Vascular Dementia and Alzheimer's Disease: A Waning Dichotomy

The concept of vascular dementia has evolved over the years from a discrete sporadic entity, characterized by a stepwise progression of neurological deterioration and associated with ischemic stroke involving a critical mass of cerebral volume (e.g., multiple infarct dementia), to a heterogeneous collection of disease processes that include multiple infarct dementia, as well as rare genetic syndromes (e.g., cerebral autosomal dominant angiopathy with subcortical infarcts and leukoencephalopathy, or CADASIL), small vessel ischemic disease, radiographic-only evidence of vascular disease, and "mixed" processes that include Alzheimer's disease (AD), or potentially other dementing illnesses, in addition to vascular disease. To be sure, the definition of vascular dementia is a moving target. Indeed, in a recent large analysis of vascular dementia from the Cardiovascular Health Study Cognition Study, the various consensus criteria for vascular dementia failed to identify the same group of subjects [5], consistent with previous studies showing the same overall phenomenon [6], while imaging components of clinical criteria are similarly unhelpful in predicting associated dementia [5]. Noteworthy in their paucity are large studies with autopsy correlation, although the rare studies that do exist generally show limited sensitivity and specificity when consensus criteria for vascular dementia are applied, and they generally fail to exclude underlying AD [3].

With respect to AD, pathogenic analysis as well as attempts at etiopathogenesis-based therapeutic intervention, are frustrated not by a perseveration on clinical and radiographic manifestations, as is the case for vascular dementia, but by perseveration on pathological lesions. Such undue focus on AD lesions (plaques and tangles) has impeded understanding of AD pathogenesis [1,2], much like the undue focus on clinical signs in vascular dementia (often without direct knowledge of underlying pathology), has impeded understanding of the relationship between vascular disease and cognitive decline. In essence, the classical approach to nosology and classification of vascular dementia that seeks to identify a dichotomy (vascular dementia vs. AD) continues to be hampered by the inability of clinicoradiographic and even clinicopathologic analysis to cleanly separate these putative entities, raising the possibility that vascular disease and AD are pathogenically related and that, perhaps, vascular dysfunction plays a role not only in so-called vascular dementia, but also in AD. This paradigm has gained increasing support in recent years, and warrants continued investigation [4].

In the present issue of this journal, Qi and colleagues [7] further this concept of the inter-relationship between vascular disease and AD-type neurodegeneration by demonstrating that ischemic human hippocampus is characterized by dramatic up-regulation of not only amyloid-β peptides 1–40 and 1–42, but also apolipoprotein E. The authors appropriately conclude that cerebral ischemia may play a critical role in the genesis of AD pathology and dementia. The findings add to the growing evidence of vascular dysfunction in aging and AD, and provide an impetus to investigate further a therapeutic avenue in AD that has not been fully exploited.

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