The New Criteria for Alzheimer's Disease - Implications for Geriatricians*

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ABSTRACT

Two new sets of criteria for Alzheimer's disease (AD) are now in play, including one set released in 2014, and a proposal for a "new lexicon" for how to describe the disease spectrum. A 2012 Canadian consensus conference said that to then, none of the new criteria or terminology would change primary care practice; that is still likely to be so. For dementia consultants, however, the new criteria pose challenges and offer opportunities.

In general, the new criteria see an expanded role for biomarkers. Even so, the evidence base for this remains incomplete. Our understanding of the neuropathological criteria for dementia changed as the evidence base included more community cases. This is likely to inform the experience with biomarkers. At present, each of the criteria specifies an exclusive research role. Still, wider uptake is likely, especially in the United States.

Geriatricians should be aware of the fundamental change in the terminology now being employed: AD diagnosis no longer obliges a diagnosis of dementia. Until more data emerge—something to which geriatricians can contribute—there is reason to be cautious in the adoption of the new criteria, as they are likely to be least applicable to older adults.

Key words: Alzheimer's disease, biomarkers, criteria, dementia, frailty, geriatric medicine, mild cognitive impairment

INTRODUCTION

Since the 1984 clinical criteria for Alzheimer's disease (AD), diagnosis has required the presence of symptoms.(1) Classically, a dementia diagnosis is made when progressive cognitive impairment, including typical amnesia, is severe enough to interfere with daily functioning. By this account AD was the most common cause.

Clinic-based studies have showed that up to 80% of subjects with mild cognitive impairment (MCI) develop dementia after six years.(2) On the other hand, population-based cases tend to show less progression,(3) regardless of the criteria used.(4) Interestingly, although the Canadian experience is that people with a "pre-AD" profile of MCI tend to convert to AD, it also shows MCI to be a heterogeneous category, including some groups who recover cognitive function.(5) Legitimate questions therefore are raised: Is MCI a risk factor for AD or is it rather an early stage? Should we extend the concept of AD beyond the stage of dementia? In brief, should we define AD by its clinical manifestations or by the underlying pathological process? While there is no doubt that a pre-dementia stage of AD exists, terminology and criteria to describe it are still evolving.

Recent advances in neuroimaging and neuropathology allowed the development of biomarkers that reflect *in vivo* the neuropathological changes traditionally thought to define AD: amyloid plaques, neurofibrillary tangles, and associated synaptic dysfunction and neuronal loss.(6) These changes can occur several years before the clinical manifestations of the disease. These discoveries, set against the background of what has been learned from community-based autopsy series and from the evolving understanding of dementia in relation to general health and frailty, has fueled the controversy regarding the nomenclature to be adopted. More than the results of community-based autopsy series, biomarkers have motivated the new lexicon and the two new sets of criteria for the diagnosis of AD. With the amyloid cascade hypothesis still generating debate,(7,8) are these recent advances robust enough to be incorporated into new diagnostic criteria? Are these new criteria susceptible to change our practice as geriatricians? This is what we will discuss here.

THE NEW CRITERIA

IWG-2 Criteria

In 2007, the International Working Group (IWG) for New Research Criteria for the Diagnosis of AD proposed research criteria (widely known as the Dubois criteria), allowing AD to be diagnosed in its prodromal phase, before it interferes with daily functioning.(9) To do so, the core clinical criterion of impaired episodic memory should be accompanied by at

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least one biological "footprint" of the disease (by which is meant a biomarker).

In response to the resulting debate, the IWG proposed a "common lexicon" for the clinical and research communities.[10] They differentiate "Alzheimer's disease" from "Alzheimer's pathology". The latter refers to the underlying neurobiological changes, regardless of the presence of symptoms, whereas the label "Alzheimer's disease" is restricted to the clinical disorder and encompasses both the prodromal and dementia phases. The preclinical stage was further divided into two categories: carriers of an autosomal dominant monogenic mutation who will develop AD (pre-symptomatic AD), and subjects in whom there is *in vivo* evidence of brain amyloidosis. Reflecting the unknown prognostic value of biomarkers, the latter category defines "asymptomatic at-risk for AD".

