Are the revised diagnostic criteria for Alzheimer’s disease useful in low- and middle-income countries?

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Summary: Alzheimer’s Disease (AD) is a leading cause of disease burden among elderly individuals that is increasingly important in middle-income countries like China where improvements in overall health (which increase longevity) and other factors are leading to a rapidly aging population. The diagnostic criteria for AD have recently been revised to reflect advances in the understanding of the condition over the past three decades. Different international organizations have proposed algorithms for diagnosing AD that subdivide the AD spectrum into overlapping stages and, in some cases, require the concurrent presence of memory impairment and specific biomarkers. There are, however, several substantial limitations to these revised criteria: highly trained clinicians are needed to make the fine discriminations between the stages; the role of the proposed biomarkers in the onset and course of AD remain uncertain; and assessment of these biomarkers requires the use of expensive, high-tech equipment by well-trained technicians. These problems limit the clinical utility of these diagnostic criteria, particularly in low-resource settings where the clinicians responsible for identifying and treating individuals with AD have limited training and where the equipment needed to identify the biomarkers are either non-existent or in short supply.

Key words: Alzheimer’s disease; diagnostic criteria; low- and middle-income countries

1. Recent history of the diagnosis of Alzheimer’s disease

During the past 30 years, the diagnostic criteria of Alzheimer’s Disease (AD) have undergone multiple revisions as our understanding of the condition has improved:

(a) the United States National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) (1984),[1]
(b) the International Classification of Diseases-10th edition (ICD-10, 1993),[2]
(c) the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders-IV-TR (DSM-IV-TR, 1994),[3]
(d) the International Working Group for New Research Criteria for the Diagnosis of AD criteria (IWG, 2007/2010),[4,5]
(e) the United States National Institute of Aging-Alzheimer’s Association (NIA-AA) diagnostic guidelines for Alzheimer’s disease (2011),[6-9]
(f) the fifth edition of the DSM criteria (2013),[10] and
(g) the second edition of the IWG criteria (2014).[11]

The current consensus is that AD is a brain disease that differs from other types of dementia. Over time the diagnosis has changed from being a diagnosis of exclusion (after excluding ‘known’ causes of dementia) that is only confirmed by postmortem autopsy to a diagnosis that is actively identified in living individuals who have both clinical symptoms and specific biomarkers. This article provides a summary of the changes in the diagnostic criteria of AD over the past 30 years and discusses the utility of the current criteria in clinical and research settings.

2. Characteristics of the traditional diagnostic algorithms

For a long time, AD – the most common subtype of dementia – was almost equivalent to dementia. The 1984 NINCDS-ADRDA Alzheimer’s criteria categorized the AD diagnosis in living individuals as ‘possible’ or ‘probable’ based on the clinical presentation and only classified AD as ‘definite’ when specific histopathologic changes were found on autopsy. Globally, the 1993 ICD-10 criteria for AD are the most widely used diagnostic criteria employed in clinical practice and the 1994 DSM-IV diagnostic criteria for AD are the most commonly used criteria employed in mental health research. In
all three diagnostic systems, the diagnosis of AD in living individuals is based on the clinical presentation of memory loss and cognitive decline that follows a recognizable pattern of onset and progression and that cannot be attributed to other physical diseases or organic brain diseases. Using these criteria, AD can only be diagnosed when the cognitive impairment is quite advanced; by the time of the formal diagnosis the length of survival is usually less than 10 years. In the absence of sensitive biomarkers it was difficult to differentiate AD from other types of dementia prior to death.[22]

These widely used criteria have several important limitations. Their assumption that clinical symptoms are synchronous with pathological changes ignores the fact that antecedent pathologic changes usually occur years before the presence of any clinically significant symptoms.[8] The criteria do not classify cognitive impairments that don’t meet the full criteria of dementia. The criteria do not consider comorbidity issues, which are common in individuals with AD.[13,14] And the criteria do not include the behavioral symptoms of AD that often become the target of clinical interventions in patients with AD. These limitations result in delayed diagnosis, delayed treatment, and unsatisfactory clinical outcomes.

