMT), particularly those targeting the earliest symptomatic phases of AD, there is an increasingly strong argument in favour of early diagnosis.

Whilst some patients would prefer not to receive a diagnosis, others, such as those with a family history of AD, are more likely to seek out screening opportunities to pursue early identification. Screening is usually carried out with apolipoprotein E (APOE) genotyping, as APOE is a significant genetic biomarker; however, clinical judgment remains crucial in determining cognitive decline and ultimately providing a diagnosis of AD. Differential diagnoses of other neurodegenerative diseases with similar initial presentations, such as vascular cognitive impairment, dementia with Lewy bodies, and frontotemporal dementia, should also be considered. Before widespread screening could be rolled out, there is still a need for advancements in diagnosis protocol, specifically concerning biomarker-based approaches that, when partnered with APOE genotyping, could provide an even higher disease prediction rate.

BIOMARKERS: WHAT ARE THE OPTIONS?

The three core biomarkers used in the identification of AD are fluid, imaging, and blood biomarkers, the presence of which indicates the onset of neurodegeneration. Other signs of neurodegeneration include the levels of neurofilament light chain in cerebrospinal fluid (CSF), a nonspecific marker for neuronal injury or neurodegeneration, a decrease in hippocampal volume, and a decline in cognitive function as measured by subjective questionnaires.

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FLUID BIOMARKERS

Kramberger discussed how fluid biomarkers, measured in plasma or CSF, are initially used to determine the presence of AD. The primary detectable fluid biomarker, found up to 18 years before symptom onset, is the amyloid beta peptide (Aβ). The secondary fluid biomarker is phosphorylated tau (P-tau), which is detectable 11 years before cognitive decline and has numerous isoforms that present at varying points along the AD continuum. The increased levels of these P-tau in CSF are in response to Aβ deposition in early AD, and as Aβ accumulates, the more widespread deposition of P-tau can be seen on tau-PET scans. However, in their 2020 study, Mattsson-Carlgren et al.[1] discovered that two isoforms, P-tau217 and P-tau181, preceded a positive AD Tau-PET scan. Furthermore, elevated plasma phospho-tau concentrations correlate with greater cognitive decline over time, validating its utility in assessing disease progression.

IMAGING TECHNIQUES

Neuroimaging biomarkers are detected using MRI or PET scans and are used to assess the stage and severity of the disease. CT scans are also utilised to observe atrophy and vascular changes, while MRI offers more detailed insights that have proved a useful tool for decisions regarding patient suitability for DMTs. Other, more specific, neuroimaging biomarkers can be used collectively to create a detailed picture of a patient's disease status. These include fluorodeoxyglucose-PET, which shows levels of neurodegeneration; amyloid-PET, which provides visualisation of amyloid plaques; and tau-PET, which detects the density and distribution of aggregated tau neurofibrillary tangles.

A recent study suggests that plasma P-tau, which surpasses amyloid-PET and structural MRI in sensitivity for forecasting cognitive decline, could rival tau-PET in predicting cognitive impairment over 6 years.[2] Additionally, tau-PET scans are high-cost, and given the predictive accuracy of P-tau serum, the fluid biomarker test could overtake tau-PET as the go-to method for tau protein identification.

BLOOD-BASED BIOMARKERS

Blood-based testing is also used, and, although currently less established, these tests offer a promising first step in a multi-

stage diagnostic process. Krambereger discussed a recent study that has underscored the growing significance of blood biomarkers given their high sensitivity and specificity in AD identification.[3] These biomarkers demonstrate high sensitivity and specificity, making them a point of interest. However, real-life cohorts differ significantly from controlled research cohorts, introducing complexities such as comorbidities that can influence biomarker outcomes. To integrate blood-based biomarkers into routine clinical practice, substantial advancements are necessary. This includes standardising populations, establishing reference standards, and leveraging real-world datasets to comprehensively evaluate various factors that may impact diagnostic accuracy for AD.

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In the new revised criteria, these biomarker types are further subcategorised into three groups: core biomarkers, non-specific biomarkers, and biomarkers of common non-AD co-pathologies.[4] Kramberger explained: "The two latter markers are relevant to AD diagnosis and staging because AD most often occurs with co-pathologies in older adults." Therefore, testing for these specific types of biomarkers could significantly impact clinical outcomes in older adults.

