alzheimer's research&therapy

VIEWPOINT

Con: Can neuropathology really confirm the exact diagnosis?

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Abstract

Clinical diagnostic accuracy using revised consensus criteria and newly developed biomarkers ranges from 65 to 96% for Alzheimer's disease (AD), with a diagnostic specificity versus other dementias of 23 to 88%. Neuropathological assessment using molecular biology and immunohistochemistry, homogeneous definitions, harmonized interlaboratory methods, and assessment standards can identify 54 to 97% of AD cases and can eliminate 62 to 100% of nondemented subjects, but only between 8 and 42% of non-AD dementias, without, however, being able to clarify the etiology of most of these disorders. The value and pitfalls of pathological diagnostic criteria are critically discussed.

Introduction

Dementia encompassing deteriorations in several cognitive domains can be caused by a large variety of disorders, disturbing brain functions due to loss of synapses and neurons. Consensus criteria for the clinical diagnosis of major dementing disorders exist and have recently been revised [1]. The combination of clinical data with biomarkers has improved the diagnostic accuracy of Alzheimer's disease (AD) from 65% to between 92 and 96%, while the sensitivity and specificity versus other dementias are much lower. Fusion of the best cerebrospinal fluid biomarkers and magnetic resonance imaging data will lead to a more precise diagnostic prediction [2].

Diagnostic guidelines for the neuropathological diagnosis of AD and other dementias rely on (semi)quantitative and topographic assessment of morphological and bio/histochemical signposts; in particular, specific protein inclusions in neurons and glia [3]. Diagnostic criteria for AD – in addition to cut-off values of senile plaques and tangles, their semiquantitative assessment and age adjustment in the Consortium to Establish a Registry for Alzheimer's Disease protocol – include the topographic staging of neuritic AD pathology, re-evaluated recently [4].

The combination of the Consortium to Establish a Registry for Alzheimer's Disease and the Braak scores in the National Institute of Aging–Reagan Institute criteria relates dementia to AD typical lesions with high, intermediate and low likelihood [5]. Evaluation of the criteria showed their validity in AD – high lesion stages identifying 54 to 97% of AD cases and eliminating between 62 and 100% of nondemented subjects with low Braak stages, whereas only between 8 and 42% were identified among non-AD neurodegenerative dementias [1].

Specific problems in the diagnosis of Alzheimer's disease

The current algorithms for the neuropathological diagnosis of AD, based on assessment of plaques and tangles, despite reasonable interrater agreement when using standardized criteria, only consider the classical plaque and tangle phenotype of AD but do not recognize other subtypes.

The plaque-predominant type with abundant amyloid plaques, with no or very little neuritic pathology restricted to the hippocampus and with abnormal phosphorylated tau in neocortical pyramidal cells, but lacking overt tangle formation, accounts for 3.5 to 8% of demented subjects over age 85 years [6]. Many of these cases are associated with cortical Lewy bodies, representing a specific type of dementia with Lewy bodies.

Tangle-predominant dementia occurring in the very old (age 80+ years) and accounting for 5 to 7% of dementia cases shows tau pathology often restricted to the limbic system, an absence of neuritic plaques, and no or very little (diffuse) amyloid deposits. Since the tangles in this type react with three-repeat and four-repeat tau similar to those in classical AD, it could be considered a subtype of AD; tangle-predominant dementia, however, is clinically sometimes different and associated with different apolipoprotein E genotypes [7].

Standard metrics for plaques and tangles are usually semiquantitative; good agreement was reached only

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when the lesions were substantial in isocortical structures (Braak stage V to VI with absolute agreement 91%), while for mild stages the agreement was poorer [8], limiting the ability to make accurate correlation of antemortem cognitive status and pathology. Although the sensitivity and specificity of the National Institute of Aging–Reagan Institute criteria are suggested to be 90%, only 30 to 57% of the brains of patients with a clinical diagnosis of probable AD show pure AD pathology [1]. Their predictive value may thus be reduced to 38 to 44% [9]. In a retrospective clinicopathological study of 1,700 demented persons (66% female; Mini-Mental State Examination score <20; mean age at death 84.3 to 6.0 years; 90% over age 70 years), AD-related lesions were present in 83.2%, but pure AD without other pathologies was present in only 42.0%, AD with other pathologies including mixed dementia in 41.2%, vascular dementia in 12.8%, other disorders in 4.1%, and negative pathology in 0.9% [10].

Although cognitively unimpaired subjects may show variable neocortical AD pathology, and although good correlations between the severity and extension of tau pathology and/or of β-amyloid load have been found, at least in those without superimposed other brain diseases [11], the distinction between physiological and pathological aging (often but not consistently associated with cognitive decline) may be difficult. Specific problems arise from considerable differences between genetic/familial AD and sporadic AD [12] and between oldest-old patients and younger patients, with considerable differences in both the intensity and distribution of AD pathology. Increased densities of neuritic plaques and tangles are absent in demented patients over age 90 years, with considerable overlap between demented and nondemented cases [13]. A high percentage of demented persons aged 80+ years do not meet the pathological criteria of AD or were classified as dementia of unknown etiology [14]. In a prospective study of 180 demented patients (mean age 85 ± 3.4 years), autopsy showed AD in 48%, AD with vascular pathology in 19%, vascular dementia in 11%, dementia with Lewy bodies in 9%, and dementia of unknown etiology in 13% (KA Jellinger, unpublished observations).

An important problem is the frequent presence of confounding processes in the aged brain that coexist with AD – such as cerebrovascular disease, Lewy body pathology, argyrophilic grain disease, hippocampal sclerosis, and so forth – with about two-thirds of cases showing mixed pathologies (see [1,15]), which have, however, frequently been missed clinically and could not be identified without neuropathological examination using modern biochemical and molecular-biological analyses [3,16]. Since 50 to 85% of the brains of oldest-old patients show cerebrovascular lesions, a specific problem is their impact in relation to AD pathology [15]. The burden of vascular and AD-type pathologies are considered independent of each other, and are consistent with an additive or synergistic effect of both types on cognitive impairment [1,17]. It should be borne in mind that all additional pathologies may interact, although their mutual impact often remains unclear.

There is increasing use of biochemical (and genetic) approaches for refinement of diagnosis and analysis of the relevant contribution of different disease processes to neurodegeneration of AD and other dementias [1,3,16,18]. Since the majority of degenerative dementing disorders are associated with intracellular and/or extracellular deposition of misfolded proteins (proteinopathies), most of them can be classified and diagnosed by morphological, immunohistochemical and/or molecular-biological (neurochemical) identification of these deposits representing characteristic markers and signposts of particular disorders. Algorithms for the molecular-pathological classification of sporadic (nongenetic/nonhereditary) forms of neurodegenerative dementias have been proposed recently [3,16,18]. Since there is considerable clinical and morphological overlap between many of these disorders, however, the reliability and clinical relevance of the current diagnostic criteria need better qualification and validation.

Conclusion

Although molecular genetics, biochemistry and animal models, at least in part reproducing the morphology of human AD and related disorders, have produced a large and convincing body of data on the pathogenesis and pathophysiology of the disease and have made an increasing contribution to postmortem studies of the cellular and molecular changes that underpin AD and other causes of dementia, the molecular backgrounds, the basic etiological factors, the pathogenic interrelationships of various concomitant pathologies, and the impact for an exact diagnosis of AD need further validation. Harmonized techniques are required to increase the accuracy and reproducibility of neuropathological diagnosis as a basis for further successful treatment and neuroprotection.

Abbreviations

AD, Alzheimer's disease.

Competing interests

The author declares that he has no competing interests.

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