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Review Article

The enigma of mixed dementia

Kurt A. Jellinger*

Institute of Clinical Neurobiology, Kenyongasse 18, A-1070, Vienna, Austria

Abstract Mixed type dementia (MD) refers to a combination of Alzheimer disease (AD) and vascular encephalopathy (VE) and other dementia disorders, but the distinction between these diseases is difficult. For the diagnosis of MD, the clinical/neuroimaging criteria of probable AD plus vascular cognitive impairment (VCI) as separate entities are used. Both disorders increase exponentially with age, but their interactions are common and controversial. Pathologic diagnosis is based on the combination of autopsy-proven AD with multiple vascular or ischemic brain lesions. The population-based incidence and prevalence of MD is unknown. In retrospective and prospective autopsy studies, its prevalence ranges from 2% to 58% with reasonable means of 6% to 12%, although findings from several recent studies indicated frequent coexistence of AD with multiple cerebrovascular lesions (CVLs) in cognitively impaired elderly subjects. In both AD and VCI, vascular lesions frequently involve subcortical regions (basal ganglia, thalamus, hippocampus, white matter) or are multiple microinfarcts, whereas in MD large/hemispheral infarcts and multiple microinfarcts are more frequent, suggesting different pathogenic mechanisms. There is increasing evidence that critically located small CVLs can induce/promote cognitive impairment in early-stage AD but not once AD pathology becomes more advanced. Discussion of the major pathogenic factors inducing AD, VCI, and MD suggests synergistic relations between these disorders. Currently available clinical and morphologic criteria for AD and VCI are of limited value for the diagnosis of MD, and the ability of current consensus criteria to distinguish between AD, VCI, and MD is limited. Therefore, future development of methods that more accurately characterize the impact of both AD-related and vascular brain injuries are warranted.

Keywords: Mixed dementia; Alzheimer's disease; vascular encephalopathy; consensus criteria; neuropathology

1. Introduction

The term *mixed type* or *mixed dementia* (MD) refers to a combination of definite (pathologically confirmed) Alzheimer's disease (AD) and vascular encephalopathy (VE) and vascular dementia/vascular cognitive impairment (VaD/VCI) with multiple vascular or ischemic brain lesions or other dementia disorders, but the distinction between these conditions is controversial. Because of multiple sources of uncertainty, the accuracy of current clinical and pathologic criteria to distinguish between AD, VaD, and MD is limited [1–8]. Recent emphasis on comorbidity or AD and cerebrovascular disease (CVD) [9–11a], the link between AD and atherosclerosis [12], vascular pathology, detected in 20% to 80% of AD brains and showing a large variety of lesions [13–15], cognitive impairment associated with cerebral amyloid angiopathy (CAA) present in up to 100% of AD brains [8,16–18], significant cerebral microvascular pathology [19,20], and deficient clearance of beta amyloid (Aβ) across the blood–brain barrier in AD [21,22] all indicate that vascular disorders are an important factor of the chronic neurodegeneration in AD [22a]. Therefore, neurovascular dysfunction could have a major role in the pathogenesis of AD [23], which, by some investigators, even has been considered a primary cerebrovascular disorder [24]. *APOE* e4 and e2 with its potential amyloidogenic role may be responsible for some of the microvascular changes found in AD [25]. A close relationship between AD and VaD has been suggested because strokes are common and increase

*Corresponding author. Tel.: +43-1-5266534; fax: +43-1-5238634.
E-mail address: kurt.jellinger@univie.ac.at

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with age [26], and age-related changes in cerebral blood vessels that are the basis of CVD and VaD [27,28] may be responsible for the failure of elimination of Aβ from the brain in AD [29].

Moreover, autopsy series show the frequent concurrence of vascular and Alzheimer-type pathology [8,13,14,30–34]. Many patients with dementia have neuroimaging and neuropathologic features of AD and VE, with classical neurofibrillary tangles (NFTs) and plaques, together with cerebral infarctions, lacunes, microinfarcts, and ischemic lesions characteristic of VaD, but categorical labels are poorly suited to capture mixed condition. This review is restricted to MD owing to combined pathologies of AD and VE, describing the currently available clinical and neuropathologic diagnostic criteria, the epidemiology of MD, the relationship between AD and vascular/ischemic brain lesions and their impact on cognitive impairment, and pathogenic factors in the development of MD.

