A brief history of “Alzheimer disease”

Multiple meanings separated by a common name

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Abstract

The field of Alzheimer disease (AD) has a nosologic problem: The diagnostic label “Alzheimer disease” has several distinctive meanings. The term probable AD was introduced in 1984 to designate a clinically diagnosed acquired and progressive amnesic dementia for which there was no evidence for another etiology. Probable AD represented a clinicopathologic entity that assumed a specific and sensitive linkage between amnesic dementia and the neuropathology of β -amyloid-containing neuritic plaques and tau-containing neurofibrillary tangles. The clinicopathologic model represented by probable AD was adapted in abbreviated form for population-based studies and general clinical practice, although the uncertainty connoted by “probable” was often overlooked. Representing the growing public awareness of later life cognitive impairment, a vernacular meaning of AD arose out of the clinicopathologic model in which AD represented all dementia not due to another clinically apparent cause. In contrast, by the 1990s, neuropathologists settled on a definition of AD based entirely on a sufficient burden of neuritic plaques and neurofibrillary tangles at postmortem examination, regardless of antemortem clinical status. In the last decade, the availability of fluid and imaging biomarkers that measure β -amyloid and tau abnormalities has enabled antemortem pathobiological diagnoses, highlighting the divide between the clinicopathologic model, the vernacular usage, and the pathobiological models. Each definition has value. However, the meanings of AD as defined by each of these models are not interchangeable. The pathobiological one is the only one that is unambiguous.

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Glossary

AA = Alzheimer's Association; **AD** = Alzheimer disease; **DSM** = *Diagnostic and Statistical Manual of Mental Disorders*; **IWG** = International Work Group; **MCI** = mild cognitive impairment; **NFT** = neurofibrillary tangle; **NIA** = National Institute on Aging; **NINCDS-ADRDA** = National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association.

The field of Alzheimer disease (AD) has a problem: The diagnostic label “Alzheimer disease” has several distinctive meanings. Each meaning represents a model that connotes some aspect of the disease, but there is a striking diversity in their core meanings. The purpose of this review is to examine the evolution of the use of AD in the modern era that began in 1968¹ up to the present era of antemortem biomarkers.² This is not a story about mechanisms, but rather a story of how different meanings of the term AD have proliferated. We discuss 3 usages: AD as (1) a clinicopathologic entity and its derivative vernacular meaning, (2) a postmortem pathobiological entity, and (3) its most recent operationalization as an antemortem pathobiological model.

AD as a clinicopathologic entity

Prior to the 1970s, AD was regarded as a presenile dementia as exemplified by Alzheimer's original patient.^{3,4} Pioneering research challenged the idea of a distinction between presenile and senile forms of the histopathology.⁵ In the early 1980s, the term AD came into wide use as a designator for cognitive impairment at any age due to “senile” (the designator used in that era) plaques and neurofibrillary tangle (NFT) pathology.^{5,6} A clinicopathologic model of a clinical syndrome (amnesic dementia) that was invariably linked to a specific pathologic dyad (β -amyloid-containing neuritic plaques and tau-containing NFTs) and vice versa was a reasonable first approximation⁷ for conceptualizing a disease about which very little was known.

In 1984, the diagnostic term “probable AD” was adopted by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) workgroup,⁸ and was almost universally accepted in the research community. The DSM-III-R definition⁹ was very similar; its terminology was “degenerative dementia of the Alzheimer type.” Probable AD or dementia of the Alzheimer type indicated an acquired amnesic disorder in which at least 2 cognitive domains (including memory) were impaired and impairment in daily life was present. The cognitive disorder was to represent a decline from prior levels of functioning and was to be progressively worsening. The clinical definitions arising from NINCDS-ADRDA and DSM-III-R supplanted the one used in the earlier 20th century on multiple grounds including emphasis on the amnesic nature of the dementia.

The diagnosis of probable AD⁸ was based almost exclusively on information obtained from the medical history and

neurologic examination. The authors of the 1984 document¹⁰ were explicit in their nomenclature that the assignment of etiology was provisional, hence the modifier “probable.” They limited the term “definite” AD to those cases with autopsy confirmation. The NINCDS-ADRDA definition adhered to the clinicopathologic model of AD, but signaled its reservations with the modifier “probable.”

