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Editorial

On the 2024 Alzheimer's Association Criteria: Still Not Ready for Clinical Use

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Main text

Alzheimer's disease (AD) is the leading cause of dementia worldwide (1). However, since dr. Alois Alzheimer first described senile plaques and neurofibrillary tangles (NFTs) in the brain of a woman suffering from early-onset dementia in 1906, the definition of AD has changed multiple times, often in parallel with advancements in our understanding of the complex pathophysiology behind the typical clinical presentation of anamnestic dementia. Until recently, proposed definitions of the disease have been clinico-biological in nature (2), that is, requiring both pathological and clinical hallmarks of the disease. The proposed diagnosis criteria from the Alzheimer's Association (AA) break from this tradition, as it relies solely on the biological hallmarks of the disease (plaques, and biomarkers detecting plaques), while symptoms are no longer necessary for diagnosis of AD (3). In their article, the authors state that "… detection of AD neuropathologic change by biomarkers is equivalent to diagnosing the disease". While the AA does not recommend biomarker tests in asymptomatic individuals, the definition of a decades-long asymptomatic phase of AD is likely to have great implications for how both researchers and clinicians understand the disease.

We applaud recent advances in the development of blood-based biomarkers for AD, which will increase availability of AD diagnosis in many different healthcare settings. However, while we support the use of AD biomarkers in clinical practice to aid the diagnostic process and to help physicians choose between management options, we cannot agree that biomarker positivity alone should define AD in persons without any detectable cognitive symptoms. The AA system is reliant on the amyloid cascade hypothesis (4), which is well-supported by genetic evidence and recent successes in clinical trials of amyloid-targeting monoclonal antibodies. However, the basic version of the amyloid cascade hypothesis, which postulates that amyloid deposition is the starting event of the disease, leading to sequential tau hyperphosphorylation, neuronal death, and cognitive decline, is clearly too simplistic to describe the complexity of clinical dementia disease. Glaringly, many individuals with evidence of amyloid deposition in the brain do not develop dementia. Clearly, there are important inter-individual variation in the response to amyloid plaque deposition, likely related to risk or resilience factors (5, 6). By claiming that the presence of amyloid plaques is sufficient to define AD, the weaknesses of the amyloid cascade hypothesis are inherited by the AA criteria.

In the new AA criteria, they on one hand aim to provide "… a common framework for AD diagnostic and staging criteria to inform both research and clinical care" (3), but on another hand, they "do not provide detailed guidance on clinical workflow". It is thus unclear to which extent they recommend that clinicians should integrate the AA's diagnostic criteria in clinical practice. We previously warned against widespread clinical use of the 2011 NIA-AA criteria on biomarker-based AD diagnosis (7), because it is not possible to predict when, or even if, biomarker positive but asymptomatic persons will develop dementia. Ethical issues arise, as an earlier diagnosis of AD would cause psychological distress, with negative personal implications for employment, insurance policies and self-image (8). As AD biomarkers become more readily available for testing, it would be difficult, if not impossible, to stop the proliferation and commercialization of biomarker tests, which could create many "worried well" individuals. Furthermore, biomarkers of AD are still not properly validated in more diverse, population-based cohorts. Finally, there is no pharmacological intervention that is proven to have effect in an asymptomatic population. The 2024 AA criteria now explicitly aims to bridge the gap between research and clinical practice, even though none of these critical issues have been properly addressed since 2011.

As treatments are emerging, the proposed biological definition of AD leaves unresolved questions. As shown in Phase III trials of monoclonal anti-amyloid antibodies such as lecanemab or donanemab, patients in the treatment arm show near-complete cerebral amyloid clearance, but still exhibit cognitive decline, albeit at a slower rate compared to placebo control (9, 10). Thus, at least at this point of the disease, amyloid is not necessary for dementia disease progression. If AD is equal to

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amyloid PET positivity, would the treated patients be considered AD-free? We believe that these individuals clearly still have a neurodegenerative disease, and that this disease is AD, even though these patients now are amyloid negative. How do these individuals fit in within the AA framework? In our opinion, these individuals exemplify why cerebral amyloidosis cannot define AD on its own.

Similar developments of defining broader presymptomatic stages of a disease are present elsewhere in medicine, such as the controversy regarding the diagnosis criteria for prediabetes in individuals with elevation of fasting glucose levels below that of the commonly accepted threshold for diabetes (11). The debate on whether presymptomatic or preclinical disease stages should be defined, diagnosed, and treated illustrates the difficulty in many diseases to differentiate between "sick" individuals and "at-risk"-individuals. As this threshold is arbitrary by design, it should be drawn according to the expected benefit of individuals who will be considered "sick". In the case of AD, the AA proposal would classify over 20% of all individuals 50 years or older as living with AD (12). It is unclear whether these individuals have any potential for benefit due to this classification. Certainly, there is great risk for harm.

In summary, equating amyloid positivity alone with AD creates unresolved problems both in biology and in society. Although progress have been made in understanding pathological changes and biomarker trajectories years and decades before the onset of symptoms, our current knowledge of the presymptomatic phase of AD is not sufficient to comfortably label all amyloid-positive individuals with "AD", a term which is commonly associated with a debilitating illness in the public. Instead, biomarker positive asymptomatic individuals should be considered at risk for AD, rather than having AD (13).

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