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Mini Review

Alzheimer's Disease: Current Clinical and Neuropathologic Diagnostic Criteria

Jellinger KA*

Institute of Clinical Neurobiology, Medical University Vienna, Austria

***Corresponding author:** Jellinger KA, Institute of Clinical Neurobiology, Kenyongasse 18, A-1070 Vienna, Austria

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Abstract

Alzheimer's disease is the most common cause of dementia, accounting for 50-60% of cases at clinical and autopsy series. Recent advances have enabled detailed understanding of the molecular pathogenesis of this devastating disease, and the updated consensus criteria for its clinical and neuropathological diagnosis have increased the diagnostic accuracy and sensitivity versus other dementias considerably. However, due to frequent overlap between dementing disorders and multiple confounding pathologies in the aged brain, both clinical and postmortem studies entail biases that affect both their general applicability and validity. This brief critical review discusses the diagnostic validity and limitations of currently used clinical and morphological criteria for the diagnosis of Alzheimer's disease and gives recommendations for future clinico-pathologic research.

Keywords: Alzheimer's disease; Diagnostic criteria; Neuropathology; Clinico-pathologic subtypes; Mixed pathologies

Abbreviations

AA: Alzheimer's Association; AD: Alzheimer's disease; ADRDA: Alzheimer's disease and Related Disorders Association; Aβ: β-amyloid; CCCD: Canadian Consensus Conference on the Diagnosis and Treatment of Dementia; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CSF: Cerebrospinal Fluid; CVD: Cerebrovascular Disease; DLB: Dementia with Lewy Bodies; EFNS: European Federation of Neurological Societies; ENS: European Neurological Societies; IWG: International Working Group; MCI: Mild Cognitive Impairment; MRI: Magnetic Resonance Imaging; NACCR National Alzheimer's Coordination Center Registry; NCD: Neurocognitive Disorder; NFT: Neurofibrillary Tangles; NIA: National Institute on Aging; NIA-RI: National Institute on Aging and Reagan Institute; NICDS: National Institute of Neurological Disorders and Stroke; PET: Positron Emission Tomography; TDP-43: TAR DNA Binding Protein 43.

Introduction

Alzheimer's disease (AD) is a form of Neurocognitive Disorders (NCD) characterized by a progressive multidomain cognitive impairment with profound decrease in the abilities to perform daily living activity [1]. AD affects more than 35 million people worldwide – 5.5 million in the USA. AD is the most common form of dementia, accounting for 50-60% of cases in clinical and autopsy series, however, it is frequently associated with other confounding pathologies in the elderly. The principal risk factor for AD is age; its incidence doubles every 5 year after age 65, and the odds for a diagnosis of AD after age 85 exceed one in three. With the disproportional growth of the elderly population, the prevalence of AD will approach around 100 million worldwide and 11 to 16 million cases in the USA in 2050 [2,3]. Thus, AD has become a major public health and socio-economic problem [4] that threatens to become the scourge of the 21st century.

Clinical diagnostic criteria

Early diagnosis of AD and its distinction from other dementing disorders is crucial to implement effective treatment strategies and management of AD patients. Diagnostic procedures play a major role in the detection process but evidence on their respective accuracy is still limited. Updated consensus criteria for the clinical diagnosis of AD include: revised NICDS-ADRDA guidelines recommended by the NIA-AA [5,6], EFNS- ENS guidelines for the diagnosis and management of disorders associated with dementia [7], consensus from the Canadian CCCD [8], and the IWG-2 criteria for AD [9]. All these updated diagnostic criteria for AD considering clinical phenotypes (typical and atypical forms, preclinical states and mixed AD), pathophysiological CSF biomarkers and neuroimaging procedures (volumetric MRI and fluorodeoxyglucose PET) are suggested to increase the clinical diagnostic accuracy of AD.

