Primary progressive multiple sclerosis takes centre stage

P M Matthews

PPMS takes centre stage

Multiple sclerosis (MS) remains an enigmatic disease. Not only is the cause unknown, but the last decade of work has led to uncertainty concerning some of the previous, most strongly held, convictions about the disease. Recently, attention has shifted from understanding demyelination to understanding how axons are injured.

It has been attractive to hypothesise that axonal damage occurs with inflammation in white matter lesions. Histopathological and imaging provide clear evidence for axonal transaction in lesions. However, rates of progression are independent of relapses even if just as “vectors” in three dimensions, which provide quantitative measures of the relative rate of diffusion along three orthogonal axes. In white matter, this allows axonal tract anatomy to be inferred. Axonal loss is associated with an increase in relative diffusion values for tensors orthogonal to the major direction of the relevant white matter tract. The three types of measurements, therefore, should show quantitative relations with axonal loss in a tract. Pelletier and colleagues measured the relative NAA and diffusion properties of water in the corpus callosum of healthy controls and patients with RR/SPMS or PPMS. As expected, the MS patients all showed decreases in relative NAA and increases in diffusion tensor values orthogonal to the fibre tract direction (as well as loss of fractional anisotropy (FA) and increase in ADC) consistent with axonal loss. The relative amount of axonal loss was similar for the two patient groups. However, while there was a strong correlation between the volume of T1 hypointense lesions around the corpus callosum and the measures of axonal loss for the RR/SPMS group, there was no significant relationship (not even a trend) for the PPMS patients. Thus, while axonal injury and transection in the focal lesions might explain distant loss of axons in the corpus callosum for the RR/SPMS group, another process must be dominant in PPMS.

What other processes might be involved? One possibility is that the lesions responsible for axonal injury in PPMS are too small to be imaged or that the inflammation is simply diffuse. Another possibility is that cortical lesions—difficult to image using current methods—are responsible for neuronal injury and axonal transaction in PPMS.

A less popular notion is that PPMS is a primary neurodegenerative disease in which (like adrenoleukodystrophy) inflammatory changes may be an epiphenomenon. Spinal cord axonal pathology of MS shares features with hereditary spastic paraparesis; for example, in showing features of “dying back”. Prominent callosal axonal loss is not inconsistent with this. For example, a recent diffusion MRI study of amytrophic lateral sclerosis has shown that, despite predominant clinical involvement of the motor cortex projection tracts, changes in transcortical paths are most prominent—perhaps as a “trans-synaptic” consequence of motor neuron degeneration.

To the extent that PPMS and RR/SPMS are different expressions of the same disease, this possibility also needs to be entertained for MS more generally. Perhaps neurodegeneration in MS is not secondary to inflammation and chronic demyelination, but is a primary manifestation of the causative pathology. Inflammation then may be a response to the neurodegeneration, rather than the primary pathology.

After being side lined for so many years by the focus on studies related to anti-inflammatory treatments, PPMS patients now may well take centre stage in the search for the cause and cure for MS.


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REFERENCES

9 Peterson JW, Bo J, Work S, et al. Transected neurites, apoptotic neurons, and reduced fractional anisotropy—a measure of relative preference of diffusion for particular directions. Assessment of direction of diffusion can be made more specific by calculating values for diffusion tensors (that may be considered just as “vectors” in three dimensions), which provide quantitative measures of the relative rates of diffusion along three orthogonal axes. In white matter, this allows axonal tract anatomy to be inferred. Axonal loss is associated with an increase in relative diffusion values for tensors orthogonal to the major direction of the relevant white matter tract. The three types of measurements, therefore, should show quantitative relations with axonal loss in a tract.
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