



Alzheimer's disease, cerebrovascular disease and dementia: lump, split or integrate?

This scientific commentary refers to 'Cerebral amyloid angiopathy interacts with neuritic amyloid plaques to promote tau and cognitive decline' by Rabin *et al.* (<https://doi.org/10.1093/brain/awac178>).

Dementia is a condition mostly occurring in old age, and much feared because of its profound impact on virtually all aspects of life. Beyond affecting individual patients and their relatives, it poses an increasing burden on society through the demands it places on healthcare and economic resources. Dementia is also a topic of considerable controversy among clinicians and researchers. Some still regard dementia as the almost inevitable outcome of brain ageing, with a hodgepodge of causes so broad that trying to identify and treat separate causes in an individual patient makes little sense. Others consider dementia to be the end result of specific potentially treatable disease entities, that could be separated from each other if our diagnostic tools were sufficiently refined. In clinical practice, we have become used to diagnosing patients with 'Alzheimer's disease', 'vascular dementia' or other nosological terms, using mostly syndromal diagnostic criteria that primarily rely on typical constellations of symptoms. In many cases these diagnoses are right, in the sense that the assumed cause is often present in those who come to autopsy and receive neuropathological verification. One can also argue that the criteria are mostly wrong, because few patients only have the neuropathological entity linked to the presumed singular diagnosis: mixed pathologies are the rule rather than the exception in people with dementia. This is certainly the case for Alzheimer's disease and cerebrovascular disease. Of those with a clinical diagnosis of Alzheimer's disease in life, up to 75% have co-occurring vascular pathology at autopsy.¹ And vice versa, in those with a clinical diagnosis of vascular dementia, many have biomarker evidence of co-occurring Alzheimer pathology; more than 25% in patients over the age of 75.² Given this frequent co-occurrence of Alzheimer's disease and cerebrovascular disease, rather than trying to keep them in different 'diagnostic silos', it might be more useful to work on understanding how their combination affects disease processes and cognitive decline. Are their effects additive, are they synergistic, or do they even share pathophysiological pathways? The article by Jennifer Rabin and co-workers³ in this issue of *Brain* provides important answers to these questions.

In themselves these questions are not new. Over the past decades we have seen many epidemiological studies document how vascular risk factors increase the risk of clinically diagnosed Alzheimer's disease.⁴ But while these epidemiological observations

highlight the numerical importance of the interplay between vascular factors and Alzheimer's disease at the population level, they provide limited insight into potential mechanisms. This is where recent advances in dementia biomarker development, but also well designed population-based brain autopsy studies with increasingly enriched designs, like that of Rabin and co-workers, have important added value. For example, studies using biomarkers for Alzheimer's pathology such as amyloid-PET, have shown that hypertension and diabetes are associated with neurodegeneration but not with cerebral amyloid accumulation.^{5,6} This demonstrates divergence in clinical diagnoses and in the underlying pathologies associated with these risk factors and also reflects the dimensionality of dementia aetiologies.

The study by Rabin *et al.*³ now zooms in on the interplay between cerebral amyloid angiopathy (CAA) and Alzheimer pathology, in particular neuritic amyloid plaques (Fig. 1), in promoting tau accumulation and cognitive decline. The authors analysed data from 1722 autopsied subjects recruited through three longitudinal clinical-pathological cohort studies: the Rush Memory and Aging Project, the Religious Orders Study, and the Minority Aging Research Study. Participants were on average 89.5 years of age at death and had completed standardized annual clinical and cognitive evaluations in the years prior to death. While all were without a dementia diagnosis at study entry, 45.2% were diagnosed with dementia at the time of death, on average 9 years later. At autopsy, 64.6% of all participants had a pathological diagnosis of Alzheimer's disease and 36.1% moderate-to-severe CAA. The high burden of dementia and its underlying pathologies in this cohort may, to some extent, reflect the inclusion criteria of the studies, particularly for the Rush Memory and Aging Project and the Minority Aging Research Study. However, previous population-based autopsy studies have come up with similar numbers,⁷ further emphasizing the major impact of dementia among the oldest old.

