The multiple sclerosis mystery: is there a vascular component?

The definition of multiple sclerosis (MS) as a chronic inflammatory demyelinating disease that affects the white matter of the CNS is challenged repeatedly. During the past few decades, findings from pathological and MRI studies have suggested that neuroaxonal injury and dysfunction are consistent features of the disease and play a major part in its heterogeneous clinical manifestations. More recently, the vascular aspects of MS have been receiving a great deal of attention. A pathological pattern of demyelination was described in patients with MS several years ago, and this pattern closely mimicked tissue alterations typically found at the early stages of ischaemia and might be associated with hypoxic damage to the white matter; however, vascular abnormalities associated with MS have been investigated systematically only in the past few years. As comprehensively and thoroughly discussed by D’haseeleer and colleagues in their Review in this issue of The Lancet Neurology, three forms of vascular abnormalities have been associated with MS: an increased risk for ischaemic disease, global cerebral hypoperfusion, and a chronic state of impaired venous drainage. As pointed out by the authors, defining whether a relation exists among these three vascular aspects of MS needs further investigation. Additionally, such aspects can be traced to the classic immunological signature of the disease, the pathological changes that occur and their clinical implications are at present unclear.

Findings from epidemiological studies have shown an increased risk of ischaemic stroke and ischaemic heart disease in patients with MS compared with those without MS, which was associated with risk factors such as smoking and limited physical activity. Although an abnormality of endothelial function might be at work, such involvement needs to be confirmed. Additionally, stroke-like lesions on brain MRI scans of patients with MS have been reported in only a few single-case studies, and, remarkably, the presence of these lesions is usually considered to be a red flag in the diagnostic work-up of patients with suspected MS.

Several cerebral perfusion studies have shown diffuse hypoperfusion in focal lesions, white matter, and grey matter of patients with MS, which is in contrast to the patchy pattern of focal hypoperfusion described in ischaemic and neurodegenerative disorders such as Alzheimer’s disease and Parkinson’s disease. The factors associated with an increased risk for ischaemic stroke and heart disease in MS as well as those underlying a reduced cerebral blood flow are unknown and, as a consequence, need systematic investigation. In this context, the combined use of different magnetic resonance modalities that can be used to assess different aspects of the disease process might represent a valuable approach to try to shed light on this aspect of the disease. For instance, in a combined perfusion and diffusion MRI study, there was an association between decreased perfusion and decreased mean diffusivity—a measure of tissue integrity—in the corpus callosum of patients with relapsing-remitting MS. This finding seems to be more consistent with what would be expected in primary ischaemia rather than as a result of secondary hypoperfusion associated with Wallerian degeneration. Additional mechanisms that have been suggested to explain cerebral hypoperfusion in MS include diffuse astrocyte dysfunction, possibly associated with an abnormal release of potassium in the perivascular space, which impairs vasodilatation, and mitochondrial injury secondary to toxic inflammatory mediators, reactive oxygen species, and nitric oxide species.

The third vascular aspect of the disease, which has recently raised great interest and attention in the MS community, is the theory of a role for cerebral venous circulatory abnormalities in the pathogenesis of MS.

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Several commentaries on this topic propose a critical view on this theory, given the many methodological limitations of the studies supporting it and the immunological and MRI-based evidence against it. Additionally, in recent studies that have applied the echo-colour doppler criteria proposed to detect cerebral venous circulatory abnormalities, there was only modest diagnostic accuracy, again suggesting that venous circulatory abnormalities are unlikely to have a primary causative role in the development and progression of MS. As a consequence, the guidelines from the Cardiovascular and Interventional Radiological Society of Europe suggest that endovascular dilatation treatment for venous stenoses in patients with MS should not be done outside well designed clinical trials.

As elegantly discussed by D’haeseleer and colleagues, vascular dysfunction is likely to be yet another factor in the complex pathogenesis of MS. However, available data to support the presence and importance of vascular dysfunction are still scarce and insufficient to draw definitive conclusions. Also, whether the three vascular aspects discussed represent a continuum of the same process, possibly secondary to the known immunological abnormalities of MS, or are separate entities over and above the classic features of the disease remains to be established. Clearly, improving the knowledge of these aspects is important because it might change the way we treat patients and the methods needed to monitor disease progression.

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Revised criteria for Alzheimer’s disease: what are the lessons for clinicians?

Diagnostic criteria are not only essential for the practice of clinical medicine, but also to reflect the current conceptualisation and understanding of the disease process. Landmark criteria for Alzheimer’s disease (AD) were published in 1984 (the NINCDS-ADRDA criteria) and have since constituted the benchmark for clinical diagnosis. Much of what we now understand about the cause, pathophysiology, course, and treatment of AD has been based on this diagnostic algorithm, which focuses principally on the exclusion of all other possible cerebral causes of progressive, acquired cognitive impairment. Increased insight gained in recent years...