Combination of the best CSF and MRI data using standardized operating measures allowed a more precise diagnostic prediction [10,11], and will be further increased by using multimodal techniques and novel CSF biomarkers already in biomarker-positive early (preclinical) stages [12-16]. The validity of plasma biomarkers for the (preclinical) diagnosis of AD has been reviewed recently [16-20]. A large proportion of cognitively healthy people who develop Aβ pathology have signs of neurodegeneration prior to amyloid positivity [12], but there are conflicting results with biomarker changes and disease progression [21-25]. Although identification of fibrillar Aβ by [^{11}C]PiB-PET is feasable for both research and clinical settings, recent evidence comparing it with postmortem or biopsy results raised doubts about this method as representative of Aβ loads in the living human brain [26,27], since a 55% prevalence of PIB-positivity was observed in non-demented subjects over age 80 [28]. However, in some PIB-negative cases, a combination of pre-existent non-AD pathology or tau-mediated degeneration may occur prior to Aβ pathology [12]. Meanwhile, the advances in tau imaging ligands

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[29-31] will enable the identification of AD and non-AD tauopathy patients in clinical and research settings.

A review of two sets of autopsy cases from the NACCR database revealed a high diagnostic accuracy for AD (sensitivity from 70.9 to 87.3%,and 85%, respectively and a specificity of 44.3 to 70.8, and 51.1%, respectively), when the clinical diagnosis was confirmed by minimum levels of AD pathology [32]. A recent meta-analysis of 20 (among 1,189) records on the accuracy in distinguishing AD from other dementia types and healthy controls using autopsy as standard for truth calculated a sensitivity of 85.4% (95% CI 80.9-90.0%) and a specificity at 77.7% (95% CI 70.2-85.1%), both values being slightly better for imaging procedures than for CSF markers. This study also highlights the limited evidence on autopsy-confirmation and the heterogeneity of study design [33].

Neuropathologic diagnostic criteria

Histopathologic examination of the brain establishes that AD-related lesions are present in sufficient densities and extension to distinguish AD from age-related and other degenerative disorders [34]. The current algorithms for the neuropathologic diagnosis of AD are based on semiquantiative assessment of senile plaques and NFTs, providing reasonable interrater agreement when using standardized criteria [35]. Guidelines for the neuropathologic diagnosis of AD include (a) cut-off quantitative values for senile plaques and tangles [36-38], (b) their semiquantiative assessement and age-adjustment in the CERAD protocol [39], (c) topographic staging of neuritic/tau pathology [40], re-evaluated recently by using immunohistochemistry [35,41], and (d) the progress and distribution of Aβ deposition which is different from tau pathology [42]. The causes of Aβ accumulation in sporadic AD remain unclear and its relation ot tau pathology, microglia and neuronal/synaptic activity are under discussion [43]. Using semiquantitative assessment of NFTs and neuritic plaques, good agreement can be reached in diagnosis only when the lesions are substantial, having involved isocortical structures (Braak neuritic stage V and VI), with 91% absolute agreement, while for mild lesions it was poorer (Braak stage I and II, agreement 50%), thereby limiting the possibility to make accurate correlation of cognitive status and morphologic findings [35,44].

The combination of the CERAD and Braak scores in the NIA-RI criteria relates dementia to AD-typical lesions with high, intermediate and low likelihood, which, however, applies only to demented persons [45]. Evaluation of the NIA-RI criteria confirmed their easy use in AD and non-demented individuals, high Braak and CERAD stages identifying 54% and 97% of AD cases, respectively, and eliminating between 62 and 100% of non-demented ones with low Braak and CERAD stages, whereas among non-AD dementias only between 8 and 42% were identified [44]. Although the sensitivity and specificity of the NIA-RI criteria has been suggested to be around 90%, only 30 to 57% of the brains of patients with the clinical diagnosis of probable AD showed "pure" AD pathology [46], thus reducing their predictive value to 38-44% [47]. A retrospective clinico-pathologic study of 1700 elderly demented patients from two large chronic hospital in Vienna, Austria, (MMSE score < 20; mean age at death 84.3±6.0 SD years) revealed AD-related pathology in 83.2%, but "pure" AD (ABC levels 3/3/3) without other essential pathologies in only 41.0%, AD with concomitant pathologies in 44.8%, vascular encephalopathy and other disorders in 10.7% and 5.5%, respectively, while 0.9% showed no pathologic changes [44]. Although cognitively intact elderly subjects often show variable pathologies [48-50], in general, the density of isocortical NFTs correlates best with the severity of cognitive impairment, and the predictive value of widespread tau pathology (Braak neuritic stages V and VI) for dementia is high [51]. Other studies suggested that both diffuse and neuritic plaques, rather than tangles in neocortical regions distinguish non-demented and AD subjects with high sensitivity and specificity [52], while reduction of neuronal numbers in hippocampus and cerebral cortex relates to dementia, but not to plaques and tangles [53]. The cortical Aβ burden usually does not correlate with disease duration and the stage of tau pathology [54]. Correlations between AD pathology and cognitive status have been reviewed critically [51].

