ALZHEIMER'S DISEASE

Dementia is not synonymous with Alzheimer's disease

Clifford Jack is a Professor in the Department of Radiology, Mayo Clinic, Rochester, MN 55905, USA. Email: jack.clifford@mayo.edu

David Holtzman is Professor and Chair of the Department of Neurology, Washington University, St. Louis, MO 63130, USA. Email: holtzman@wustl.edu

Reisa Sperling is a Professor in the Department of Neurology, Brigham and Women's Hospital, Boston, MA 02115, USA. Email: reisa@rics.bwh.harvard.edu

A debate is underway in the field of Alzheimer's disease (AD) research over the definition of the disease itself. Diagnostic criteria for AD were first formalized in 1984 (*1*). Individuals with a clinical presentation dominated by progressive memory impairment that led to dementia were given the diagnosis of "probable Alzheimer's disease in life." A definitive diagnosis of AD required demonstration of β amyloid plaques and tau neurofibrillary tangles in the brain at autopsy. This distinction between probable and definite was necessary because the clinical diagnosis was neither sensitive nor specific for the neuropathological identification of β amyloid plaques and tau neurofibrillary tangles, which are considered the gold standard for a diagnosis of AD (*2*). Unfortunately, in most public discourse and often in medical practice, the terms dementia and AD have become interchangeable. The term AD is used to describe two very different entities: On the one hand, the hallmark neuropathological findings that define AD as a unique disease among several that lead to dementia, and on the other, what is ascertained clinically, which is termed Alzheimer's Clinical Syndrome (*3*). Alzheimer's Clinical Syndrome denotes the typical cognitive abnormalities that are present when there is underlying AD pathology but is not specific for this underlying pathology. Confusion is inevitable when the same term is used to refer to different entities.

To address the nonspecificity of the clinically diagnosed entity, namely, Alzheimer's Clinical Syndrome, revised diagnostic criteria have been developed over the past 10 years using brain imaging or fluid biological markers to increase or decrease confidence that observed clinical symptoms are due to AD. With some exceptions, however, the definition of AD has not been completely separated from the presence of clinical symptoms in these revised criteria.

Within the past two decades, positron emission tomography (PET) imaging probes that bind to β amyloid plaques and tau neurofibrillary tangles in the brain and fluid biological markers reflecting the pathophysiological states associated with these pathological protein deposits have been developed and tested in thousands of participants in clinical research studies. This research shows that the pathological hallmark diagnostic plaque and tangle deposits can be detected in the human brain in vivo. Consequently, it is no longer necessary to wait for autopsy to definitively diagnose AD. On the basis of these developments, a working group commissioned by the National Institute on Aging and the Alzheimer's Association (NIA-AA) has published a research framework in which AD is defined biologically in vivo by PET imaging and fluid biological markers of both β amyloid plaques and tau neurofibrillary tangles (*3*). This framework was developed for use in clinical research studies, not routine clinical care (www.alzheimersanddementia.com/article/S1552-5260(18)30072-4/fulltext).

This framework uses a system, termed AT(N), for classifying research participants who have AD. PET imaging and fluid biological markers are grouped on the basis of the pathological process measured as follows: β amyloid plaques (A), tau neurofibrillary tangles (T), and neurodegeneration or neuronal injury (N). The A and T are specific for β amyloid and pathological tau deposits and are used to define the disease in vivo. Biological markers of neurodegeneration (N) are not specific for any one disorder and therefore are placed in parentheses and are used for staging of disease but not for diagnosis. Disease severity is staged using a combination of both biological markers and clinical features (*3*).

The NIA-AA research framework has generated debate that is centered on the definition of AD itself. Some in the AD research field favor a clinical/syndromal definition over a biological definition of the disease. A variety of reasons for this have been proposed, among them that the term AD has become so thoroughly conflated with dementia in the public sphere that change is not possible. The NIA-AA working group in contrast maintains that in the modern research environment a biological definition is needed to address several key issues.

One of the most compelling advantages of a biological versus a clinical diagnosis for AD is that the latter is not specific for any etiology. Alzheimer's Clinical Syndrome can have many causes in addition to AD including cerebrovascular disease, Lewy body disease, hippocampal sclerosis, transactive response DNA binding protein 43 kDa (TDP43)–driven proteinopathy, and more (*2*). In addition, in older individuals, Alzheimer's Clinical Syndrome is most often seen in the presence of combinations of neuropathological abnormalities rather than a single disease (*2*). Last, AD can present with a variety of clinical phenotypes besides impairments in memory. These include predominant impairments in language, visuospatial ability, or behavior; thus, no clinical phenotype can predict the neuropathological findings with certainty. In contrast to a clinical diagnosis, disease-specific biological markers offer greater specificity for detecting β amyloid plaques and tau neurofibrillary tangles.

