A diagnostic dilemma: is "Alzheimer's dementia" Alzheimer's disease, vascular dementia, or both?

In this issue of the journal, Jack de la Torre[1] strongly emphasises the possible importance of vascular factors as causes of Alzheimer's disease (AD). However, in our opinion, it remains to be determined whether ischaemic cerebrovascular disease (ICVD) contributes directly to the development of AD pathology or whether it is merely an independent comorbid process that increases the likelihood of a dementia diagnosis in patients with asymptomatic low-grade AD pathology. The term dementia of AD (DAD) is used here to refer to dementia specifically associated with advanced AD pathology (ie, Braak stage IV). DAD is not synonymous with pathologically "confirmed" AD because the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria allow for the diagnosis of AD at preclinical stages.

Both ICVD and AD pathology are prevalent in elderly people. In fact, vascular dementia is the second most common dementia.[2] Hence, these pathologies coexist in a substantial proportion of patients with late-onset dementia. However, although vascular dementia seldom presents without at least some comorbid AD pathology in this age group, these pathologies are inversely related,[3] which argues against ICVD as the cause of AD pathology. Moreover, the existence of "pure AD" and "pure vascular" dementias in young people does not support a direct association between these pathologies in late life. Stroke, and other types of ICVD, are common in patients with the highly prevalent late-onset form of AD. In contrast, ICVD is rarely found in patients with genetically determined early-onset AD. Similarly, AD pathology is absent in early-onset genetic forms of vascular dementia such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy. Therefore, the epidemiological evidence of a vascular cause of AD decreases after adjustments for age at onset.

The biggest challenge to the hypothesis that ICVD is a direct cause of AD is that AD pathology (tauopathy and neurofibrillary tangles) progresses along neuroanatomical pathways in a well defined hierarchical sequence.[4] Cytoskeletal changes begin in the basal nucleus of Meynert[5] and transentorhinal and entorhinal cortices in the mesial temporal lobes at about 47 years of age[6]—well before any sign of comorbid ICVD—and continue over decades to involve the hippocampal formation, amygdala, and associative neocortex in frontal, temporal, and parietal lobes.[4] No vascular pathology or endothelial disorders could account for either the selective location of the early pathology in AD or its hierarchical progression over time.

We believe that comorbid ICVD is more likely to convert patients with preclinical AD (pAD) to clinical "Alzheimer's dementia" than to cause AD itself. Neurofibrillary changes are endemic in the elderly, yet only a small proportion of octogenarians reach a Braak stage sufficient for a diagnosis of DAD.[6] ICVD is found in a substantial proportion of patients who are clinically diagnosed with dementia despite lesser degrees of AD pathology.[3,6] This may be because clinicians rarely diagnose DAD until the AD pathology has reached the cortical regions related to executive functions.[7] In the absence of such pathology, frontal-lobe dysfunction may appear after lesions of the subcortical structural frontal system.

If executive impairment caused by subcortical vascular disease is superimposed on pAD pathology, then "Alzheimer's dementia" is likely to be diagnosed. Although memory loss is still a prerequisite for the clinical diagnosis of dementia, the conversion to dementia requires additional cognitive impairments associated with functional disability. Executive impairment is a strong independent indicator of functional outcome.[8] If executive impairment of vascular cause appears in the early stages of pAD, the patient is likely to satisfy the clinical criteria for the diagnosis of AD. ICVD of the frontal system is commonly "silent" and may not be recognised by clinicians as stroke,[9] despite significant changes in functional status or executive control. If the vascular executive impairment develops in isolation, it is likely to be diagnosed as either vascular cognitive impairment or cognitive impairment no dementia.

In the absence of neuropathological confirmation, only clinical acumen will allow the distinction between clinical dementias that resemble AD and DAD itself. Fortunately, the placebo groups in randomised trials of DAD, vascular dementia, and AD plus ICVD have different population characteristics, cognitive abilities, and typical outcomes, which suggests that clinical distinction is possible.[10] The need for accurate diagnosis is particularly important for epidemiological studies. In either case, de la Torre[1] reminds us of the crucial importance of ICVD as a potentially preventable, or even reversible, cause of cognitive decline.

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