Axonal lesions in multiple sclerosis: an old story revisited

The paper by Lovas et al. (2000) published in this issue of Brain is the latest in a series of studies dealing with axonal pathology in multiple sclerosis lesions. The recent re-emergence of interest by researchers in this aspect of multiple sclerosis pathology may at first seem to be at odds with the concept that defines multiple sclerosis as an inflammatory demyelinating disease of the central nervous system with (relatively) spared axons. The recognition that axonal damage occurs in multiple sclerosis lesions is, however, not new, as several of the classical studies documented axonal degeneration, described the presence of Wallerian degeneration and even attempted to quantitate axonal loss.

The recent renaissance of interest in the axonal aspect of multiple sclerosis pathology has been chiefly initiated by a series of MRI, MR-spectroscopy and magnetization transfer imaging studies, which for the first time have provided non-invasive probes of pathology (McDonald, 1994; Davie et al., 1995; Losseff et al., 1996; Davie et al., 1999). Several such studies have raised the possibility that (i) axonal pathology may be an early feature of multiple sclerosis, (ii) axon loss is likely to be a major cause of patients’ permanent disability, and (iii) axonal pathology can be the major determinant of the development of the secondary progressive form of the disease (McDonald, 1994; Matthews et al., 1996; van Waesberghe et al., 1999). Assuming that cerebral and cord atrophy measured by means of MRI imaging represents the final irreversible stage of axonal loss, it has been proposed that atrophy could also be used as a meaningful surrogate marker of axonal loss in life (Kidd et al., 1993; Paolillo et al., 1999; Trapp et al., 1999).

Recent pathological studies, applying modern morphological techniques, have provided further evidence for the time course, over which axonal damage develops in the multiple sclerosis lesions. The important study by Ferguson et al. (1997), published in this journal 3 years ago, used β-amyloid precursor protein (β-APP) immunohistochemistry with the rationale that its accumulation can only be detected in damaged axons with a compromised anterograde axonal transport (Ferguson et al., 1997). These authors demonstrated that accumulation of β-APP takes place in damaged axons in acute and active chronic multiple sclerosis lesions, i.e. in areas of acute inflammation and demyelination. This study also raised the possibility that axonal transections take place and that these could provide the underlying substrate for long-standing axonal depletion. Trapp and colleagues used confocal microscopy and immunohistochemistry applying an antibody to non-phosphorylated neurofilament epitopes, which are increased in demyelinated axons, for a three-dimensional reconstruction of terminal axonal ovoids (Trapp et al., 1998). These investigators elegantly showed that axonal ovoids, which are observed only transiently after nerve transection, are abundant in active multiple sclerosis lesions and that their frequency correlates with active inflammation. In addition to axonal transections they found further axonal abnormalities, which included a discontinuous staining of axons and significant alterations of axonal calibre, both representing damaged axons with retained active-transport systems and connection to the neuronal perikarya. The findings of the study by Trapp and colleagues further supported the notion, raised by Ferguson and colleagues that axonal transections can begin very early in the disease process and that axonal changes, demyelination and tissue inflammation are closely associated events (Ferguson et al., 1997; Trapp et al., 1998). There is, however, no evidence to suggest that axons are the primary target of the disease process in multiple sclerosis, but it seems more likely that the demyelinated axons are damaged through an immunological attack from soluble inflammatory cytokines, oxidative products, free radicals and proteolytic enzymes produced by inflammatory and glial cells.

Although the number of terminal axonal ovoids, investigated and quantitated in the study by Trapp and colleagues (Trapp et al., 1998), is a good measure of the ongoing transection of axons, it gives no information about total axonal loss. In this respect the above-mentioned study by Lovas and colleagues provides a further contribution to our understanding of axonal pathology that may be observed in chronic multiple sclerosis lesions (Lovas et al., 2000). The researchers from Budapest, Hungary, applied neurofilament immunohistochemistry, using an antibody recognizing both phosphorylated and non-phosphorylated epitopes, and a quantitative approach for their study. They showed that, compared with normal controls, at least two-thirds of the axons are lost in inactive, chronic multiple sclerosis lesions in the cervical spinal cords of individuals who had a history of secondary progressive multiple sclerosis and a disease duration ranging from 9 to 21 years. Although the technical difficulties of determining axonal loss in the central nervous system are well known to researchers applying morphological
methods, from the data that are now available, including those provided by the current study, a loss of about 50–80% of axons is likely in chronic spinal cord lesions from patients with severe disability (Trapp et al., 1999; Lovas et al., 2000).

The study by Trapp and colleagues showed that terminal axonal ovoids are also present in the hypocellular centres of chronic active lesions (Trapp et al., 1998), which confirms that axonal damage is not limited to the active multiple sclerosis lesions, but is a continuous feature of the pathological process. It may, therefore, be hypothesized that the severe depletion of axons that is now documented in the secondary progressive phase of multiple sclerosis, occurring over a background of little or no evidence of disease activity on MRI scans, is due to a multifactorial pathological process including an inflammatory component and also degeneration of chronically demyelinated axons. Such a degenerative process leading to severe cytoskeletal disorganization of axons is also documented by quantitative data of neurofilament staining of altered axons in the study of Lovas and colleagues (Lovas et al., 2000).

In summary, recent pathological studies have confirmed that axonal pathology is an important aspect of multiple sclerosis lesions. The observation that axonal damage starts early is of considerable importance, because if axonal loss is associated with the active phases of the disease, a therapeutic strategy preventing or decreasing the number of relapses may also influence the survival of axons. There is also pathological evidence that axonal damage and loss is not restricted to the active phase of the disease, but is a continuous process resulting in severe depletion of axons. This knowledge, one may trust, will facilitate the design of appropriate treatment strategies.

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References