The 1980s criteria explicitly excluded patients who had obvious evidence of cerebrovascular disease or other neurodegenerative diseases. The emphasis on recognizing other conditions in order to make a diagnosis of probable AD gave rise to the belief that a diagnosis of AD was one of exclusion. Years elapsed before rigorous clinical–neuropathologic studies showed that a clinical diagnosis of probable AD was, in fact, often associated with neuritic plaques and NFT pathology.^{11–14} But with a sensitivity of about 81% and specificity of about 70%,¹⁵ the clinical–pathologic correlation was far from ideal. Moreover, one early clinical–pathologic study¹⁶ noted that while the positive predictive value of a clinical diagnosis of AD dementia was high (81%), more than half of cases with neuritic plaques and NFTs had additional pathologies.

Problems with the insensitivity of probable AD for neuritic plaque and NFT pathology first became apparent in the 1990s. Clinicians had, by then, become more adept at diagnosing overt cognitive impairment prior to impairment in daily functioning.^{17–19} The 1984 criteria explicitly excluded most such individuals, so that a new diagnostic category was created to fill that gap. The term mild cognitive impairment (MCI) was utilized²⁰ and gradually gained traction in clinical practice and research. (Debate over the boundary between MCI and dementia need not enter into our discussion about AD.) The stage of amnesic cognitive impairment without functional impairment was presumed to represent a prodrome of probable AD,²¹ and by extension, senile plaques and NFTs. Subsequent longitudinal studies have shown that persons with a diagnosis of MCI who then go on to develop dementia had neuritic plaques and NFT pathology much of the time (71%), but not all of the time.²² Persons dying while still considered to have amnesic MCI often had other pathologic changes besides neuritic plaques and NFT pathology.^{23–25} The other pathologies included α -synucleinopathy, hippocampal sclerosis, frontotemporal degenerations, argyrophilic grain disease and other tauopathies, and cerebrovascular disease.^{22,23} Cognitive impairment without substantial impairment of daily activities is clearly part of the

symptomatic spectrum and course of neuritic plaque and NFT pathology, but amnestic MCI is not specific for neuritic plaque and NFT pathology.

A second challenge to the sensitivity of the diagnosis of probable AD came from the recognition that several non-amnestic syndromes were due to neuritic plaques and NFT pathology. The “visual variant of AD,”²⁶ now referred to as posterior cortical atrophy,²⁷ was the most prominent of these syndromes, while 2 other nonamnestic cognitive syndromes were also found in the same category: logopenic primary progressive aphasia^{28,29} and a dysexecutive syndrome.³⁰ Corticobasal syndrome is also often due to neuritic plaques and isocortical NFT pathology.^{31,32} Separate from their relationship to neuritic plaque and NFT pathology, the non-amnestic cognitive disorders showed that definitions of dementia or MCI with respect to AD could not remain memory-centric.

Diagnosis in epidemiologic investigations is necessarily based on limited clinical histories, limited cognitive assessments, and until the 2000s, rarely brain imaging. Deploying expert neurologic diagnosticians to detect other neurologic diseases, and, of course, obtaining autopsy confirmation, are not practical in large-scale epidemiologic studies. It was necessary to adapt the definitions of probable AD⁸ or dementia of the Alzheimer type^{9,33} that were intended for use in well-resourced clinical practice settings to the abbreviated assessments that were feasible in large-scale field work. The term AD came to be used in epidemiologic investigations for cases of amnestic dementia lacking another obvious etiology. The modifiers “probable” or “clinically diagnosed” were often not emphasized. Very few clinical–pathologic correlation studies

exist in persons diagnosed with AD in community-based samples. In one well-regarded analysis, only 63% of persons diagnosed during life with probable AD had intermediate or higher burden of neuritic plaque and no other pathology.²⁵ While overall, 88% of those diagnosed in life with probable AD had some neuritic plaque and NFT pathology, the authors concluded that probable AD as diagnosed in the epidemiologic setting was “pathologically heterogeneous.”²⁵