3. The new diagnostic algorithms

Recently, it has become clear that neuropathologic changes often occur much earlier than clinical manifestations of AD.[15-17] Antecedent pathologic changes in the brain that are auto-progressive, such as amyloid plaque, can occur 20 years earlier than the clinical symptoms of AD.[18] The identification of two categories of sensitive and reliable biomarkers of early AD has lead NIA-AA and IWG to redefined the course of AD: (a) biomarkers of amyloid-beta (Aβ) accumulation including tracer retention on amyloid PET imaging and low cerebrospinal fluid (CSF) Aβ42; and (b) biomarkers of neuronal degeneration or injury including CSF tau, abnormal fluorodeoxyglucose uptake on PET in a specific topographic pattern, and atrophy on structural magnetic resonance imaging (MRI) in a specific topographic pattern. Based on these findings, some scholars have proposed criteria for different levels of AD spectrum disorder’ including preclinical AD, mild cognitive impairment (MCI), prodromal AD, and AD.[19]

3.1 IWG criteria

In 2007 the revised IWG diagnostic criteria added the aforementioned biomarkers as criteria for prodromal AD and AD; at the same time the IWG also eliminated the traditional clinical symptom of decreased levels of daily functioning from the diagnostic algorithm. These criteria were proposed for use in research on classic AD (i.e., amnesic cognitive impairment), which emphasizes hippocampal memory loss as the core symptom. Two limitations in these 2007 criteria were that they give equal weight to all biomarkers and they did not specify the temporal sequence of the occurrence of the various biomarkers.[20]

In 2010 the IWG made additional changes to the criteria that expanded the coverage of AD spectrum by providing detailed criteria for the different subtypes of AD, including classic AD, atypical AD, mixed AD, and preclinical AD. The new diagnostic algorithm proposed two states of preclinical AD: an asymptomatic at-risk state for AD and pre-symptomatic AD. Asymptomatic state refers to individuals with evidence of amyloid accumulation but no clinical symptoms; these individuals may or may not develop AD.[21] Pre-symptomatic AD refers to individuals who have AD genetic mutations but normal cognitive functioning; they almost always develop AD.

These revised IWG criteria also reflected research findings about the progressive nature of the disease and about the sub-classification of biomarkers. Biomarkers were categorized as histopathologic biomarkers (including CSF Aβ42, CSF tau, and amyloid plaques on PET imaging) or as topographic biomarkers (including low and abnormal fluorodeoxyglucose uptake on PET in a specific topographic pattern, and atrophy on structural magnetic resonance in a specific topographic pattern). The criteria also group biomarkers into diagnostic (trait) markers and progression (state) markers. Diagnostic markers include CSF Aβ, CSF tau, amyloid plaques on PET, and mutations on AD autosomal genes (APP, PS1, and PS2); they reflect the innate physiopathological processes of AD and are present regardless of the stage or severity of the disease. Based on the IWG algorithm, the diagnosis can be made whenever any of these markers is present. Progression markers include medial temporal lobe atrophy on MRI and low fluorodeoxyglucose uptake in the temporal parietal area; these markers are not specific to AD and are possibly absent at early stages of AD, but they can indicate the progression of the disease.