In 2014, the second version (IWG-2), while biomarker-based, acknowledged less frequent, but well-defined, atypical AD phenotypes.[11] In typical AD, the core clinical criterion remains identification of "an amnestic syndrome of the hippocampal type", in which episodic memory is characterized by a low free recall that is not normalized by cueing. The key modifications introduced by IWG-2 rest with a new conceptualization of the biomarkers (Table 1). "Pathophysiological markers", which identify AD's signature in the brain, are now contrasted to "topographical markers". According to this model, the pathophysiological markers are largely static, at least in the symptomatic stage of the disease, whereas topographical markers change more. Despite their apparent non-specificity for symptomatic AD, the IWG therefore endorses the use of the pathophysiological markers to diagnose AD at any point on the disease continuum (Table 2). In contrast, topographical markers are now reserved to measure disease progression and have been removed from the diagnosis algorithm.

NIA-AA Criteria

In 2011, the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease (NIA-AA) published new diagnostic criteria for each of preclinical AD, MCI, and dementia.[12-14] In addition to recognizing that AD may have non-amnestic presentations, the NIA-AA suggested that AD should be seen as a continuum and diagnosed in its early phases, including asymptomatic patients (preclinical stage) and those with MCI.

To diagnose AD in asymptomatic subjects, the NIA-AA criteria rely on biomarkers. Markers of brain amyloid beta (Aβ) accumulation and those indicative of neuronal injury are the basis for further dividing preclinical AD into three stages (Table 1). Patients with subtle cognitive changes not yet meeting standardized criteria for MCI are also included under the rubric of "preclinical AD" when biomarkers are positive (Table 2). These recommendations, intended initially for research purposes, thus pave the way to diagnosing AD before the onset of symptoms.

In symptomatic patients, biomarkers are used to indicate the probability of AD etiology (high, intermediate or low). Even so, the NIA-AA does not currently advocate the use of biomarker tests for routine diagnostic purposes. The core clinical criteria provide good diagnostic accuracy; criteria incorporating biomarkers have yet to be validated, and access to biomarkers and standardization in their use is limited.

Comparison of the Criteria

For clinically evident AD, the IWG-2 criteria are much simpler, as they have eliminated what can be an ambiguous barrier between MCI and dementia. Their diagnostic approach is the same, regardless of disease severity. On the other hand, the NIA-AA criteria do not oblige biomarkers, which are employed to suggest the odds that symptoms are caused by AD. The proposed AD definitions also differ. The NIA-AA defines AD as encompassing the underlying pathophysiological disease process, as opposed to having AD connote only the clinical disorder.

Against this background, and mindful of both the lessons from community-based autopsy series and the lack of follow-up data on biomarkers, the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4) recommended that the criteria for MCI due to AD be used cautiously and only in specialized clinical practice.[15] Specifically, the CCCDTD4 considered it premature to refer to brain amyloidosis as an asymptomatic state of AD and rejected the label "preclinical AD" as proposed by the NIA-AA. Moreover, ethical and financial impact of its use would be considerable. IWG's definition of "asymptomatic at risk" has been endorsed only for research purposes.

Considering the substantial disparities in the terminologies employed, a group of investigators led by experts who were integral to the development of both the IWG-2 and the NIA-AA criteria was formed in 2012, with the objective to harmonize the criteria. They suggested that AD should be defined as a brain disorder, regardless of the clinical status, and that "symptomatic AD" should denote the clinically expressed disorder, including its prodromal stages.[16]

VALIDATION OF THE CRITERIA

In vivo studies of brain Aβ deposition and markers of neuronal injury, understood as detecting the pathology that gives rise to AD, undoubtedly will lead to a wider reliance on biomarkers, regardless of expert endorsement or otherwise. It already has motivated earlier intervention studies, aimed at reducing biomarker burden, in the expectation that clinical disease expression will thereby be lessened. This expectation has received early setbacks, such as the requirement for an Aβ biomarker for prodromal AD or MCI not in fact leading to more efficient clinical trials[17] and clearance of pathology without improvement in dementia,[18] on the grounds that the studies were undertaken too late in the disease course. It remains, however, that there is much to learn about the trajectories of the individuals in whom biomarker changes

TABLE 1.
Biomarkers used to define AD

IWG-2	*NIA-AA*
Pathophysiological markers • ↓ $A\beta_{42}$ together with ↑T-tau or P-tau in CSF • ↑ tracer retention on amyloid PET	Aβ biomarkers • ↓ Aβ42 in CSF • ↑ tracer retention on amyloid PET
Topographical markers • AD-like pattern of atrophy on brain MRI • AD-like pattern of hypometabolism on FDG-PET	Markers of neuronal injury • ↑ T-tau or P-tau in CSF • AD-like pattern of atrophy on brain MRI • AD-like pattern of hypometabolism on FDG-PET
AD autosomal dominant mutation • PSEN1, PSEN2 or APP	

AD = Alzheimer's disease; Aβ = amyloid-beta; CSF = cerebrospinal fluid; FDG = fluorodeoxyglucose; IWG = International Working Group; MRI = magnetic resonance imaging; NIA-AA = National Institute on Aging-Alzheimer's Association; PET = positron emission tomography.

have been detected. In consequence, prospective validation of the new criteria is essential.

