A brief history of "Alzheimer disease"

Multiple meanings separated by a common name

David S. Knopman, MD, Ronald C. Petersen, PhD, MD, and Clifford R. Jack, Jr., MD

Neurology® 2019;92:1053-1059. doi:10.1212/WNL.0000000000007583

Correspondence
Dr. Knopman
knopman@mayo.edu

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 amnestic dementia for which there was no evidence for another etiology. Probable AD represented a clinicopathologic entity that assumed a specific and sensitive linkage between amnestic 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.

From the Departments of Neurology (D.S.K., R.C.P.) and Radiology (C.R.J.), Mayo Clinic, Rochester, MN.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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 1968[1] 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 (amnestic 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 approximation[7] 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 definition[9] was very similar; its terminology was "degenerative dementia of the Alzheimer type." Probable AD or dementia of the Alzheimer type indicated an acquired amnestic 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 amnestic nature of the dementia.

The diagnosis of probable AD[8] was based almost exclusively on information obtained from the medical history and neurologic examination. The authors of the 1984 document[10] 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 study[16] 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 utilized[20] 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 amnestic 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 amnestic 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

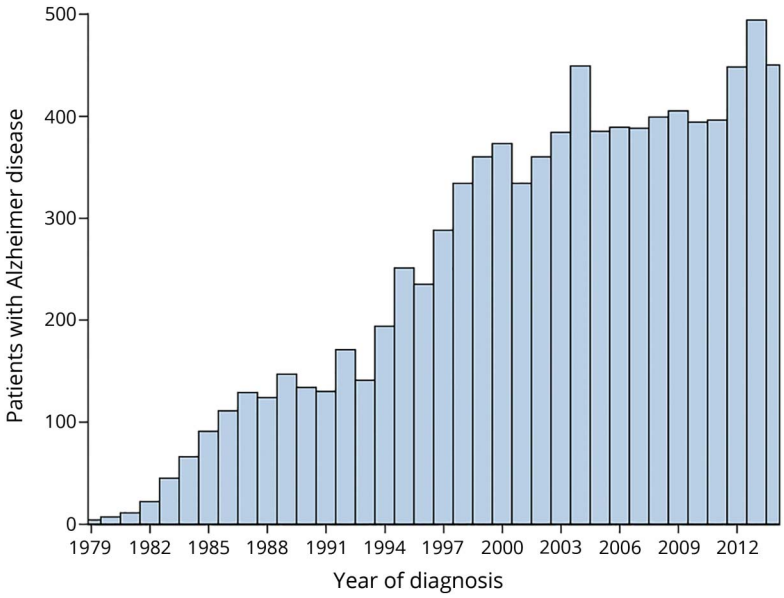
symptomatic spectrum and course of neuritic plaque and NFT pathology, but amnestic MCI is not specific for neuritic plaque and NFT pathology.

A second challenge to the sensitivity of the diagnosis of probable AD came from the recognition that several nonamnestic 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 nonamnestic 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 AD[8] 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 Project[34] 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-R[9] 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 clinical–pathologic 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 dementia[33] 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 imaging[46] 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-amyloid$_{42}$ reasonably closely approximated amyloid PET measures (especially in a ratio with tau or β-amyloid$_{40}$) 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 2014[51] 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 criteria[45] 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 2012[55] 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 amnestic 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 group[58] 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 disease[65] or Lewy body disease[66] that was either dominant to or additive with AD. The relevance of TDP43 inclusions[67] and hippocampal sclerosis[68,69] as an etiology of amnestic 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 multietiologic 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 multietiology 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 amnestic 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.

Study funding

Supported by NIH grants P50 AG16574, U01 AG06786, R01 AG034676, R01 AG011378, and R01 AG41851.

Disclosure

D. Knopman serves on a Data Safety Monitoring Board for the DIAN study; is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals, and the University of Southern California; and receives research support from the NIH/NIA. R. Jack receives research support from the NIH/NIA and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Foundation. C. Petersen serves on data monitoring committees for Janssen Alzheimer Immunotherapy and is a consultant for Biogen, Roche, Merck, and Genentech, Inc.; receives publishing royalties from *Mild Cognitive Impairment* (Oxford University Press, 2003); and receives research support from the NIH/NIA. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* December 6, 2018. Accepted in final form February 25, 2019.

