Challenges in a Biological Definition of Alzheimer Disease

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Abstract

It has been suggested that the diagnostic landscape of Alzheimer disease (AD) is undergoing a profound transformation, marked by a shift toward a biomarker-based approach, as proposed by the Revised Criteria for Diagnosis and Staging of Alzheimer's Disease. These criteria advocate for diagnosing AD solely on biomarkers, without requiring clinical symptoms. This article explores the drivers behind this transition, primarily influenced by the Food and Drug Administration's approval of amyloid-lowering treatments. We evaluate the proposed criteria, which allow for an AD diagnosis based on amyloid "A" or phosphorylated tau "T1" positivity through surrogate amyloid PET imaging, CSF, or plasma biomarkers, and consider the arguments for and against their use. The merits of the new criteria include a clearer definition of AD, which is currently used interchangeably to refer to both the presence of neuropathology and the clinical syndrome. We argue that a purely biological definition risks a category error and emphasize the need for longitudinal data to establish the lifetime risk of dementia in amyloid-positive and tau-positive individuals. We also caution against limiting the scope of biomarker-based AD diagnosis to amyloid and tau alone. In conclusion, we recommend that the criteria remain within the research domain for the present while advocating for the considered adoption of plasma biomarkers in clinical practice.

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Introduction

Recent years have seen rapid evolution in Alzheimer disease (AD) research. In 2021, the Food and Drug Administration (FDA) approved aducanumab to treat patients with Alzheimer disease, and in 2023, it approved lecanemab for a similar indication.[1] That same year, at the Alzheimer's Association International Conference, the phase III clinical trial data for donanemab and data on the utility and adoption of a range of AD plasma biomarkers were presented.[2-4] At that meeting, the National Institute on Aging and the Alzheimer's Association (NIA-AA) convened a working group that presented a draft proposal for revised criteria for the diagnosis of AD.[5] Because the National Institute on Aging now serves on an advisory capacity, its cosponsorship came under scrutiny because it was seen to extend beyond its research scope. The recently published 2024 AA criteria are known as Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup.[6-8]

The NIA-AA initially published AD diagnostic guidelines in 2011.[9] These characterized an AD disease continuum, from preclinical AD to mild cognitive impairment (MCI) due to AD to AD dementia. Around the time when these guidelines were published, in vivo biomarkers of AD (amyloid and tau) PET and CSF (amyloid and tau measures) were developed, and these allowed an antemortem diagnosis of AD neuropathologic change. As a result, the 2018 NIA-AA research criteria proposed the amyloid (A)/tau (T)/neurodegeneration(N) system, with an A+T+ biomarker profile required for a biological definition of AD.[10]

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Glossary

Aβ = amyloid-beta; **AD** = Alzheimer disease; **FDA** = Food and Drug Administration; **MCI** = mild cognitive impairment; **NIA-AA** = National Institute on Aging and the Alzheimer's Association.

The 2024 AA criteria propose the adoption of a purely biologically based construction of AD to inform clinical practice and research.[5] Based on these criteria, a diagnosis of AD can now be made based on either amyloid "A" or phosphorylated tau "T_1" positivity using surrogate amyloid PET imaging or CSF or plasma biomarkers (*p*-tau217). The "N" classification was removed from the core biomarker criteria. Crucially, although the criteria highlight the value of clinical judgement for the diagnosis, the biological AD definition does not require the presence of clinical symptoms. The criteria do not advocate for the screening of preclinical disease, although those with subjective cognitive concerns may be tested. A diagnosis of AD, which can be made in the absence of clinical symptoms, will have significant implications for clinical practice and patient care. In addition, 2024 draft US FDA guidance proposes that a change in a surrogate biomarker concentration alone can be accepted as evidence of efficacy in the licensing of treatments for asymptomatic preclinical AD individuals.[11] This could mean that a biomarker result could be used to both diagnose AD (2024 AA criteria) and as evidence of treatment response (2024 FDA draft criteria), in an asymptomatic individual.

Proposed Reasoning for Updating the Criteria

The 2024 AA criteria can be seen as an inevitable outcome of FDA approval of amyloid-lowering treatments based at least partly on surrogate biomarker endpoints and the proposed sole use of biomarker concentrations as indicators of treatment efficacy in asymptomatic trial participants.[11-13] The criteria distinguish between an asymptomatic AD "disease" phase and an "illness" stage, when symptoms are evident. Proponents of the criteria assert that this approach aligns with other areas of medicine, particularly oncology, where surrogate biomarkers are used to screen and diagnose disease before symptom development. With the advent of treatments targeting AD pathology, the new definition seeks to conceptually align the diagnosis of AD with an integrated set of biological markers and clinical stages that begin in the presymptomatic state. This approach aims to improve diagnostic precision, identify eligible participants for clinical trials (including those without symptoms), and target and monitor treatment responses.

Arguments for and Against the Proposed Draft Criteria

One advantage of a purely biological definition is that it clearly conceptualizes AD as a distinct pathologic process, separate from the clinical manifestations of the various diseases that cause cognitive decline. This strictly biological definition may help to avoid the confusion caused by the term "Alzheimer disease," which can refer to both the underlying biology and the dementia syndrome. If abnormal amyloid and tau accumulation are risk factors for developing Alzheimer dementia, it would be important to identify and mitigate this at the earliest possible timepoint. This could be comparable with identifying and treating cerebrovascular disease risk factors, such as hypertension. Ongoing studies such as AHEAD 3-45 Study (BAN2401-G000-303) may provide valuable insights into treatment outcomes in this asymptomatic amyloid-positive population.[14] However, secondary prevention studies may not have a long enough period of follow-up or adequate sample size to provide meaningful information on efficacy in dementia risk reduction.[15] A consensus biological definition of AD could set the stage for earlier and more precise identification of clinical trial participants. The second advantage is that biomarker use in clinical trial recruitment has helped to increase diagnostic validity within those trials.[16] Patients and carers could use such information to facilitate earlier care planning and inform decisions to enter presymptomatic treatment trials.