In the early 1980s, AD entered clinical practice as a diagnostic entity. We were unable to find any publication documenting this process, but we used the resources of the Rochester Epidemiology Project³⁴ to determine how AD as a stand-alone “codable” diagnosis appeared over time. The Mayo Clinic adopted the Hospital Adaptation of the International Classification of Diseases, Second Edition, in 1975 (mayo.edu/research/documents/biostat-83pdf/doc-10026715), and with that system, “AD” as a diagnostic code first became available. It was little used prior to 1980, after which its use dramatically increased (figure). In a study of Medicare diagnostic codes for AD from 2009 to 2012, 84% were from nonspecialist physicians.³⁵ The introduction of AD as a diagnostic code preceded both DSM-III-R⁹ and the NINCDS-ADRDA criteria,⁸ indicating that the diagnostic code was not linked to either of these published definitions. Even after the publication of those diagnostic criteria, awareness of the nuances of presentations of amnestic dementia compared to other distinct syndromic presentations was, and is, a skill generally limited to specialists in cognitive disorders. Feedback on accuracy of clinical diagnoses from postmortem examinations exists almost exclusively in major research centers. As a consequence, the cautionary modifiers of the diagnosis of AD would be subjected to very little validation in the experience

Figure Unique patient diagnoses of “Alzheimer disease” in persons in Olmsted County, Minnesota, from 1980 to 2014

We used the Rochester Epidemiology Project resources to identify persons aged ≥ 65 years with an International Classification of Disease (ICD-8) or Hospital Adaptation of the ICD, 2nd edition (HICDA) diagnostic code for “Alzheimer disease.” The term “Alzheimer disease” was introduced into the HICDA system only in 1975. The x-axis represents the year, and the y-axis the number of unique persons assigned in that year with a diagnosis of “Alzheimer disease.”

of a typical nonspecialist practitioner. In the absence of specific therapies or specific actionable risk factors, primary care physicians would rarely encounter the divergence of clinicopathologic AD definition from a neuropathologically based definition.

The relative frequency of (1) amnestic cognitive syndromes not due to neuritic plaques and NFTs and (2) nonamnestic, nondementia syndromes that are due to neuritic plaques and NFTs in cognitively impaired persons showed the model of probable AD has far from ideal sensitivity and specificity in research settings, clinical practice, and population-based studies. Prior to the biomarker era, only specialists with access to neuropathology services were confronted with the flaws in the clinicopathologic model of AD.

AD as a neuropathologic constellation: The pathobiology model

A vestige of the designation of AD as a presenile dementia remained in the neuropathologic literature until the 1990s. In an attempt to preserve specificity, a neuropathologic diagnosis of AD was to be made only if dementia were present antemortem.³⁶ This became recognized as unworkable and misleading. It was nonsensical to label a particular pattern of neuritic plaques and NFT pathology as one thing in an allegedly asymptomatic person and another thing in a cognitively impaired person. With the recognition that multiple pathologies typically co-occur in persons with dementia,^{25,37–39} inclusion of clinical status as a part of a neuropathologic diagnosis could not be limited to AD. The neuropathology community adopted a new definition of AD in 1997 based solely on pathobiology, namely the combination of some substantial level of neuritic plaques and NFT pathology as observed at postmortem examinations.^{40–42} Removing the clinical status requirement had an interesting consequence that received little attention at that time: the diagnosis of AD applied to a substantial minority of individuals who clearly were cognitively normal within a year or 2 of death.^{43,44}

AD represents all dementia not due to an obvious alternative: The vernacular model

In addition to the adoption of AD as a codable diagnosis unlinked to a specific definition, a confluence of public policy, advocacy, and scientific demands in the 1990s led to AD acquiring the vernacular meaning of all dementia not attributable on simple clinical grounds to other causes. The vernacular meaning of AD focused on the big-picture concept and shed the caveats and conditions of the rigorous definitions.^{8,9} Such usage seemed justifiable because it was a natural extension of how the NINCDS-ADRDA criteria were being used. The DSM-IV criteria for dementia³³ also

tended to collapse dementia not due to an obvious alternative into AD, by defining dementia as an amnestic disorder. The vernacular usage of AD brought the term into common usage, but the price was a loss of precision in meaning.