WHAT ARE THE CURRENT TREATMENT OPTIONS?

Engleborghs started his talk by explaining that addressing behavioural and psychological symptoms of dementia involves both non-pharmacological approaches, such as behavioural therapies, and pharmacological interventions, such as cholinesterase inhibitors and memantine, tailored to manage specific symptoms. Additionally, controlling cardiovascular risk factors, promoting cognitive and physical activities, and moderating alcohol intake have been shown to positively influence disease progression in individuals with AD. These multifaceted approaches underscore the comprehensive nature of current treatment strategies in managing AD symptoms and improving the overall quality of life (QoL) for patients. Engleborghs stated that the introduction of anti-amyloid treatments as DMTs for AD changes the field drastically. From there, the operational, societal, and ethical considerations of DMTs were outlined.

DISEASE-MODIFYING THERAPIES: A BRIEF HISTORY

Although there are currently two DMTs available in the USA, neither of these options were available in Europe at the time of the EAN 2024 Congress. The first DMT was granted approval by the FDA in 2021, with a 2016 study demonstrating the drug's ability to clear amyloid plaques in patients with AD.[5] As explained by Engleborghs, the effects of the drug on cognitive decline were initially inconclusive; subsequent post-hoc analyses indicated potential cognitive benefits at higher doses, although further rigorous evidence is needed to confirm these findings. Despite these uncertainties, the conditional approval from the FDA marked a significant step forward in the treatment landscape for AD.

The second DMT showed a significant slowdown in cognitive decline among patients receiving the drug compared to those on a placebo. A 2022 study demonstrated that the drug exhibited promising results in preserving QoL with less decline observed in treated individuals compared to those in the placebo group.[6] These clinical findings were considered meaningful, leading to its approval by the FDA. The third and final DMT demonstrated a slowing in cognitive decline by approximately 30%, offering a clinically relevant effect.[7] However, only a small proportion of patients with AD will be eligible for these DMTs. There is an indication, though not yet conclusive evidence, that the earlier these treatments are introduced, the more significant the impact on delaying disease progression.

In his closing remarks, Engleborghs emphasised that several clinical and ethical questions remain unanswered, including the necessity for clinical trials in preclinical AD, the requirement for post-marketing monitoring and research, and the need for ongoing research into new therapeutic targets. In the near future, DMTs are anticipated to include anti-amyloid monoclonal antibodies that activate microglia, facilitate phagocytosis of fibrillar amyloid, and promote degradation in the endosomal/lysosomal system.

WHAT CAN WE DO NOW?

The final speaker of the session, Saleh, reflected on what researchers and healthcare professionals could be doing going forward. This included selecting the right patients for DMTs, assessing the efficacy of these treatments, and monitoring disease progression. One method of measuring disease progression between these stages involves using neurofilament light chain as a biomarker of neuronal injury, which sensitively detects neurodegeneration and can predict progression to an AD diagnosis. While it serves as a primary endpoint in clinical trials for amyotrophic lateral sclerosis, neurofilament light chain has not yet been fully validated for use in AD. Unlike serum biomarkers, PET imaging provides a spatial view of pathology, offering insights into disease staging and progression monitoring. It has been effectively utilised to assess treatment efficacy, employing a PET-based staging system.

CONCLUSION

Considerations regarding diagnostic procedures and their ethical implications are multifaceted as the psychological burden of a patient being diagnosed with

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an incurable disease must be taken into account. There is ongoing debate regarding the implementation of population-level screening versus targeted case-finding strategies. The potential benefits of such approaches include the ability to detect AD early, which could lead to earlier interventions and better patient QoL. Proposed methods include initial evaluation by general practitioners, followed by confirmatory biomarker tests. Another ethical dilemma surrounds the routine use of APOE genotyping in AD diagnosis, given its strong association with increased risk but not a definitive diagnosis, necessitating careful genetic counselling. The overarching goal is to promote early diagnosis of AD to facilitate timely treatment with DMTs, underscoring the importance of ethical sensitivity in navigating these diagnostic pathways.

Finally, while biomarkers are the primary tool for AD identification, it is pertinent to remember that approximately 30% of cognitively intact elderly people are amyloid positive, and the eventual development of symptoms cannot be predicted.[8] Therefore, it is when neuropsychological assessments, neuroimaging techniques, and biomarkers are used collectively that a definitive diagnosis can be made.

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