IWG Criteria

IWG-1 criteria have been compared to the 1984 NINCDS-ADRDA criteria in a memory clinic population.[19] Their specificity was excellent in non-demented subjects (95%) and their sensitivity was 86% in patients with AD. These results suggest that the IWG-1 criteria were effective in confirming the diagnosis in "pure" AD presentations; however, they seem much less useful when there is a clinical doubt about the type of dementia. Indeed, given a specificity of 49% for the comparison with other demented patients, they have no added value in that setting. Similar findings were observed in a retrospective analysis conducted on a cohort with post-mortem confirmed diagnoses.[20] This overlap could partly be explained by the high prevalence of mixed pathologies in the post-mortem examination of patients with dementia.[21] This observation is especially relevant for interpreting biomarker data in older patients, in whom mixed pathologies are more frequent.[22,23]

The first Dubois criteria were also tested in a young Swedish population, at a lower risk of mixed pathologies.[24] They were valid in 55% of cases to identify patients with a clinical diagnosis of AD. This discrepancy was partly attributed to the difficulties in defining norms for biomarker pathology and to the question of whether age-specific cut-off values for diagnostic markers should be employed, and if so, exactly what that would imply. In brief, whatever their usefulness in selecting "pure" AD cases for clinical trials, the IWG-1 criteria seem less suitable for wider use, particularly when mixed pathologies are likely.[25-28]

Vos and colleagues used the IWG-2 criteria to study the prevalence and prognosis of prodromal AD/MCI in 13 cohorts.[29] Of 766 subjects with CSF markers, 308 (40%) had prodromal AD. Their three-year progression rate to AD-type dementia was 61% compared to 22% for subjects without prodromal AD. Unfortunately, a cued recall test to define memory impairment, as recommended in the IWG-2 criteria, was not available for most patients. It is also possible that the use of amyloid-PET (in combination) could have led to different results and decreased the proportion of subjects without prodromal AD who progressed to AD dementia.

NIA-AA Criteria

To illustrate their operationalization, the NIA-AA criteria were applied retrospectively in individuals from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. Note that ADNI's initial objective was to characterize biomarkers of AD and identify a combination of tests that could lead to a more accurate and early diagnosis.[30] Studies on this cohort have, therefore, served as foundations for the new AD criteria and conceptualization.[31,32] In this well-defined AD dementia population, 87% of subjects could be categorized as "high probability" for AD, whereas 5% of the subjects fit the criteria of "dementia unlikely due to AD" and about 10% had negative amyloid markers.[33] This work drew attention to the complexity in interpreting the multitude of possible biomarker combinations, something not yet informing the NIA-AA criteria.

Clinic and population-based studies with the NIA-AA criteria for MCI due to AD have exposed the same problems: lack of standardization in the measurement and interpretation of the biomarkers, and conflicting results.[34,35] Vos and colleagues compared the NIA-AA and IWG-2 criteria head to head for prodromal AD/MCI.[29] The NIA-AA approach classified 46% of the subjects in whom both amyloid and neuronal injury markers were available in the "high AD likelihood" group, while 6% were in the "isolated amyloid pathology" (IAP) group, 29% in the "suspected non-AD pathophysiology" (SNAP) group, and 19% in the "low AD likelihood" group. The SNAP group denotes subjects with normal Aβ biomarkers, but abnormal markers of neurodegeneration. The three-year progression rate to AD-type dementia was 59% in the "high AD likelihood" group, 22% in the IAP group, 24% in the SNAP group, and 5% in the "low AD likelihood" group. IAP and SNAP were heterogeneous conditions, with some people progressing to AD dementia. The specificity and