References

1. Tomlinson BE, Blessed G, Roth M. Observations on the brains of non-demented old people. J Neurol Sci 1968;7:331–356.
2. Petersen RC. How early can we diagnose Alzheimer disease (and is it sufficient)? The 2017 Wartenberg lecture. Neurology 2018;91:395–402.
3. Alzheimer A. Uber eine eignartige Erkrankung der Hirnrinde (about a peculiar disease of the cerebral cortex; English translation Alz Dis Ass Dis 1:3-8, 1987). Allgemeine Z Psychiatrie Psychisch Gerichtliche Medizin 1907;64:146–148.
4. Amaducci LA, Rocca WA, Schoenberg BS. Origin of the distinction between Alzheimer's disease and senile dementia: how history can clarify nosology. Neurology 1986;36:1497–1499.
5. Tomlinson BE, Blessed G, Roth M. Observations on the brains of demented old people. J Neurol Sci 1970;11:205–242.
6. Katzman R. Editorial: the prevalence and malignancy of Alzheimer disease: a major killer. Arch Neurol 1976;33:217–218.
7. Khachaturian ZS. Diagnosis of Alzheimer's disease. Arch Neurol 1985;42:1097–1105.
8. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.
9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (Third Edition, Revised). Washington, DC: American Psychiatric Association; 1987.
10. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. Alzheimers Dement 2011;7:263–269.
11. Holmes C, Cairns N, Lantos P, Mann A. Validity of current clinical criteria for Alzheimer's disease, vascular dementia and dementia with Lewy bodies. Br J Psychiatry 1999;174:45–50.
12. Jobst KA, Barnetson LP, Shepstone BJ. Accurate prediction of histologically confirmed Alzheimer's disease and the differential diagnosis of dementia: the use of NINCDS-ADRDA and DSM-III-R criteria, SPECT, X-ray CT, and apoE4 in medial temporal lobe dementias: Oxford Project to Investigate Memory and Aging. Int Psychogeriatr 1998;10:271–302.
13. Lim A, Tsuang D, Kukull W, et al. Clinico-neuropathological correlation of Alzheimer's disease in a community-based case series. J Am Geriatr Soc 1999;47:564–569.
14. Beach TG, Monsell SE, Phillips LE, Kukull W. Accuracy of the clinical diagnosis of Alzheimer disease at national institute on aging Alzheimer disease centers, 2005–2010. J Neuropathol Exp Neurol 2012;71:266–273.
15. Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Neurology 2001;56:1143–1153.
16. Bowler JV, Munoz DG, Merskey H, Hachinski V. Fallacies in the pathological confirmation of the diagnosis of Alzheimer's disease. J Neurol Neurosurg Psychiatry 1998;64:18–24.
17. Flicker C, Ferris SH, Reisberg B. Mild cognitive impairment in the elderly: predictors of dementia. Neurology 1991;41:1006–1009.
18. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–308.
19. Morris JC, McKeel DW Jr, Storandt M, et al. Very mild Alzheimer's disease: informant-based clinical, psychometric, and pathologic distinction from normal aging. Neurology 1991;41:469–478.
20. Petersen RC, Smith GE, Ivnik RJ, et al. Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals. JAMA 1995;273:1274–1278.
21. Morris JC, Storandt M, Miller JP, et al. Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol 2001;58:397–405.
22. Jicha GA, Parisi JE, Dickson DW, et al. Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. Arch Neurol 2006;63:674–681.
23. Petersen RC, Parisi JE, Dickson DW, et al. Neuropathologic features of amnestic mild cognitive impairment. Arch Neurol 2006;63:665–672.
24. Abner EL, Kryscio RJ, Schmitt FA, et al. Outcomes after diagnosis of mild cognitive impairment in a large autopsy series. Ann Neurol 2017; 81:549–559.
25. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. Ann Neurol 2009;66:200–208.
26. Levine DN, Lee JM, Fisher CM. The visual variant of Alzheimer's disease: a clinicopathologic case study. Neurology 1993;43:305–313.
27. Crutch SJ, Schott JM, Rabinovici GD, et al. Consensus classification of posterior cortical atrophy. Alzheimers Dement 2017;13:870–884.
28. Gorno-Tempini ML, Brambati SM, Ginex V, et al. The logopenic/phonological variant of primary progressive aphasia. Neurology 2008;71:1227–1234.
29. Mesulam MM, Weintraub S, Rogalski EJ, Wieneke C, Geula C, Bigio EH. Asymmetry and heterogeneity of Alzheimer's and frontotemporal pathology in primary progressive aphasia. Brain 2014;137:1176–1192.
30. Ossenkoppele R, Pijnenburg YA, Perry DC, et al. The behavioural/dysexecutive variant of Alzheimer's disease: clinical, neuroimaging and pathological features. Brain 2015;138:2732–2749.
31. Hu WT, Rippon GW, Boeve BF, et al. Alzheimer's disease and corticobasal degeneration presenting as corticobasal syndrome. Mov Disord 2009;24:1375–1379.
32. Lee SE, Rabinovici GD, Mayo MC, et al. Clinicopathological correlations in corticobasal degeneration. Ann Neurol 2011;70:327–340.
33. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
34. Rocca WA, Yawn BP, St Sauver JL, Grossardt BR, Melton LJ. History of the Rochester Epidemiology Project: half a century of medical records linkage in a US population. Mayo Clin Proc 2012;87:1202–1213.
35. Kirson NY, Desai U, Ristovska L, et al. Assessing the economic burden of Alzheimer's disease patients first diagnosed by specialists. BMC Geriatr 2016;16:138.

