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Introduction to Revised Criteria for the Diagnosis of Alzheimer's Disease: National Institute on Aging and the Alzheimer Association Workgroups

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Introduction

Criteria for the clinical diagnosis of Alzheimer's Disease (AD) were established by a National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) workgroup in 1984 [1]. These criteria were universally adopted, have been extremely useful, and have survived intact without modification for over a quarter of a century. In the intervening 27 years, however, important advances in our understanding of AD, in our ability to detect the pathophysiological process of AD, and changes in conceptualization regarding the clinical spectrum of the disease have occurred.

By 2009 broad consensus existed throughout academia and industry that the criteria should be revised to incorporate scientific advances in the field. In response to this imperative the National Institute on Aging (NIA) and the Alzheimer's Association (AA) sponsored a series of advisory round table meetings in 2009 whose purpose was to establish a process for revising diagnostic and research criteria for the continuum of AD. These advisory meetings included members from academia and industry with an international representation. The consensus from the advisory meetings was that three separate work groups should be formed under the auspices of the NIA and AA. One work group was assigned the task of formulating diagnostic criteria for the dementia phase of AD. A second was asked to focus on diagnostic criteria for the symptomatic pre-dementia phase of AD. The third workgroup was asked to propose a research agenda for the asymptomatic, preclinical phase of AD. Individuals were selected to serve in these work groups, by the NIA and the AA, with the objective of having balanced expertise and international representation from academia and industry. From early to mid 2010 the three work groups met via conference call and in person (as feasible). Each formulated a set of recommendations. These recommendations were presented in a symposium at the 2010 ICAD meeting. They were posted on the Alzheimer's Association website for a period of public comment over the summer of 2010. Comments received during this period, from the website and other venues, were given to the individual workgroups and incorporated into revisions of each document in the fall of 2010. Lastly, a subcommittee representing individuals from each of the workgroups was asked to review the recommendations, particularly with regard to the approach to biomarkers, and a final round of revisions was made to each document in the late fall of 2010 for purposes of

harmonizing the discussion of biomarkers. The final documents were submitted simultaneously in early 2011 to the NIA for review and to the journal for peer review.

The charge to the workgroups was very specific and did not include several related topics. First, it was decided at the outset that a fourth, separate workgroup would be organized to develop revised pathological criteria. Thus, while neuropathologists were represented on each of the three workgroups, the recommendations of the three workgroups do not include a detailed discussion of neuropathologic criteria. The deliberations of the neuropathology workgroup are expected to appear later in 2011. Second, the workgroups were asked to outline future issues that need to be addressed by the research community as a whole, but the specifics for how this will be done, including potential timelines, are not included in these recommendations. This is particularly relevant to the discussion of biomarkers in each of the three documents. There was a consensus among the members of the workgroups that it was premature to define specific cut-points denoting normal vs abnormal values for the biomarkers discussed, and that much work remains to be done with regard to uniform assessment and standardization of biomarkers. Third, the workgroups were specifically asked to focus on the spectrum of AD, and not to try to revise criteria for other neurodegenerative diseases or cerebrovascular dementias. Thus, the set of recommendations presented here only refer to other disorders as they relate to differential diagnosis of AD.

Historical Background

The original NINCDS-ADRDA criteria rest on the notion that AD is a *clinical-pathological* entity [1]. The criteria were designed with the expectation that in most cases, subjects who met the clinical criteria would have AD pathology as the underlying etiology if the subject were to come to autopsy. When the NINCDS-ADRDA criteria were formulated, it was believed that AD, like many other brain diseases, always exhibited a close correspondence between clinical symptoms and the underlying pathology such that (1) AD pathology and clinical symptoms were synonymous, and (2) individuals either had fully developed AD pathology in which case they were demented, or they were free of AD pathology in which case they were not demented (at least not due to AD). In the intervening 27 years it has become clear however that this clinical-pathological correspondence is not always consistent. Extensive AD pathology, particularly diffuse amyloid plaques, can be present in the absence of any obvious symptoms [2–4]. And AD pathophysiology can manifest itself with clinically atypical presentations and prominent language and visuospatial disturbances [5–7]. Accordingly, in the revised NIA-AA criteria, a semantic and conceptual distinction is made between AD pathophysiological processes (abbreviated here as AD-P) and the various clinically observable syndromes that result (abbreviated here as AD-C). Therefore in this document and in the three associated diagnostic work group documents, a distinction is made between the syndromic labels that denote different qualitative and quantitative clinical expressions of disease (AD-C), and the pathophysiological process (AD-P) that underlies the syndrome.