TABLE 2.
Comparison of the criteria for AD incorporating biomarkers

	Cognitive Criteria	*Biomarker Criteria*		
		PRECLINICAL STAGES		
IWG-2				
Asymptomatic at risk for AD	No impairment	Any pathophysiological marker		
Presymptomatic AD	No impairment	AD autosomal dominant mutation or other proven genes		
NIA-AA				
		Aβ Biomarker		Injury Marker
Stage 1	No impairment	+		–
Stage 2	No impairment	+		+
Stage 3	Subtle cognitive change	+		+
		CLINICAL STAGES		
IWG-2				
Typical or atypical AD	Specific clinical phenotype	Any pathophysiological marker or AD autosomal dominant mutation		
NIA-AA				
MCI due to AD	MCI	Biomarker Probability of AD Etiology	Aβ Biomarker	Injury Marker
AD dementia	Dementia	Uninformative[a]	Unavailable, conflicting or indeterminate	
		Lowest[b]	–	–
		Intermediate	+	?
			?	+
		High[c]	+	+

[a]Diagnosis is based on clinical criteria.
[b]Unlikely due to AD.
[c]Possible AD dementia with evidence of AD pathophysiological process does not preclude the possibility that a second pathophysiological condition is also present.
AD = Alzheimer disease; Aβ = amyloid-beta; IWG = International Working Group; MCI = mild cognitive impairment; NIA-AA = National Institute on Aging-Alzheimer's Association; + = positive; – = negative; ? = unavailable or indeterminate.

positive predictive value were highest for the IWG-2, whereas the sensitivity and negative predictive value were highest for NIA-AA. More data on progression are needed.

The NIA-AA criteria for preclinical AD have been studied in the population-based Mayo Clinic Study of Aging (MCSA). At cohort inception, 31% of 450 cognitively normal subjects (median age 78; interquartile range 74 to 82) met the NIA-AA criteria for preclinical AD (stages 1–3) and 23% were classified in the SNAP group.[36] Most importantly, this analysis found that only 43% of cognitively normal subjects from a population-based sample had negative biomarkers (group 0). After a 15-month follow-up period, the proportion of patients who progressed to MCI or AD dementia was linked to the attributed preclinical stage (stage 0, 5%; stage 1, 11%; stage 2, 21%; stage 3, 43%).[37] These preliminary results support the NIA-AA criteria's predictive validity in asymptomatic subjects; however, since biomarkers were being tested against clinical criteria, not everyone will be persuaded of their added value. Longer validation studies with pathological correlation are needed.

Community vs. Clinic Cohorts

Recent hypothetical models of the biomarkers of AD and the new diagnostic criteria derived from them have mainly been studied in subjects from memory clinics.[38] This selection bias influences the pre-test probability of having AD, even in healthy individuals.[39] Indeed, subjects from population-based studies are, by definition, more heterogeneous, so that post-mortem diagnosis of AD is usually confirmed less often than in clinic-based studies.[40-42] In ADNI, hippocampal volume declined faster than in the population-based MCSA cohort.[43] These results suggest that individuals recruited by the ADNI cohort have a more aggressive brain pathology than is seen in the general population. In addition, subjects recruited voluntarily were more educated and had a stronger family history of AD. Another study even revealed that the neuropathological diagnosis of AD was more common in subjects without cognitive impairment from a memory clinic than in those of community-based studies.[44] Furthermore, community-based individuals with MCI and probable AD

dementia more often had infarcts and mixed pathologies, while clinic-based patients had more severe AD pathology and more atypical pathologies.

Recently it has been suggested that studying homogeneous subjects might not be essential to improving our knowledge of AD pathophysiology, and might even be misleading.[45] That is because the burden of deficit accumulation revealed by frailty might be necessary for the deleterious effects of plaques and tangles to be fully expressed in ageing brains. Regardless, it is clear that the new criteria need to be validated in population-based cohorts if we are to understand their generalizability well enough to change practice.[46]

USE OF THE NEW CRITERIA IN OLDER ADULTS

Alois Alzheimer described Auguste D. in 1907.[47] Her dementia symptoms arose in her fifties, making case as "early onset" by today's standards. To this day, research in the field retains an emphasis on relatively young patients with few comorbidities and a "pure" presentation. In contrast to early onset cases, past age 85 the phenotypic expression of AD is more attenuated, with slower disease progression.[48,49] The association between the pathological features of AD and dementia weakens with age, suggesting that the pathophysiological process that causes dementia differs in some older people.[50] For example, most population-based studies suggest that AD pathology is associated with subtle changes in episodic memory, even in patients without MCI.[51-53] This link was found to be absent, however, in a population-based sample of non-demented individuals aged 90+ years in whom cognitive performance was assessed biannually three years prior to autopsy.[54] Such observations raise questions about biomarker-based criteria in older adults.

