DEVIC'S NEUROMYELITIS OPTICA (NMO) IS A SEPARATE ENTITY FROM MULTIPLE SCLEROSIS AND SHOULD BE TREATED BY PLASMAPHERESIS?

A. Compston
Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK

Multiple sclerosis is recognised throughout the world but has a characteristic epidemiology that informs concepts on the aetiology and origins of the disease. Genetic analyses, observations in migrant populations, and age-related studies of infectious disease suggest interplay between susceptibility genes, environmental triggers and cultural factors in determining the distribution and individual risk of developing multiple sclerosis. Relapsing-remitting multiple sclerosis in Europeans is a polygenic trait – the major contribution to susceptibility being made by genes encoded within the major histocompatibility complex but with several other susceptibility loci now identified; the environmental trigger operates in childhood or early adult life; and the risk of disease is increased in individuals experiencing Epstein Barr infection at a relatively older age than the normal population. But is multiple sclerosis exclusively a disorder of Europeans?

Until recently, the typical form of demyelinating disease seen in Africa, Asia, the Far East and Aboriginal populations was neuromyelitis optica or optic-spinal multiple sclerosis. The relapsing-remitting phenotype, affecting many sites within the brain and spinal cord was uncommon. With the identification of anti-aquaporin (AQP) 4 antibodies as biomarkers of neuromyelitis optica, awareness of neuromyelitis optica in northern Europeans has increased. Diagnostic criteria for neuromyelitis optica are: optic neuritis and myelitis with ≥2 of 3 supporting criteria; a contiguous spinal cord lesion ≥3 segments in length; brain MRI at onset that is not diagnostic for multiple sclerosis; and NMO-IgG seropositivity.

Neuromyelitis optica is characterised by demyelination and necrosis of the spinal cord white and grey matter, acute axonal injury, antibody deposition and perivascular complement activation. AQP4 is not detectable in the optic nerve and spinal cord lesions. Conversely, AQP4 expression is increased in active and recently remyelinated lesions of multiple sclerosis but lost in the chronic plaques. In Japan, not all AQP4 antibody positive patients show the typical phenotype of optic-spinal multiple sclerosis. Up to one third of sero-positive cases and some with relapsing-remitting multiple sclerosis also show the long thoracic spinal lesions, and the same cord appearance may be seen in AQP4-negative individuals. This spectrum suggests cases that are intermediate between sero-positive neuromyelitis optica and sero-negative relapsing-remitting multiple sclerosis. Perhaps the most telling link is the switch in clinical phenotype from optic-spinal to conventional multiple sclerosis observed over a short period in Japan coinciding with changes in industrialisation, and in the French West Indies with patterns of migration. One interpretation is that cultural changes expose the intrinsic vulnerability of individuals at risk of demyelinating disease encountering infections later in childhood and at a crucially altered phase of maturation in their immune repertoire.

Genetic analyses are predicated on the assumption that multiple sclerosis is one disease but there is some evidence for genetic heterogeneity. For example, although mitochondrial genes do not contribute generally to susceptibility in multiple sclerosis, mutations of mitochondrial DNA are responsible for a rare multiple sclerosis-like illness characterised by disproportionate involvement of the anterior visual pathway. The gratifying response to plasma exchange in some patients with neuromyelitis optica suggests a primary pathogenic role for antibody and complement in these cases but this response is also seen with the pattern II neuropathology of multiple sclerosis. One argument favouring the distinction between neuromyelitis optica and multiple sclerosis is the comparative neuropathology. It has been proposed that specifically different immunological and neurodegenerative processes are involved in the pathogenesis of tissue injury in groups of patients with multiple sclerosis. These are:

- T cell infiltrates and macrophage associated tissue injury (pattern 1).
- Antibody and complement-mediated immune reactions against cells of the oligodendrocyte lineage and myelin (pattern 2).
- Hypoxia-like injury, resulting either from inflammation-induced vascular damage or macrophage toxins that impair mitochondrial function (pattern 3).
- A genetic defect or polymorphism resulting in primary susceptibility of the oligodendrocytes to immune injury (pattern 4).

These separate mechanisms may explain differences in the extent of demyelination, oligodendrocyte injury, remyelination and axonal damage seen across the spectrum of multiple sclerosis and related conditions – neuromyelitis optica (pattern 2) and Balo's concentric sclerosis (pattern 3). But separation of multiple sclerosis into distinct patterns is not now so secure and an alternative interpretation is that the core process of T cell mediated brain inflammation is merely modified by different immunological effector mechanisms, thus creating a state of mechanistic complexity rather than true disease heterogeneity. The original proposal that each individual with multiple sclerosis has only one type of pathological lesion is now challenged by evidence suggesting that the immunopathological appearance of active demyelinating lesions in established multiple sclerosis is uniform. Initial heterogeneity of demyelinating lesions seen in the earliest phase of lesion formation may disappear over time as different pathways converge into one general mechanism of demyelination. The consistent presence of complement, antibodies, and Fc gamma receptors in phagocytic macrophages suggests that antibody- and complement-mediated myelin phagocytosis is the dominant mechanism of demyelination in established multiple sclerosis. Thus, since the individual features may evolve, qualitative differences between the neuropathology of multiple sclerosis and NMO may be more apparent than real.

In terms of debate, it is self-evident that many differences do exist in the phenotype, immunopathogenesis, epidemiology and response to treatment between neuromyelitis optica and multiple sclerosis. But there are subtle differences between complexity and heterogeneity; and disorders need to be understood in terms of their complex aetiologies and origins in which pathogenesis is part of the evolving interplay between population genetics, host response and environmental triggers. An alternative formulation to one of absolute difference between these disorders is that neuromyelitis optica may be a prototypic demyelinating disorder from which, through genetic stratification and selection in response to epidemic microbial challenge, changes occurred in the immunopathogenesis, histological complexity and distribution of lesions converting to the phenotype of relapsing remitting multiple sclerosis.