Knowledge about the neuropathology of AD has also expanded over the past quarter century, and several sets of criteria for the neuropathological diagnosis of AD have been published, including an initial effort by the NIA [8], one from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [9], and one from the NIA and AA that is the one most widely used currently, the NIA-Reagan Institute criteria [10]. The current effort at redefining the clinical diagnosis of the preclinical and symptomatic disorders associated with AD-P assume that the fundamental characteristics of AD pathology – namely the presence of at least a moderate number neuritic plaques containing β-amyloid in a low power microscopic section of some region of neocortex and the extent of the regional

distribution of neurofibrillary tangle pathology corresponding to Braak and Braak stage IV or higher will continue to define the neuropathological entity of AD.

Over the past 26 years it has become abundantly clear that the cognitive deficits that accompany AD-P evolve gradually. A now voluminous literature on Mild Cognitive Impairment (MCI) has arisen since the mid 1990's that documents the gradual impairments of cognitive function that precede the point where significant interference in daily activities occur [11]. The clinical dementia rating (CDR) scale likewise reflects gradual development of clinical disease severity [12]. The 1984 criteria did not account for cognitive impairment that did not reach the threshold for dementia. The 1984 one-to-one clinical pathological correspondence model did not account for the fact that AD-P develops slowly over many years with dementia representing the end stage of many years of pathology accumulation in those patients who do become demented. Moreover, intermediate levels of AD pathological severity map onto clinical impairment which is intermediate between normality and dementia [13–16]. Issues pertaining to intermediate clinical and pathological states and pertaining to clinical-pathological discordance are addressed in the revised criteria. Two recent publications by an international working group also emphasize the importance of identifying individuals in this intermediate stage of disease [17, 18].

Because knowledge of the non-AD dementias was considerably more rudimentary in 1984, the 1984 criteria were vague in defining how distinctions between AD dementia and the major alternatives should be made. A prevalent notion, which is no longer widely held, was that reversible systemic disorders (e.g., thyroid disease, B12 deficiency, etc) were common mimics of AD dementia [19]. The concept of Lewy Body disease did not exist [20, 21]. That there was an entity of frontotemporal dementia due to something other than Pick's disease (which was thought to be extremely rare and not diagnosable in life) was not a consideration [22–24]. While the concept of aphasia due to neurodegenerative disease had been described only 2 years earlier [25], its pathological and neuropsychological features would begin to crystalize only 20 years later [26]. The fact that neuropsychiatric symptoms can be associated with AD was also not widely appreciated at the time, despite the fact that Alzheimer's celebrated first case had prominent delusions. The common co-existence of covert cerebrovascular disease, Lewy body disease, and AD pathology in elderly persons was not appreciated [27, 28]. Thus, it has been only in the past decade that a better understanding of the distinctions and overlaps of the non-AD dementias with AD have begun to emerge. These concepts are embodied in the revised criteria.

Genetic discoveries in familial forms of early onset AD indicate that the initiating molecular events ultimately leading to both clinical and pathological AD begin with disordered beta-amyloid (A-β) metabolism [29]. Recent data suggests that while familial AD can be characterized by over production of A-β 42, late-onset sporadic AD may be characterized by decreased clearance of A-β [30]. The major genetic risk factor for late onset AD is the e4 allele of the APOE gene, which is involved in A-β trafficking [31]. Therefore, the available genetic risk data overwhelmingly points to the A-β amyloid pathway as the initiating, or at least a very early pathophysiological event in the disease cascade [32].