Biomarkers in the Very Old

The biomarkers' ability to distinguish normal subjects from AD patients lessens with age. The typical pattern of AD-related, MRI-based morphometric brain changes seen in the young old (60–75 years old) appears to be less salient in very old patients (80–91 years old), despite similar levels of cognitive impairment.[49] Mild cases of AD may, therefore, go undetected in these patients if diagnosis relies on brain morphometry markers.

Given the age-dependant increase of AD-type brain pathology in cognitively unaffected elderly, the diagnostic accuracy of CSF AD biomarkers also decreases with age.[55] CSF biomarkers, alone or in combination, show significant overlap with other non-AD forms of dementia like dementia with Lewy Bodies and vascular dementia, which are more likely to be found as coexisting pathologies in older patients, even those without dementia.[56] Thus, while CSF biomarkers may be useful to rule in AD in younger subjects, their specificity for controls may be problematic in older adults. Furthermore, the density of neuritic plaques and neurofibrillary tangles can rise by more than tenfold as function of the severity of dementia in individuals aged between 60 and 80 years old.[57] Even so, this difference is absent in patients over 90 years old, reflecting a lower density of AD lesions in brains of oldest-old persons with dementia rather than more such lesions in the brains of non-demented controls.[58] How these age-related differences in the neuropathological features of dementia correlate with biomarkers remains unknown.

Two recent meta-analyses found that the prevalence of amyloid PET positivity decreases with age in subjects with AD, whereas it increases in most non-AD dementias and in non-demented subjects. Indeed, while the prevalence of amyloid positivity increased from age 50 to 90 years (from 10% to 44%) among cognitively normal participants,[59] it dropped from 86% to 68% in patients with AD.[60] Such results challenge claims about the diagnostic utility of biomarkers. Moreover, the high degree of overlap in neuropathology between cognitively normal and cognitively impaired individuals aged over 90 years[23] makes it appropriate for geriatricians to be cautious about joining in the full-throated choruses of enthusiasm for biomarker strategies.

Dementia—a Geriatric Syndrome

The variable expression of AD remains an unsolved and pressing mystery. Protective factors (e.g., education, exercise), as well as multiple risk factors, have been proposed to elucidate why two individuals with the same neuropathology can have different trajectories. Further, a wide variety of health deficits, apparently without direct impact on AD pathophysiology, can interact to modulate expression of dementia.[61]

Perhaps the explanation lies in the frailty concept and the theory of deficit accumulation. It is well described that the addition of comorbidities seen with aging increases the risk of cognitive decline.[62] The risk of developing dementia in frail elderly patient may thus be linked more to the overall health status, including the number of health problems, rather than specific risk factors.[63] Recent data also suggest that the co-morbidity burden is associated with a faster cognitive decline.[64] Although vascular, hormonal, nutritional, and inflammatory changes have been observed, the mechanisms underlying the link between frailty and cognitive impairment remain to be clarified.[45,65-67] In other words, frail elderly people can be viewed as complex systems on the edge of failure. Cognition being one of the highest-order functions, cognitive impairment may thus represent an early manifestation of whole-system failure.[68] As these considerations have had no influence on the new AD criteria and lexicon, their use by geriatricians must be made cautiously.

In short, to explicate the weak correlation between neuropathology and cognitive impairment in older adults, perhaps dementia should be approached as any other geriatric syndrome,[69] as reflecting an accumulation of deficits.

To this end, the study of frail and older subjects is likely to contribute to our understanding of the heterogeneity in dementia expression, as much as the study of "pure" AD cases occurring in younger people has already helped us understand AD pathophysiology.

CONCLUSION

Our knowledge about pathophysiological mechanisms in AD has evolved and laudable efforts have been made to incorporate the new conceptualization of AD (as a continuum) into diagnostic criteria. While these criteria represent a step forward, they need to be validated in the community before being used outside of research settings. In particular, the ability of biomarkers to identify representative, asymptomatic individuals who progress to symptomatic AD needs to be tested prospectively. The new criteria are also less likely to be applicable in older adults, especially the very old, who commonly are seen by geriatricians. Their exclusion from studies as obscuring "proof of concept" might even prove to be especially misleading.

Research must continue to focus on the factors that regulate the occurrence, expression, and progression of dementia. This is where the answers to questions we ask ourselves on a daily basis reside. Meanwhile, geriatricians should be aware of the fundamental change that stems from the new terminology: a diagnosis of AD no longer requires a diagnosis of dementia.

CONFLICT OF INTEREST DISCLOSURES

The authors declare that no conflicts of interest exist.

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