A second compelling argument in favor of a biological definition of AD is that it will lead to a better understanding of the sequence of events that leads to cognitive impairment and dementia. We have known for decades

that the neuropathological features of AD appear before overt dementia becomes apparent and more recently that biological markers of AD neuropathology become abnormal up to two to three decades before clinical symptoms develop (*4*). A clinical diagnostic criterion is unable to detect pathological changes that precede onset of symptoms, whereas a biological definition enables researchers to study the sequence of antecedent events that lead to cognitive impairment. Furthermore, all biological marker abnormalities do not develop simultaneously. Much evidence indicates that amyloid deposition precedes downstream biological marker events like neurodegeneration by more than a decade (*4*). By incorporating biological markers into research studies, the sequence of pathological events denoted by these markers can be studied in vivo.

A third argument in favor of a biological definition is that AD biological markers will improve efficiency of clinical trials. This will occur not by replacing clinical or cognitive outcome measures but rather by the following: (i) excluding participants from the trial who are not expected to benefit from treatment (i.e., no amyloid or tau deposition), (ii) selecting individuals at the appropriate disease stage who are most likely to benefit from treatment, and (iii) demonstrating biological target engagement. Recent phase 3 clinical trials that used the Alzheimer's Clinical Syndrome as the entry criteria demonstrated that up to 30% of such patient cohorts are amyloid negative on PET imaging (*5*), that is, nearly one-third of participants did not have the disease they were being treated for.

Enabled by the application of biological markers, the design of clinical trials is becoming more sophisticated as scientists target specific aspects of the AD pathological cascade. For example, participants should be amyloid positive to be enrolled in clinical trials for therapeutic interventions that remove existing β amyloid deposits. Participants should have both amyloid and tau deposits to be enrolled in clinical trials of interventions designed to remove both of these deposits. Clinical trials for primary prevention interventions would need to enroll individuals without either amyloid or tau deposits. Reduction in brain amyloid load from baseline in treated individuals detected by PET imaging has provided proof-of-target engagement for antiamyloid interventions. The expectation is that the same will occur with tau PET imaging as interventions that target pathological tau are developed.

Advocates of a syndromal definition correctly point out that current AD markers are either expensive (PET imaging) or invasive (lumbar puncture to obtain cerebrospinal fluid). However, these limitations may be rendered moot by the development of blood-based markers. The AT(N) system included biological markers commonly used in AD research at that time, but it was explicitly designed to be flexible. As new markers in the amyloid, tau, and neurodegeneration categories are developed and validated, these will be placed into the appropriate mechanistic categories. Promising results have been recently reported for plasma-based markers of β amyloid. Blood-based markers would make biologically based AD diagnosis widely accessible and much less costly. In addition, the AT(N) system is designed to evolve to incorporate biological markers in new categories as discoveries are made. For example, when either imaging or fluid biological markers of α-synuclein, inflammation, and TDP43 are developed, the AT(N) system will be expanded to incorporate these markers of neuropathologies that frequently co-occur with β amyloid plaques and tau tangles and contribute to cognitive impairment.

Critics of the NIA-AA research framework have argued that β amyloid and pathological tau must be proven to be causal in AD pathogenesis for this framework to be valid. An important but often overlooked point is that this research framework does not require that β amyloid plaques and tau neurofibrillary tangles are causal. Rather, markers of these two proteinopathies define AD biologically in a way that mirrors the neuropathological definition that has been in place for decades (*2*).

We think the most scientifically productive way forward is to adopt a biological definition of AD. Dementia, including Alzheimer's Clinical Syndrome, is not synonymous with AD because AD is only one of many causes of dementia. Equating dementia or Alzheimer's Clinical Syndrome with AD erects substantial barriers to understanding interactions among the different etiologies that can lead to cognitive decline. We argue that the most constructive approach is to use imaging and fluid markers to identify the individual biological contributions to cognitive impairment. Biological markers already exist for β amyloid plaques and tau neurofibrillary tangles and therefore should be used now to define AD in vivo. As markers of other pathological processes (e.g., TDP43 proteinopathy or Lewy body disease) are found and validated, they will be added to the research armamentarium. It is only by teasing apart the individual etiological contributors to cognitive impairment that mechanisms can be effectively investigated and effective treatments developed. The diagnostic approach endorsed by advocates of a clinical definition of AD in contrast blurs the distinction between different diseases that contribute to cognitive impairment, thus confounding efforts to understand mechanisms and to find effective treatments. Last, a biological definition of AD enables study of the disease from the preclinical stage through all symptomatic stages and of all disease phenotypes not only the memory loss phenotype. A clinically based definition of AD limits the window of investigation to the later symptomatic stages of the disease, which is not the route to a deeper understanding of disease mechanisms and the development of preventative interventions.

– Clifford R. Jack Jr., David M. Holtzman, Reisa Sperling

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Competing interests: C.R.J., D.M.H., and R.S. are members of the NIA-AA working group. C.R.J. consults for Eli Lilly and serves on an independent data monitoring board for Roche. D.M.H. consults for Genentech, Denali, AbbVie, and Proclara Biosciences. He has equity in C2N Diagnostics, LLC. He is an inventor on several patents related to AD drug development. R.S. consults for Abbvie, Biogen, Genentech, Bracket, Roche, Sanofi, Lundbeck, Eisai, Otsuka, Pfizer, and Merck. She serves as Project Director for the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study and the Ante-Amyloid Prevention of Alzheimer's Disease (A3) Study.

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