The recent NIA-AA guidelines for the neuropathologic assessment of AD consider levels of AD pathology regardless of the clinical history of a given individual [36,38]. They include: 1. the recognition that AD pathology may occur in the apparent absence of cognitive impairment, 2. an "ABC" score of AD pathology that incorporates histologic assessements of Aβ plaques (A), based on its phase assessement [42], staging of NFTs (B) based on the Braak staging system [40,41], and scoring of neuritic plaques, based on semiquantitative assessment in at least five neocortical regions (C), based on CERAD criteria [39]. Table 1 illustrates how each of the A (amyloid), B (Braak), and C (CERAD) scores are transformed to state the level of AD neuropathologic change on a four tiered scale (Non, low, intermediate and high). 3. More detailed approaches for assessing co-morbid conditions, such as Lewy body disease, vascular brain injury, and TDP-43 immunoreactive lesions are considered [36]. Preliminary testing of the revised NIA-AA neuropathology guidelines in 390 autopsy cases including 199 non-demented subjects distinguished pure AD and non-AD dementia from non-demented cases with a sensitivity of 71% and a specificity of 99%. The sensitivity increased after exclusion on non-AD dementia cases, indicating that cognitive status and morphologic assessment according to the NIA-AA guidelines appear excellent for distinguishing pure AD from non-AD dementia, preclinial AD and non-demented controls [55].

Diagnostic challenges

There is a growing appreciation, not yet incorporated into consensus-based guidelines, that the neuropathology of AD is heterogeneous [37,46,56-58], which might be explained by the recent detection of two distinct strains of Aβ prions in the brains of AD patients [59]. The currently used guidelines for the neuropathologic diagnosis of AD only consider the classical "plaque and tangle" phenotype and do not recognize other subtypes or atypical forms [56,58]. These include forms predominantly observed in demented subjects over age 85 years, such as the "plaque predominant type" with abundant amyloid, no or little tau pathology restricted to the hippocampus and abnormal phospho-tau in neocortical pyramidal cells but lacking tangle formation [60], frequently representing a specific type of DLB/DLB-AD [61], and the "tangle predominant dementia" (TPD), recently redefined as "primary age-related tauopathy" (PART) [62], with tau pathology mainly restricted to the limbic system (up to Braak stages III or IV), absence of neuritic plaques, no or very little diffuse amyloid plaques and cerebral amyloid angiopathy, and low ApoE ε4 frequency (5-7% of oldest old

Table 1: ABC criteria for the diagnosis of Alzheimer's disease related pathology.

		Level of AD neuropathologic change				
Thal phase for Aβ plaques	**A**		**B**		**C**	*CERAD*
		0 or 1	**2**	**3**		
0	**0**	Not	Not	Not	**0**	*neg*
1 or 2	**1**	Low	Low	Low	**0 or 1**	*neg or A*
1 or 2	**1**	Low	Intermediate	Intermediate	**2 or 3**	*B or C*
3	**2**	Low	Intermediate	Intermediate	**any C**	*neg or A to C*
4 or 5	**3**	Low	Intermediate	Intermediate	**0 or 1**	*neg or A*
4 or 5	**3**	Low	Intermediate	High	**2 or 3**	*B or C*
		Braak 0-II	*Braak III-IV*	*Braak V-VI*		

The level of AD neuropathologic change is determined by assessing A, B and C scores. A scores are related to phases of Aβ deposition (first column), B scores to neurofibrillary Braak stages (bottom row) and C scores to CERAD stages (last column). Modified from [36].

people). Recent studies confirmed an identical tau in TPD and AD [63,64], and demonstrated absence of soluble Aβ in brain tissue, and association with the tau gene MAPT H1 haplotype, classifying PART as a specific tauopathy [57,62,64].