Various features of AD pathology have been shown to relate to clinical symptoms differently. Clinical-autopsy correlation studies demonstrate a much tighter correlation between neurofibrillary pathology and cognitive impairment than between amyloid pathology and cognitive impairment [33, 34]. The aspect of AD pathology that is most closely coupled with cognitive impairment, however, is neurodegeneration, particularly synapse loss [35–37]. Approximately 30% of cognitively normal elderly subjects have some level of AD-P, and many of these individuals meet neuropathologic criteria for AD despite being free of apparent cognitive symptoms [3, 4, 37]. This 30% figure nearly perfectly

matches the observed frequency of "amyloid positivity" in studies of cognitively normal subjects over age 65 with PET amyloid imaging and with cerebrospinal fluid (CSF) assays [38, 39, 40, 41, 42], and roughly corresponds to the prevalence of AD dementia approximately a decade later [43]. These observations have been interpreted by some to imply an ordered sequence to the development of AD-P and its clinical consequences [44–47]. Rather than developing simultaneously, amyloid pathology and neurodegenerative pathology, in the form of neurofibrillary tangle formation and neuronal/synapse loss, may occur on different time scales [44]. A-β pathology is thought to develop first during the long preclinical phase, while the development of neurofibrillary pathology accelerates slightly before the appearance of the symptomatic phase of AD [48].

Biomarkers of AD

Two notable differences from the AD criteria published in 1984 [1] are incorporation of biomarkers of the underlying disease state and formalization of different stages of disease in the diagnostic criteria. Biomarkers of various features of AD-P have been developed and are being validated [49]. Biomarkers are parameters (physiological, biochemical, anatomic) that can be measured *in vivo* and that reflect specific features of disease related pathophysiological processes. Although in the past, the term biomarker was most often used in reference to fluid analytes, the term is used in all three work group documents to describe both fluid and imaging measures. A variety of biomarkers are discussed in the three workgroup documents. Some are discussed in terms of potential future applications, for example, resting state functional network connectivity [50]. However, only the five most widely studied biomarkers of AD based on the current literature are formally incorporated into the diagnostic criteria at this time.

The probabilistic framework for the incorporation of biomarkers was discussed extensively within each of the workgroups, and by the members of the workgroups charged with harmonizing the approach to biomarkers across the three documents. There was a consensus on several fundamental issues. First, it was important to tie the biomarkers as closely as possible to the pathological criteria for AD. Evidence suggests that together, the buildup of β-amyloid protein in plaques and tau deposition in neurofibrillary tangles is associated with neuronal injury. Second, it was agreed that the specificity of any biomarker for AD needed to be incorporated into the diagnostic schema. Evidence suggests that although both Aβ deposition and elevated tau/phosphorylated tau are hallmarks of AD, alterations in these proteins are seen in other neurological disorders. Because elevations in A-β appear to be more specific than alterations in tau, it was decided to divide the biomarkers into two major categories: (1) *The biomarkers of A-β* accumulation, which are abnormal tracer retention on amyloid PET imaging and low CSF Abeta 42. (2) *The biomarkers of neuronal degeneration or injury*, which are elevated CSF tau (both total and phosphorylated tau); decreased FDG uptake on PET in a specific topographic pattern involving temporo-parietal cortex; and atrophy on structural MR again in a specific topographic pattern involving medial, basal and lateral temporal lobe, and medial and lateral parietal cortices.