3.2 NIA-AA criteria

The 2011 NIA-AA criteria updated the 1984 NINCDS-ADRDA criteria by distinguishing pathologic changes from clinical manifestations and by emphasizing the progressive nature of AD. NIA-AA defines three states of this disease spectrum: the asymptomatic stage (preclinical AD), prodromal stage (AD–related MCI), and definite AD (AD). The latter two states are further categorized into ‘highly likely’, ‘likely’, and ‘unlikely’. One purpose for proposing this sub-classification of AD was to increase the homogeneity of individuals who participated in studies about AD. Biomarkers appear in the diagnostic criteria for all three stages but play different roles for different stages. The diagnosis of preclinical AD almost completely relies on biomarkers and is only recommended for research purposes. The diagnoses of prodromal and definite AD can be made based on clinical symptoms alone without any biomarkers and, thus, is recommended for clinical use.[8] The new NIA-AA criteria emphasize the role of genetic mutations (i.e., APP, PS1, and PS2) in the diagnosis of amnesic cognitive impairment and in the differentiation of AD from other types of dementia.
3.3 Revised approach of DSM-5 to AD

DSM-5 has reformulated dementias as major or mild neurocognitive disorders (NCD) which are diagnosed when significant cognitive decline in one or more of six cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) is reported by the individual or informants and confirmed by standardized neuropsychiatric testing. (The inclusion of ‘social cognition’ as one of the six types of cognition is controversial because this type of ‘cognition’ can be heavily influenced by the sociocultural environment.) The primary distinction between major NCD and minor NCD is that the impairment in major NCD interferes with independence in everyday activities while the impairment in minor NCD does not interfere with daily functioning. Major or minor NCD is diagnosed ‘Due to Alzheimer’s Disease’ if there is insidious onset and gradual progression of decline in one or more of the six cognitive domains and there is no evidence of mixed etiology (e.g., cerebrovascular disease). Major and minor NCD Due to Alzheimer’s Disease are further subdivided into ‘probable’ or ‘possible’ cases. Probable major or minor NCD due to AD is diagnosed if a specific genetic mutation is identified (APP, PS1, PS2) in the individual or an affected family member; probable major NCD due to AD is also diagnosed if the individual has clear evidence of progressive decline without extended plateaus in memory and learning and in at least one of the other five cognitive domains that is confirmed by serial neuropsychological testing. DSM-5 states that other biomarkers are not fully validated, but predicts that such markers will soon become more widely used in clinical practice.

3.4 Similarities and differences between the new diagnostic algorithms for AD

The IWG and NIA-AA diagnostic algorithms for AD both incorporate biomarkers, highlighting the new status of AD biomarkers in both research and clinical practice. The potential of this approach is that it will promote the identification of an etiology-based diagnosis of MCI, early detection of AD, early intervention, and slowed (or stopped) disease progression. [22] Some studies that have evaluated these two diagnostic algorithms report that the biomarkers are both sensitive (i.e., are present in most persons with AD and in few persons without AD) and reliable (i.e., are stable over time). [23] On the other hand, DSM-5 suggests that the evidence is not yet conclusive enough to make biomarkers part of the diagnostic criteria for AD.

There are some important differences in these two diagnostic algorithms. The NIA-AA algorithm emphasizes the physio-pathologic processes of AD, divides AD spectrum into asymptomatic and symptomatic stages (describing preclinical manifestations in detail), retains the term amnesic MCI, considers subjective or objective memory impairment and biomarkers supportive features that are not required for the diagnosis of AD, and states that AD-like pathologic changes may occur in non-amnesic AD. In contrast, the IWG algorithm uses the term prodromal AD in place of MCI, emphasizes that both objective memory impairment and biomarkers are necessary elements for the diagnosis of AD, recommends the use of CSF biomarkers to boost diagnostic specificity, highlights the value of neuropsychological testing for confirming the diagnosis, and states that not all individuals with asymptomatic AD eventually develop AD.