36. Mirra SS, Hart MN, Terry RD. Making the diagnosis of Alzheimer's disease: a primer for practicing pathologists. Arch Pathol Lab Med 1993;117:132–144.
37. Nelson PT, Head E, Schmitt FA, et al. Alzheimer's disease is not "brain aging": neuropathological, genetic, and epidemiological human studies. Acta Neuropathol 2011;121:571–587.
38. White L. Brain lesions at autopsy in older Japanese-American men as related to cognitive impairment and dementia in the final years of life: a summary report from the Honolulu-Asia aging study. J Alzheimers Dis 2009;18:713–725.
39. Rabinovici GD, Carrillo MC, Forman M, et al. Multiple comorbid neuropathologies in the setting of Alzheimer's disease neuropathology and implications for drug development. Alzheimers Dement 2017;3:83–91.
40. Hyman BT, Trojanowski JQ. Consensus recommendations for the postmortem diagnosis of Alzheimer disease from the National Institute on Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. J Neuropathol Exp Neurol 1997;56:1095–1097.
41. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement 2012;8:1–13.
42. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol 2012;123:1–11.
43. Knopman DS, Parisi JE, Salviati A, et al. Neuropathology of cognitively normal elderly. J Neuropathol Exp Neurol 2003;62:1087–1095.
44. Schmitt FA, Davis DG, Wekstein DR, Smith CD, Ashford JW, Markesbery WR. "Preclinical" AD revisited: neuropathology of cognitively normal older adults. Neurology 2000;55:370–376.
45. American Psychiatric Association. DSM-5: Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
46. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol 2004;55:306–319.
47. Murray ME, Lowe VJ, Graff-Radford NR, et al. Clinicopathologic and ^{11}C-Pittsburgh compound B implications of Thal amyloid phase across the Alzheimer's disease spectrum. Brain 2015;138:1370–1381.
48. Clark CM, Pontecorvo MJ, Beach TG, et al. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-beta plaques: a prospective cohort study. Lancet Neurol 2012;11:669–678.
49. Leuzy A, Chiotis K, Hasselbalch SG, et al. Pittsburgh compound B imaging and cerebrospinal fluid amyloid-beta in a multicentre European memory clinic study. Brain 2016;139:2540–2553.
50. Janelidze S, Pannee J, Mikulskis A, et al. Concordance between different amyloid Immunoassays and visual amyloid positron emission tomographic assessment. JAMA Neurol 2017;74:1492–1501.
51. Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 2014;13:614–629.
52. Dubois B, Hampel H, Feldman HH, et al. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. Alzheimers Dement 2016;12:292–323.
53. Albert M, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270–279.
54. Sperling RA, Aisen P, Beckett L, et al. Towards defining the preclinical stage of Alzheimer's disease: recommendations from the National Institute on Aging and the Alzheimer's Association Workgroup. Alzheimers Dement 2011;7:280–292.
55. Morris JC, Blennow K, Froelich L, et al. Harmonized diagnostic criteria for Alzheimer's disease: recommendations. J Intern Med 2014;275:204–213.
