Research and Practice

Two definitions for the same disease: The enigma of Alzheimer's Disease?

Rita Khoury, MD

Assistant Professor of Clinical Psychiatry

American University of Beirut, Lebanon

Highlights

- Alzheimer's disease (AD) is a debilitating and complex condition with multiple underlying pathological processes that remain incompletely understood.
- Recent advancements in biomarker research have significantly improved the ability to objectify and assess these pathological processes.
- In June 2024, the NIA-AA proposed a revised definition of AD, shifting to a purely biological construct, independent of clinical symptoms.
- In November 2024, the IWG recommended a more cautious approach, advising against diagnosing AD in individuals without cognitive impairment, even if biomarkers are positive. This conservative stance aims to prevent overdiagnosis and mitigate psychological harm for individuals with a "low-risk" biomarker profile who may never develop cognitive symptoms.
- Unified diagnostic criteria are urgently needed to standardize clinical practice and advance research in neurodegenerative diseases.

Introduction

To date, Alzheimer's disease (AD) is a debilitating incurable disease, with a substantial societal burden. The quest to find a cure has been very challenging, with multiple pathophysiological pathways found to underly the disease process. A lot of efforts and funds have been mobilized in the past couple decades to enhance our understanding of these pathophysiological processes and detection of the sentinel event of the disease cascade. In addition, there has been important progress in refining biological tools and measures known as biomarkers assessed through imaging, or bodily fluids (blood/cerebrospinal fluid) for objective detection of the Alzheimer's signature, and assessment of progression and response to interventional therapies. The scientific community has witnessed recent developments in revising the definition of Alzheimer's disease to promote early detection of the disease spectrum, as well as promoting research on early interventions to prevent or delay the onset of clinical symptoms of the disease.

Two definitions for the same disease?

In June 2024, the team led by Jack and colleagues, representing the National Institute on Ageing and the Alzheimer's association (NIA-AA) published revised criteria for the diagnosis and staging of Alzheimer's disease essentially based on biological criteria, resembling other diseases such as cancer. In their newly proposed clinical definition, AD is viewed as a continuum where individuals are considered on the spectrum if they carry biological markers of the disease, even in

the absence of clinical symptoms. In this framework, the clinical symptoms are not needed for the diagnosis of AD; they are viewed as the late consequences of an already present disease, and sometimes attributed to additional pathological processes/disorders at the time of their emergence.

Per the NIA-AA definition, abnormalities on specific biomarkers (called Core 1 biomarkers) are sufficient to diagnose AD continuum, namely: amyloid PET; CSF Aβ 42/40, CSF p-tau 181/Aβ 42, and CSF t-tau/Aβ 42. This new definition was mainly driven by the finding that Core 1 biomarkers become abnormal decades before clinical symptoms arise, and could constitute the initially detectable stage of AD, in comparison with a slowly progressive cancer that can be detected by biomarker testing before symptoms arise. In that case, earlier interventions could yield more hope to reverse the disease process and prevent or delay the irreversible onset of clinical symptoms.

This new definition has been met with skepticism by several experts in the field of neurodegenerative diseases, due to the risk of overdiagnosing patients with AD, when in fact many of the individuals with positive biomarkers remained symptom-free when followed over time. The lifetime risk of AD dementia in a 65-year-old man who is amyloid-biomarker positive has been estimated at 21.9%, around 1.7 times higher than the risk of an individual of a similar age who is amyloid-biomarker negative, with an unclear timeline regarding the onset of AD symptoms. Several factors play a role in determining the risk of transition in sporadic AD such as sex, apolipoprotein E4 genotype status, cardiovascular risk factors etc. The risk is clearly different in the population with Autosomal Dominant Alzheimer's Disease, where transition to AD in those who carry positive biomarkers is almost inevitable.

Disclosing a diagnosis of AD to cognitively intact individuals in clinical settings can be overwhelmingly devastating to individuals and families, notably in those who will not develop any symptoms.

In addition, the Core 1 biomarkers of AD revolve mainly around the traditional amyloid hypothesis of AD, which is also criticized by many researchers refuting the fact that it is at the heart of AD pathophysiology. Other biomarkers have been heavily investigated in recent years including neuroinflammation, glial activation, tau accumulation etc. Additional concerns raised include the risk of over reliance of clinicians on paraclinical work up rather than clinical assessment, as well as the risk of over prescribing new disease-modifying therapies based on the amyloid hypothesis (Aβ monoclonal antibodies) in those fulfilling core 1 biomarker, especially with emerging evidence of limited benefits/risks ratio.

Considering these caveats, the International Working Group (IWG) led by Dubois and colleagues published in November 2024 an alternative definitional view of AD as a clinical-biological construct to use in clinical settings. While the IWG members recognize the importance of biomarkers in advancing AD research, they highlight the role of biomarkers as surrogates of underlying pathological processes rather than AD as a disease. They invite clinicians and researchers to be mindul of the interpretation of biomarkers according to the context and populations where they are measured (e.g. clinical trials, symptomatic versus asymptomatic individuals etc.).

In summary, The IWG and NIA-AA share a common ground when it comes to individuals who have a combination of clinical symptoms of cognitive impairment (even at the mild stage) and positive Core-1 biomarkers. These individuals are considered to be diagnosed with AD and

are potential eligible candidates to receive antiamyloid monoclonal antibodies. However, for cognitively intact individuals (who may present with subjective cognitive decline, or have a family history of AD), the IWG propose categorizing these individuals as asymptomatic at-risk for AD or presymptomatic rather than with AD. Table 1 below summarizes the difference between these diagnostic categories. The IWG incite continued research efforts to better characterize the at-risk and presymptomatic stages and determine predictors of transition to AD clinical syndrome.

Table 1: IWG 2024 criteria for AD definition

	Asymptomatic At-risk for AD	Presymptomatic	AD diagnosis
Cognitive status	Cognitively normal	Cognitively normal	Cognitively impaired (amnestic/ non-amnestic-uncommon presentations)
Biomarkers profile	Uncertain risk with positive biomarkers	*Specific pattern of biomarkers such as amyloid positron emission tomography (PET) + with tau PET(+) in neocortical regions *Highly penetrant autosomal dominant genetic variations (APP, PSEN1, PSEN2) *Down syndrome *Homozygous for APOE4 & SORL1 loss of function	Positivity of CSF or PET pathophysiological AD biomarkers. Plasma biomarkers such as p-tau 217 may soon enter the routine clinical workup.
Risk of progression	Undetermined lifetime risk of progression, although higher compared to biomarker negative	Very high lifetime risk of progression	Could be Prodromal: mild cognitive impairment or different stages of dementia (mild/moderate/severe)

Conclusion

The coexistence of two sets of criteria for the same disease raises questions about which to use. It is concerning that a diagnosis of AD may depend on the clinician's chosen definition, especially given its life-altering implications. In research, moving away from the clinical-biological model impacts the selection of primary outcomes in trials. Historically, cognitive assessments were key, with biomarkers later added. Shifting to a purely biological model risks focusing solely on biomarkers, which may not fully capture the disease's complexities. Further research to validate and unify criteria is urgently needed.

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Dr. Rita Khoury is an adult and geriatric Psychiatrist, Assistant Professor of clinical psychiatry at the American University of Beirut, Lebanon. Email: rk224@aub.edu.lb