The NIA-AA criteria can be used for both research and clinical purposes because of its separate criteria for the asymptomatic stage (which requires the presence of AD-related biomarkers) and MCI (which can be diagnosed in the absence of biomarkers). However, the specifications for three different stages of AD (asymptomatic, prodromal, and definite) and for the three probability levels (‘highly likely’, ‘likely’, and ‘unlikely’) of prodromal and definite AD make the criteria technically challenging in practice. The IWG criteria use the same criteria for all conditions along the AD spectrum and avoid the ‘very likely’ and ‘likely’ specifiers; this simplifies the diagnostic process, but the requirement of concurrent amnestic memory impairment and the presence of AD biomarkers makes the application of this diagnostic algorithm impractical for clinical settings, so it is largely limited to research applications. Some researchers recommend making the IWG criteria more practical by removing the requirement of AD biomarkers when amnestic cognitive impairment is present, but continuing to require the concurrent presence of AD biomarkers when the clinical symptoms are atypical. [11]

3.5 Unresolved problems with the new diagnostic criteria

There are several aspects of the suggested biomarkers that remain unknown: (a) What is the sequence of their appearance and how are they related to each other? (b) What is the appropriate cutoff level (i.e., threshold) for the markers that are continuous quantities? (c) How reliable and valid are they in identifying individuals on the AD spectrum? (d) How useful are they in discriminating distinct phenotypic subtypes of AD with different etiologies and different clinical trajectories? (f) Should other genetic markers with low specificity for subjective cognitive impairment (such as CLU, CR1, PICALM, and APOE ε4) that have been linked to AD be included in the diagnostic criteria? (g) Are these markers also present in individuals with atypical clinical presentations of AD?

Perhaps the most important concern is the practicality of these criteria in routine clinical practice, particularly in low- and middle-income countries (LMICs). The new diagnostic algorithms propose several new technical terms, some of which have vague or overlapping operational definitions that will be difficult for general physicians without specialized training to use reliably. Moreover, the cost of the proposed diagnostic markers is substantial and requires access to high-level equipment that is not available in most LMICs.
settings. The DSM-5 requirement of genetic testing or formal neuropsychiatric testing to establish a diagnosis of probable major or minor NCD Due to Alzheimer’s Disease will mean that in most clinical settings—particularly those in LMICs—the DSM-5 diagnosis of individuals with gradual cognitive decline will almost always be classified as possible major or minor NCD Due to Alzheimer’s Disease. For these settings, this is not much of an improvement over the DSM-IV system and may actually prove more complicated to implement.

4. Summary and future directions
The most fundamental change of the new diagnostic algorithms of AD is replacement of a clinical-pathologic definition of AD with a new bio-clinical definition that has resulted in the use of specific biomarkers as diagnostic criteria. AD is no longer considered the prototypic dementia syndrome but, rather, a complex, heterogeneous, and progressive disease with diverse clinical phenotypes. Before the discovery of an effective cure, early detection using diagnostically validated biomarkers remains the best option available for early intervention.

The current AD-related biomarkers of interest are probably only an intermediate point on the path to fully characterizing the genetic and biochemical substrates of the various subtypes of dementia that are included within the AD spectrum. Much more research will be needed to further characterize these biomarkers and to clarify how they are related to the clinical symptoms of AD.

It remains unclear how the exciting research findings that have fueled these fundamental changes in the diagnostic criteria of AD can be translated in ways that will help clinicians in low-resource settings improve the identification and management of the huge numbers of individuals with AD who are appearing as the global population ages. Given the remaining uncertainty about these biomarkers and the cost associated with using them, the original clinical-based NINCDS-ADRDA, ICD-10, and DSM-IV-R criteria will still be widely used in clinical practice. This is not necessarily a bad thing: the accuracy of diagnosis using the original criteria is as high as 92% if the diagnostic criteria are carefully followed (e.g., progressive occurrence of classic AD symptoms, results from reliable neuropsychological tests, and the exclusion of other conditions that can cause cognitive impairment).

Any biomarker-based improvement on diagnostic accuracy must, in the end, be cost-effective, particularly in low-resource settings. The assessment of the biomarker must also be culturally acceptable; for example, there is substantial resistance to invasive procedures such as conducting a spinal tap in China, so the use of different MRI techniques, though more expensive, is more feasible.

The main hope for early identification and treatment of AD in LMICs is the identification of simple and reliable markers that can be obtained via inexpensive, non-invasive methods including tests on blood, urine, and the retina.

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