Public awareness of AD has greatly expanded since the 1970s. The Alzheimer's Association (AA) began its existence in 1980 as the Alzheimer's Disease and Related Disorders Association, which is still the legal name of the organization. However, at some point, the organization began to refer to itself simply as the AA. Other advocacy groups adopted a similar approach; for example, the Alzheimer's Foundation or Us Against Alzheimer's Disease. Given the reality that the term "dementia" was perceived as having pejorative connotations,⁴⁵ AD was clearly favored as the public face for advocacy groups whose missions were to improve the lives of persons with acquired cognitive impairment of any cause by increasing awareness and by advocating for funding for research and services.

AD as defined by biomarkers: An antemortem pathobiological model

Within a few years of its introduction, β -amyloid PET imaging⁴⁶ disrupted the status quo in nomenclature. Prior to amyloid PET, the use of biomarkers to diagnose AD lacked an anchor that was specific to neuritic plaques and NFTs. Amyloid PET was different. PET imaging of β -amyloid has been validated neuropathologically as a diagnostic biomarker.^{47,48} CSF studies of β -amyloid⁴² reasonably closely approximated amyloid PET measures (especially in a ratio with tau or β -amyloid₄₀) and provided a measure of concurrent validity.^{49,50} Antemortem β -amyloid biomarkers offered the prospect of obtaining pathobiological diagnoses in life. This created new opportunities for diagnosis in the clinic and radically changed how clinical trials for AD were designed. This transformational ability brought the practical consequences of the divergence between the pathobiologic, clinicopathologic, and vernacular meanings of AD into the open.

One group of investigators, the International Work Group (IWG), formulated criteria that were the first to incorporate a combination of clinical features and biomarkers. This group's definitions went through several iterations, but as of 2014⁵¹ settled on defining AD as a combination of amnestic dementia and biomarkers of amyloid pathology and "downstream topographical markers" consistent with neuritic plaque and NFT pathology. At the time, "downstream biomarkers" referred to any biomarker of neuronal injury or dysfunction such as CSF tau, fluorodeoxyglucose PET, hippocampal atrophy, or other structural imaging biomarkers. "Downstream" implied that changes in these biomarkers were a result of β -amyloid pathobiology. This group adapted the model of AD as a clinicopathologic entity to the biomarker era, where AD stood for an amnestic dementia with appropriate biomarkers. Nonamnestic cognitive impairment with the Alzheimer biomarker pattern became "atypical AD." Cognitive impairment

without substantial impairment in daily functioning but with the Alzheimer biomarker pattern became “prodromal AD.” Persons who were considered cognitively normal who had abnormal Alzheimer biomarkers were labeled as “asymptomatic at risk for AD.”^{51,52} IWG terminology for situations in which there is evidence of a second pathobiological process would be called “mixed” AD. The IWG approach sought to maintain the model of the disease as a clinicopathologic entity, but it is clear from the several different modifiers that the model has drifted far from a parsimonious one.

A group with international representation convened by the National Institute on Aging (NIA) and AA in 2009–2011 attempted to integrate antemortem biomarkers into the diagnostic formulation of AD for symptomatic persons^{10,53} and also for cognitively unimpaired persons.⁵⁴ The NIA-AA groups formulated a diagnostic scheme that separated dementia and AD definitionally, and adopted most of the core clinical diagnostic features of probable AD from the 1984 criteria.⁸ The 2011 NIA-AA approach retained the concept of AD as a clinicopathologic entity, while using the presence of abnormal amyloid biomarkers or abnormal neurodegeneration biomarkers to add to certainty of the clinicopathologic link.

In 2013, the DSM-5 criteria⁴⁵ for acquired cognitive disorders, in a break from prior DSM formulations, separated the diagnosis of cognitive impairment from the diagnosis of its etiology. The DSM-5 approach was probably the first to call for divorcing clinical syndromes from the assignment of AD as a diagnostic label. An international consensus conference conducted at the Key Symposium in 2012⁵⁵ also declared that AD should be defined “as a brain disorder, regardless of clinical status.” While these 2 groups did not mention explicit biomarker criteria, their work was predicated on the emerging biomarker research.