Underlying the deliberations of the groups was the recognition that the onset and progression of AD biomarkers likely follows an ordered temporal pattern. Biomarkers of A-β amyloid are indicative of initiating or upstream events which appear to be most dynamic (i.e. deviate most significantly from normal) prior to clinical symptoms. Biomarkers of neuronal injury and neuronal dysfunction are indicative of downstream pathophysiological processes which become dynamic later. Current evidence suggests that amyloid biomarkers may become abnormal anywhere from 10–20 years prior to noticeable clinical symptoms. Biomarkers of neurodegeneration become dynamic at a later point; some studies suggest this

may be shortly before clinical symptoms first appear. Progression of clinical symptoms closely parallels progressive worsening of neurodegenerative biomarkers [45–48].

Thus, biomarkers are employed in the revised definitions of AD in all three disease phases, but the role of biomarkers differs somewhat in each of these stages. In the *preclinical phase* biomarkers are used to establish the presence of AD-P in research subjects with no or very subtle overt symptoms. In both the MCI and AD dementia criteria, clinical diagnoses are paramount and biomarkers are complimentary. The Core Clinical diagnostic criteria for MCI and AD Dementia are completely operational in a setting where no access to biomarkers exists. The approach to incorporation of biomarkers is more conservative in the diagnostic paradigm for symptomatic patients (MCI and AD dementia) than in preclinical research subjects. In the *symptomatic pre-dementia, MCI, phase* biomarkers are used to establish the underlying etiology responsible for the clinical deficit. Biomarker severity, particularly neuronal injury biomarkers, also indicates the likelihood of imminent progression to AD dementia. In the *dementia phase* biomarkers are used to increase or decrease, depending on the results, the level of certainty that AD-P underlies the dementia in an individual. The two major classes of biomarkers are treated equivalently in the MCI and dementia criteria. In contrast, they are ranked in a temporal hierarchy in the preclinical criteria in that amyloid biomarkers become abnormal first and neuronal injury biomarkers become abnormal later. This temporal ordering notion is central to the staging proposed in the preclinical research criteria. The more conservative use for biomarkers in symptomatic subjects was felt to be a judicious approach pending more definitive outcomes research in this area.

Relevance to Clinical Practice

The recommendations of the three working groups differ in terms of current relevance to clinical practice. The Core Clinical Criteria of the recommendations regarding AD dementia and MCI due to AD are intended to guide diagnosis in the clinical setting. However, the recommendations of the preclinical AD workgroup are intended purely for research purposes, and do not have any clinical utility at this time.

In addition, there was a broad consensus within the workgroups that much additional work needs to be done to validate the application of biomarkers as they are proposed in the workgroup documents. For example, additional biomarker comparison studies are needed, as is more thorough validation with postmortem studies, and the use of combinations of biomarkers in studies has been limited. Extensive work on biomarker standardization is needed prior to widespread adoption of these recommendations at any stage of the disease. All biomarkers exist as continuous measures of AD-P. Therefore biomarker standardization must also include gaining a broad consensus on how to obtain results that are interpretable as clearly normal, clearly abnormal, and perhaps intermediate. Moreover, obtaining standardized, reliable and reproducible diagnostic caliber read outs of biomarker tests must be possible in any setting in which biomarkers are applied – research, clinical trials, or clinical care.

In summary, the new criteria for AD are presented in three documents, even though the process is a continuous one with sometimes difficult-to-define boundaries between each discrete category. The evidence for preclinical AD is based almost entirely on AD biomarkers. Criteria for the earliest symptomatic manifestations, the mild cognitive impairment stage, represent a sharpening of prior efforts to define MCI. The MCI criteria also define an entity of MCI due to AD-P, based on the conjunction of the clinical diagnosis and the presence of AD-P biomarkers. Finally, a revision of the 1984 criteria for dementia due to AD is provided. The criteria for probable AD dementia expand the breadth of the 1984 criteria and include biomarker enhancements to the diagnosis of AD dementia.

Ultimately, it is hoped that the scientific knowledge gained over the past quarter of a century, leading to the re-conceptualization of "Alzheimer's disease" proposed by the NIA-AA workgroups, will result in improved diagnosis and ultimately in effective disease-modifying therapy.

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