Of note, while both neuritic plaques and CAA were common in Rabin's cohort, these pathologies occurred quite independently of each other: CAA explained only 18% of the variance in neuritic plaque burden. Yet, both neuritic plaque burden and CAA severity were associated with tau burden. The key finding of the study, however, is the observed interaction between neuritic plaque burden and CAA severity with respect to tau: the association between neuritic plaques and tau burden was more than 2-fold stronger in the group with the most severe level of CAA than in the group without CAA. These results were paralleled by observations on cognitive

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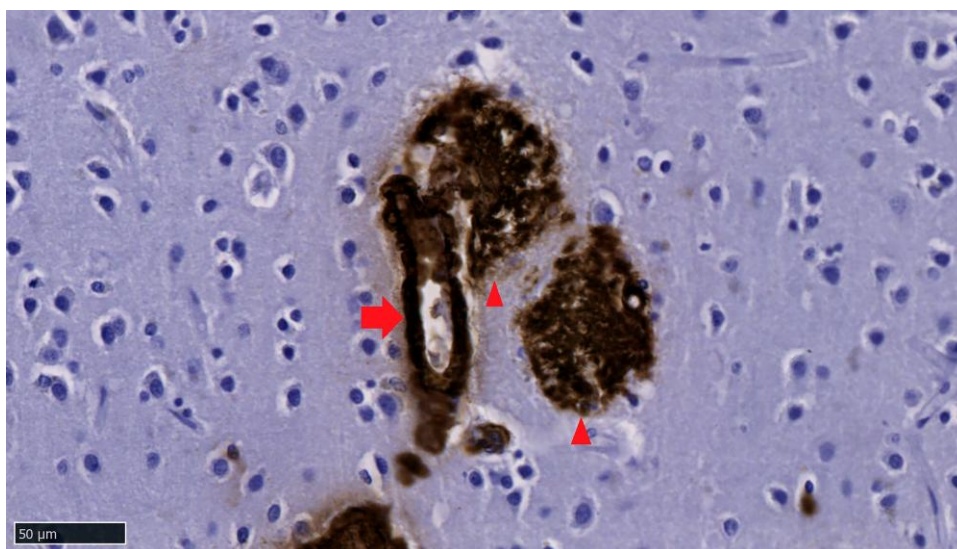


Figure 1 Amyloid plaques close to a vessel affected by CAA. Immunohistochemistry against amyloid- β (clone 6F/3D, Agilent) was performed on a 6- μ m thick section of the occipital lobe in a case with a neuropathologically confirmed diagnosis of CAA. The triangles point to plaques, and the arrow to the vessel. Image courtesy of Susanne van Veluw, Massachusetts General Hospital, Boston, MA.

decline, which also showed a clear interaction between neuritic plaque burden and CAA severity.

These findings thus imply that the prototypical stepping stones towards the clinical syndrome of Alzheimer's disease—i.e. amyloid, tau and neurodegeneration⁸—should not be regarded as simple sequential steps in a linear pathway towards dementia. The main impact of the study is that it shows that parenchymal amyloid- β -related processes converge with vascular pathways to synergistically increase tau and accelerate cognitive decline. Clearly, CAA is only one form of vascular disease contributing to dementia. Other forms of vascular disease, in particular atherosclerosis and arteriolosclerosis, also commonly co-occur with Alzheimer's pathology with and without infarcts.¹ It would be of great interest to determine if and how these other forms of vascular disease also affect tau in the brain, beyond the acute changes in tau known to occur with acute ischaemic stroke.⁹ In addition, it is important to further unravel how cerebrovascular disease and vascular risk factors contribute to neurodegeneration in dementia, interacting with but likely also independent from, amyloid- β -related processes.

This apparent interplay between cerebrovascular disease and Alzheimer's disease in dementia challenges the dogma that vascular lesions are the result of the former and neurodegeneration the result of the latter. Interactions occur at several levels, as shown by Rabin *et al.*³ but also, for example, by the observation that a higher burden of amyloid- β or tau in the brain increases the likelihood of cortical microinfarcts occurring in association with arteriolosclerosis.¹⁰ Recent advances in biomarker development for amyloid, tau, small vessel diseases, neuronal injury, neurodegeneration, and related processes, such as inflammation, together with comprehensive brain autopsy cohorts like those in the current study, should make it possible to piece together the puzzle in order to obtain a truly integrated picture of Alzheimer's disease and cerebrovascular disease in dementia.

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Competing interests

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