After tau PET became available and was shown to have close linkage to the topographic localization seen in neuropathologic studies,^{56,57} the NIA-AA group incorporated tau PET into the diagnostic framework.⁵⁸ The NIA-AA Research Framework^{58,59} asserted that pathobiological diagnosis of AD can be made using a combination of abnormal β -amyloid biomarkers and abnormal neurofibrillary tau biomarkers. Abnormal β -amyloid without abnormal neurofibrillary tau biomarkers is not AD, though it may represent a prodromal state of AD.⁵⁸ This distinction is important with the availability of amyloid PET in clinical practice. To declare that biomarkers for abnormal β -amyloid and tau are diagnostic for AD is to assert that those biomarkers represent indicators of disease “state.”⁶⁰ By focusing on diagnostic state and not stage, the differences between CSF tau and tau PET^{61–63} or CSF β -amyloid markers and amyloid PET^{49,50,63} need not distract from the success of both biomarker modalities for making antemortem pathobiological diagnoses of AD.

The Research Framework definition of AD broke from its predecessors^{10,53} in taking the stance that AD was defined solely by biomarkers regardless of clinical status, only when

both abnormal amyloid and abnormal tau biomarkers were present. The NIA-AA Research Framework diagnosis using antemortem biomarkers closely matched the neuropathologic approach to the diagnosis of AD.^{41,42} The NIA-AA group also made a novel choice in referring to symptomatic persons with the AD biomarker pattern as having MCI (or dementia) with AD. The choice reflected the reality that most elderly persons have multiple pathologies, most of which lack biomarkers.^{25,37–39} The assertion that AD could be diagnosed in cognitively unimpaired individuals followed the approach previously taken by neuropathologists. In doing so, the prevalence of pathobiological AD in cognitively unimpaired individuals was revealed to be disconcertingly high.⁶⁴ Those who accept the vernacular model may find the pathobiological definition threatening for what it says about the prevalence of the pathobiology of AD in cognitively normal people.

The pathobiological model of AD created a terminology gap for the clinical syndrome of amnesic dementia when biomarkers were unavailable. AD had been the default term, but is ambiguous and misleading if used simultaneously in the clinicopathologic and pathobiological senses. This is not a trivial concern because amyloid and tau PET scanning are available only on a very limited basis. The NIA-AA group⁵⁸ proposed the term “Alzheimer clinical syndrome” in deference to the clinicopathologic and vernacular AD models. Alternatives would have been clinically diagnosed dementia presumed with AD or major neurocognitive disorder presumed with AD (as per DSM-5). All of these seem susceptible to abbreviation with attendant loss of caution unless the field becomes more disciplined in its use of terminology.

The availability of antemortem biomarkers for neuritic plaque and NFT pathology has, ironically, expanded the antemortem recognition of other pathologies that are relevant to cognitive decline. Persons with abnormal β -amyloid but without elevations in tau biomarkers might be ones who could have arteriosclerotic cerebrovascular disease⁶⁵ or Lewy body disease⁶⁶ that was either dominant to or additive with AD. The relevance of TDP43 inclusions⁶⁷ and hippocampal sclerosis^{68,69} as an etiology of amnesic cognitive disorders has also been established by the absence of elevated amyloid or tau PET signal.⁷⁰ The work with antemortem biomarkers has already led to a greater appreciation of the multitietologic nature of late-life dementia established by neuropathologic investigations.^{25,37–39} Neuritic plaques and NFTs are members of an ensemble of several pathobiologies that are relevant to late-life cognitive impairment.² The pathobiological model of AD alone is best suited to be integrated into a multitietology framework.

AD: Its once and future name

All of us in the field have the common goal of improving the lives of persons with cognitive impairment, whether through pharmacologic or nonpharmacologic means. Our language

must help us, not mislead us. Different models and varying definitions of AD allow the term to serve different purposes, but there has to be some agreement on a core meaning. Most public policy discussions and many clinical and research contexts require a diagnostic term that connotes only that there be cognitive impairment that interferes with daily life; that is, dementia or major neurocognitive disorder. In clinical practice and clinical research, labeling a clinical amnesic cognitive syndrome and separately labeling its etiology must replace the far-from-ideal usage of AD as a clinicopathologic entity. For the study of molecular mechanisms and the conduct of clinical trials of disease-modifying interventions for AD, the specificity of the pathobiological meaning of AD is critical, even if the therapeutic targets are neither β -amyloid nor tau. The only unambiguous definition of AD is that it represents the combination of neuritic plaques and NFT, no more and no less.

Author contributions

David S. Knopman: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. Ronald C. Petersen: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, obtaining funding. Clifford R. Jack: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval.

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