2. Diagnosis

2.1. Clinical criteria

Whereas AD can be diagnosed with a high degree of accuracy (see [6,35]), the distinction between AD, VaD, and MD, where both pathologies coexist in the same patient, remains a controversial issue and one of the most difficult challenges.

Criteria for the clinical diagnosis of MD are variable, and it has been questioned previously whether MD really exists as a separate entity [36]. Conversely, prospective longitudinal studies of patients with a VaD syndrome show that many have significant Alzheimer pathology [5,32]. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria does not consider MD [37], whereas in the Alzheimer Disease Diagnostic & Treatment Center (ADDTC) criteria, a second vascular disease in addition to AD must be shown to be causally related to dementia [38]. In the National Institute of Neurological Disorders and Stroke–Association internationale pour la Recherche et l'Enseignement en Neuroscience (NINDS-AIREN) criteria, the term *AD with CVD* is reserved to patterns fulfilling the clinical criteria of possible AD with clinical and imaging signs of relevant CVD [39]. Diagnostic and Statistical Manual (DSM-IV) [40] and the International Classification of Diseases (ICD-10) code [41] have separate criteria for AD and VaD. Further criteria have been suggested for Binswanger's syndrome [42] and subcortical vascular dementia (SVD) [43] as well as for early changes of VaD termed *vascular cognitive impairment* (VCI) [44,45]. However, the diagnosis of VaD remains problematic and is a matter of discussion [5–7,46,47]. Two important challenges exist. 1) There is no accepted neuropathological scheme for quantitating cerebrovascular disease in cognitive disturbances. 2) Agreement on clinical definitions of VaD is incomplete. Currently there are no generally accepted and validated clinical guidelines for the diagnosis of MD. The currently used criteria for the clinical diagnosis of AD (CERAD, NINDS-Alzheimer's Disease and Related Disorders Association criteria [26,48]) and for VaD (see [5]) are of limited value for the diagnosis of MD, and the diagnostic rate, when applied to the same group of demented patients, between the published diagnostic protocols (see above) varies from 33% to 90% [49,50]. Reclassification of 308 dementia cases from the population-based longitudinal study from the Kungsholmen Project, using vascular risk factors retrospectively, reclassified only 47% of the AD cases as "pure" AD. Twenty-six percent of the pure AD subjects had a vascular disorder in the following 3 years, and among subjects with AD and with a vascular component, CVD was the most common (40%) [51]. Accuracy of the clinical diagnosis of VaD using four different sets of clinical criteria has been reported in 89 autopsy cases, in which VaD was defined pathologically by the presence of cortical infarcts in at least 3 areas but without subcortical lesions [52]. Using these pathologic criteria as the reference standard, the clinical criteria for VaD tended to be specific but insensitive, suggesting that they underestimate the extent of ischemic brain injury.

Evaluation of 363 autopsy cases of the updated Honolulu-Asia Aging Study (HAAS), showed a rather low correspondence between clinical and neuropathologic diagnosis, with 56% diagnosed as probable or possible AD but only 19% having neuritic plaques or NFTs as the sole or predominant dementia-related morphologic lesions. Although 16% were attributed to mixed cases during life, almost 40% were found to have significant mixtures of dementia-related lesions at autopsy [53].

Among 110 autopsy cases, 32.8% were confirmed VaD, 42% of which had not presented with stroke, whereas 30% of morphologic MD cases had been diagnosed clinically as VaD by both NINDS-AIREN and ADDTC criteria, showing a low sensitivity of these criteria [54].

In a retrospective clinicopathologic study of consecutive autopsies of 1050 elderly demented patients in Vienna, Austria, postmortem confirmation of the clinical diagnosis of possible/probable AD was achieved in 93%, of MD in 60%, and of VaD in 52.3% [55]. In a prospective study of 180 long-term elderly demented patients followed up in a chronic hospital in Vienna, the clinical diagnosis of possible/probable AD was confirmed at autopsy in 90% (one third with associated vascular or Lewy pathologies), that of MD in 83%, and of VaD in only 53.3% (Jellinger, unpublished data). These accuracy data were somewhat higher than those in other autopsy series of demented patients, in which the sensitivity for VaD ranged from 25% to 44%, and that of MD was around 31% [56,57]. There is still lack of consensus regarding both the clinical and pathologic definitions of MD. Among patients with slowly progressive dementia, the possibility of concomitant AD often arises but