56. Johnson KA, Schultz A, Betensky RA, et al. Tau PET imaging in aging and early Alzheimer's disease. Ann Neurol 2015;79:110–119.
57. Pontecorvo MJ, Devous MD Sr, Navitsky M, et al. Relationships between flortaucipir PET tau binding and amyloid burden, clinical diagnosis, age and cognition. Brain 2017;140:748–763.
58. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018;14:535–562.
59. Jack CR Jr, Bennett DA, Blennow K, et al. A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology 2016;87:539–547.
60. Mattsson N, Scholl M, Strandberg O, et al. (18)F-AV-1451 and CSF T-tau and P-tau as biomarkers in Alzheimer's disease. EMBO Mol Med 2017;9:1212–1223.
61. Mattsson N, Smith R, Strandberg O, et al. Comparing (18)F-AV-1451 with CSF t-tau and p-tau for diagnosis of Alzheimer disease. Neurology 2018;90:388–e95.
62. La Joie R, Bejanin A, Fagan AM, et al. Associations between [(18)F]AV1451 tau PET and CSF measures of tau pathology in a clinical sample. Neurology 2018;90:e282–e90.
63. Lewczuk P, Riederer P, O'Bryant SE, et al. Cerebrospinal fluid and blood biomarkers for neurodegenerative dementias: an update of the Consensus of the Task Force on Biological Markers in Psychiatry of the World Federation of Societies of Biological Psychiatry. World J Biol Psychiatry 2018;19:244–328.
64. Brookmeyer R, Abdalla N, Kawas CH, Corrada MM. Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States. Alzheimers Dement 2018;14:121–129.
65. Kim HJ, Park S, Cho H, et al. Assessment of extent and Role of tau in Subcortical vascular Cognitive Impairment using 18F-AV1451 positron emission tomography Imaging. JAMA Neurol 2018;75:999–1007.
66. Kantarci K, Lowe VJ, Boeve BF, et al. AV-1451 tau and beta-amyloid positron emission tomography imaging in dementia with Lewy bodies. Ann Neurol 2017;81:58–67.
67. Yang HS, Yu L, White CC, et al. Evaluation of TDP-43 proteinopathy and hippocampal sclerosis in relation to APOE epsilon4 haplotype status: a community-based cohort study. Lancet Neurol 2018;17:773–781.
68. Brenowitz WD, Monsell SE, Schmitt FA, Kukull WA, Nelson PT. Hippocampal sclerosis of aging is a key Alzheimer's disease mimic: clinical-pathologic correlations and comparisons with both Alzheimer's disease and non-tauopathic frontotemporal lobar degeneration. J Alzheimers Dis 2014;39:691–702.
69. Nag S, Yu L, Capuano AW, et al. Hippocampal sclerosis and TDP-43 pathology in aging and Alzheimer disease. Ann Neurol 2015;77:942–952.
70. Botha H, Mantyh WG, Murray ME, et al. FDG-PET in tau-negative amnestic dementia resembles that of autopsy-proven hippocampal sclerosis. Brain 2018;141:1201–1217.

Did You Know…

…you can browse by subspecialty topics on Neurology.org?

Go to: Neurology.org and click on "Topics" in the top navigation bar.

A brief history of ''Alzheimer disease'': Multiple meanings separated by a common name

David S. Knopman, Ronald C. Petersen and Clifford R. Jack, Jr

Neurology 2019;92;1053-1059 Published Online before print April 26, 2019
DOI 10.1212/WNL.0000000000007583