Despite these putative advantages of using a biological definition of AD in clinical trials and clinical care, several questions arise regarding the widespread use of the proposed AA criteria. First, does the biological definition of AD fall into the trap of a category error? A category error is made when we assign a problem to a category that is not appropriate for solving it. An example of a category trap is the use of blood glucose concentrations to define type II diabetes.[17] Because biomarkers such as blood glucose level are continuously distributed variables, it is difficult to establish a clear threshold that distinguishes between healthy and potentially harmful levels that warrant a diagnosis and subsequent intervention. Defining such thresholds can prove elusive, particularly when considering the heterogeneity of the populations, and contributory environmental factors that affect the risk of developing complications of diabetes. Establishing thresholds introduce an intermediate or "grey zone" for biomarker cut points, which require clinical interpretation, integrating the result in the context of the history, examination, and clinical judgment. By equating pathologic changes with the disease itself and relying on rigid biomarker causal pathways, using fixed cut points, we would move away from appreciating the complex interplay of etiologies that drive the dementia process.[18]

Further work is required to establish the lifetime risk of dementia in amyloid-positive and tau-positive individuals, particularly amyloid-beta (Aβ) biomarker positivity is not always deterministically associated with a dementia outcome[19] and tau is more strongly associated with cognitive status and neurodegeneration than amyloid.[18] Although the presence of increased brain amyloid is necessary for the propagation of tau beyond the medial temporal lobe, we know that AD Aβ biomarker positivity alone is not sufficient.[20,21] This may be due to a substantial lag before tauopathy spreads beyond the medial temporal lobe. For example, young-onset dysexecutive AD is characterized by a high tau load during the MCI phase and will progress faster than late-onset limbic-predominant AD.[22] Consequently, as late-onset limbic-predominant AD typically happens later in life, many people with elevated amyloid will die of other causes before this progression takes place.

There is a danger of narrowing of the scope of biomarker-based AD diagnosis with a focus purely on the amyloid and tau hypotheses. However, these processes are not fully elucidated with questions remaining over the causal relationship between Aβ or tau and AD.[23] This could detract from other important contributory pathologic mechanisms and that dementia in most older people is characterized by copathology, including TDP-43, Lewy bodies, and cerebrovascular changes.[24,25] Amyloid and tau imaging have revealed the constraints of solely focusing on plaque and tangle pathology. This limitation has led to the recognition of other contributors, such as limbic TDP-43 proteinopathy.[26] The heterogeneous nature of late onset AD with both a long natural history of the disease and a variation in presentation may mean that the specificity of these biomarkers for AD dementia is uncertain.

Technological progression should not automatically be assumed to be beneficial for the health and well-being of populations. Are we risking overmedicalization and introducing iatrogenic harm? The balance between risks and potential benefits of a biological AD diagnosis will differ between AD severity stages, for example, compared with patients with 'early' symptomatic AD, the potential clinical benefits of amyloid-lowering agents in asymptomatic individuals are even more uncertain, mainly owing to limitations in interpreting trial outcomes in the context of a long natural disease course.[15,27]

The prevalence of amyloid positivity in asymptomatic individuals aged 80–89 years is around 40%, and the same study estimated that 22% of all adults aged older than 50 years will be amyloid-positive.[28] This means that 26 million people in the United States alone may be amyloid-positive. According to the new criteria, such individuals can now be classified as having AD. Because the predictive accuracy of amyloid positivity for dementia is uncertain,[19] diagnosing them with AD will introduce unintended harms including distress for patients and carers. Who will benefit from the potentially significant expansion in the number of people who qualify for a drug treatment? Focusing resources on amyloid-lowering and tau-lowering treatments will divert funds from already underfunded effective evidence-based psychosocial interventions and social support for patients and caregivers.[29,30] We do not yet have effective treatments that can arrest the disease process before it causes symptoms; if we did, we would support these biologically defined criteria.

Looking Toward the Future

Defining the presence of AD purely on biomarker evidence of amyloid and tau positivity does not reflect the complexity of the dementia construct, and we are concerned that such an approach may cause more harm than good. Such an approach has value in research settings, where it can be used to frame hypotheses, but it is not yet appropriate for use in clinical practice. We do not propose rejecting the criteria in its entirety. The incorporation of plasma biomarkers may have diagnostic utility for diagnosing people with symptomatic AD.[4] However, it is important that the criteria incorporate the full range of pathologic mechanisms that contribute to the AD dementia process. A biologically reductionist approach cannot capture the multiple processes involved in Alzheimer dementia, including the role of psychological and social factors. Rather than eliminating these from our understanding of dementia, we must embrace complexity. This will ensure that we do not invest false therapeutic certainty in the dominant hypotheses of the day. To date, there is no evidence that targeting tau is associated with clinical benefit in people with AD. Indeed, the modest clinical outcome data from Aβ therapy trials show the danger of assuming that risk factors or biomarkers for a disease are the disease.[2,18]

The proposed narrowly defined biological model of sporadic AD is currently insufficient, unrelated to etiologic complexity and a long pathologic process, and overshadows other biopsychosocial models[31] and risk-modification strategies.[32] It is important to maintain a clear distinction between the definition of AD pathology and the clinical syndrome of AD dementia. If there really was utility in defining an illness on the basis of a minimal set of features that are (1) present in all patients and (2) potentially modifiable, then the most propitious definition of AD dementia would be as a disorder of social function because it is the quality and quantity of social support that can determine a patient's quality of life and speed of disease progression.

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