A recent quantitative autopsy study separated three primary AD subtypes: a) limbic-predominant with lower cortical NFT counts and tau burden (14%), b) hippocampal-sparing with lower NFT counts in hippocampus and more frequent plaques (11%) compared to c) typical AD (75%) that showed clinical, demographic, and genetic differences [56,57,65]. Volumetric MRI analyses could reliably track the distribution of NFT pathology and predict pathologic subtypes of AD [66]. It is possible that these AD subtypes are along a common continuum with PART, but there are important distinctions, in particular with regard to temporal lobe tau pathology and Aβ burden [56,63,65]. In the future, markers may be developed to assist in this distinction. A working classification for PART that requires staging of AD-type NFT pathology using NIA-AA or CERAD staging has been proposed recently [62].

Further diagnostic challenges are the fact that neuropathology of AD in the very old demented subjects differs considerably in both intensity and distribution from that in younger age groups [67,68], and there is a considerable overlap in the pathologies found in demented and non-demented oldest patients [69]. Recent studies suggest that dementia in the oldest-old group (90+ years) is only modestly related to AD, while both cardiovascular ands cerebrovascular pathologies may cause cognitive impairment in patients with low AD pathology scores [70-72]. While several clinico-pathologic studies showed that neuritic Braak staging remains a significant predictor of cognitive status even in the oldest-olds [73,74], others found significant positive correlations between the severity of dementia and senile plaque density but not for NFT score [75]. Although much late life cognitive decline is not due to common neurodegenerative pathologies [76], there may be no evidence for some elderly subjects suffering from dementia without an apparent causative morphologic background [44,46,73], and dementia lacking a known pathologic substrate is extremely rare [44,46,77].

Another major diagnostic problem is the frequent presence of multiple pathologies in the aged brain that coexist with AD, such as cerebrovascular and Lewy pathologies, argyrophilic grain disease, hippocampal sclerosis and others. About 10-40% of AD brains have concomitant Lewy bodies, which likely affects the clinical course of AD [78,79]. About two-thirds of aged human brains show non-AD type neuropathology [48,80-82], which however, frequently has been missed clinically and could not be identified without neuropathologic examination [46,83,84]. Several autopsy studies showed that global AD pathology significantly correlated with global cognition, whereas infarcts and Lewy pathology did not [85]. However, a recent study of 2083 autopsy cases from the NACC database showed that the cause of mild-to-moderate AD remained uncertain in 14% of the patients, while concomitant CVD strongly correlated with cognitive impairment in the sample representing the AD continuum, confirming the uncertainty of AD clinico-pathologic correlations based only on plaques and tangles [86]. A community-based autopsy series of 233 subjects over age 75 from the Vienna VITA study, in addition to some degree of NFT in 100%, showed Aβ deposits (68.7%), CVDs (48.9%), non-AD tauopathies (23.2%), TDP proteinopathies (13.3%), and others (15.1%), the number of observed pathologies correlated significantly with AD-relate changes [87]. The burden of vascular and AD type pathologies are considered to be independent of each other, and are consistent with an additive or synergistic effect of both types of lesions on cognitive impairment [72,88,89]. The synergistic interaction between Aβ, tau, aSyn and other pathologic proteins, accelerating neuropathology and cognitive decline, has been reviewed recently [90-92].

Conclusion

Recent advances in pathobiological, genetic and experimental approaches provided insights into the molecular pathogenesis of AD and other neurodegenerative dementias, and updated clinical and neuropathologic consensus criteria have increased the diagnostic accuracy of these devastating disorders considerably. Interdisciplinary projects for the standardized assessment of clinical, neuroimaging and biomarker data are currently under way [21,24,93-96]. However, due to frequent overlap between disorders and multiple confounding pathologies in the aging brain, both clinical and postmortem studies entail biases that affect both their general applicability and validity. Using modern immunohistochemical, molecular and genetic approaches, homogenous and harmonized definitions, standardised inter-laboratory methods for the assessment of nervous system lesions, and considering exact clinical data, neuropathology can achieve a diagnosis or classification in up to 96% of the cases. In the majority of cases except those with known genetic or metabolic

backgrounds, however, pathologic examination may not be able to clarify the causes/etiology of AD and other dementing disorders. Therefore, the reliabiliy and clinical relevance of the current criteria for the neuropathologic diagnosis of AD and its differentiation from other neurocognitive disorders need better qualification and validation, and harmonized interdisciplinary approaches are required to increase the accuracy and reproducibility of AD diagnosis as a basis for further disease-modifying treatment and neuroprotection.

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