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Cerebral hypoperfusion and white matter disease in healthy elderly and patients with Alzheimer's disease

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Cerebral white matter hyperintensities (WMH) seen on T2 or FLAIR MRI have become an area of active research over the past two decades. The medical literature is inundated with studies exploring the clinical associations of WMH in different patient cohorts, whereas research on its pathophysiological mechanisms is relatively scarce. Part of the difficulty in studying these mechanisms stems from the following issues: (i) WMH occur and progress over many years and therefore carefully designed longitudinal studies are needed to study cause–effect relationships; (ii) WMH are invariably age-related and associated with some (but not all) vascular risk factors, making it difficult to tease out the potential effect of parenchymal neurodegenerative processes that share similar risk factors; (iii) WMH are primarily a radiological entity with inadequately characterized pathological appearance; it is difficult to perform animal studies to identify the causative factors. To date, the most widely accepted mechanism is chronic ischaemia, and data from multiple cohorts suggest small vessel pathologies as the most important contributors [1,2]. One of these vascular pathologies, cerebral amyloid angiopathy (CAA), is shown to be associated with vascular dysfunction, a potential mechanism for WMH and lacunar infarcts. Patients with CAA have higher amounts of WMH compared with healthy elderly (HE) and patients with Alzheimer's disease (AD) who have similar age and vascular risk factor profile [3,4]. A functional transcranial Doppler study showed that patients with CAA had a decreased visual evoked flow velocity response in posterior cerebral arteries compared with healthy controls [5], a finding supported by well-designed animal studies [6]. A more recent fMRI study showed delayed timing and smaller amplitude of the BOLD response to visual stimulation in advanced CAA, lending further support to CAA-related decreased vascular reactivity as a contributor to microvascular damage [7].

Alzheimer's disease and CAA are two distinct clinical conditions with totally different diagnostic criteria, but these pathologies overlap in a large number of patients. Vascular contributions to AD constitute another very important area of research as they might provide important targets for the prevention or treatment of this devastating condition. WMH also occur in patients with AD; mechanistic theories include vascular factors such as CAA, atherosclerotic risk factors and elevated homocysteine, but theories involving primary parenchymal neurodegeneration such as wallerian degeneration are not refuted at that point.

Whether chronically impaired white matter perfusion contributes to WMH is a reasonable theory that Makedonov *et al.* [8] have tested in HE and patients with AD using single-photon emission computed tomography (SPECT). As cerebral blood flow is tightly coupled to local brain metabolism and energy use, it is impossible to fully understand the direction of the cross-sectional relationship between WMH and perfusion using SPECT, that is, whether low perfusion causes WMH or whether areas of white matter damage have decreased metabolic rates resulting in lower perfusion. The authors have nevertheless used multiple well-designed approaches to assess the correlation between white matter disease and cerebral perfusion. In both AD patients and HE, the global perfusion in areas with WMH was lower than areas with normal appearing white matter, and there was a negative correlation between the volume of a lesion and its mean perfusion. In the voxel-wise white matter comparison, voxels with the highest probability of WMH had reduced perfusion, a finding that was more pronounced in AD patients with a possible threshold effect, cohorts equalizing below a normalized perfusion value of 0.38. After adjusting for atrophy, white matter perfusion was similar between AD and HE cohorts. Overall, the authors' findings show an association between decreased perfusion and the occurrence/ size of WMH in AD patients and HE. These findings again support vascular mechanisms as the cause of WMH in AD patients and HE, as opposed to primary parenchymal neurodegenerative processes. The specific causes and mechanisms of decreased perfusion in these cohorts and the poorer perfusion seen in AD patients in arterial border zone regions are still unclear. Besides the well-known atherosclerotic risk factors and CAA, newer theories to explain AD-related cerebral hypoperfusion include leucocyte plugging of capillaries [9], alteration of thrombosis and fibrinolysis by the interaction between fibrinogen and β -amyloid [10], and convergence of vascular, coagulation and inflammatory pathways in patients with AD [11]. These circulatory factors and other reciprocal interactions between ischaemia and neurodegeneration should be studied with the aim of understanding their structural consequences. Future studies should also include other radiological markers of microvasculopathy such as lobar and deep microbleeds, markers of severity of vascular amyloid and hypertensive damage respectively, to assess their impact on chronic cerebral hypoperfusion in patients with AD. Better understanding of the vascular pathways in AD patients can identify new targets for intervention, paving the way to efficient treatments.

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