Complexity and heterogeneity in demyelinating disease

In 1894, Eugène Devic (1858–1930) described a 45-year-old female hatter in whom ‘l’autopsie révèle l’existence d’un foyer de myéline aiguë diffuse localisé à la région du renflement lombaire et d’une névrite optique double bien marquée’... the autopsy showed a focus of acute diffuse myelitis localized to the lumbar enlargement, as well as a distinct bilateral optic neuritis (Devic, 1894). He called the condition ‘neuromyélite optique aiguë’.

Subsequently, it has not proved easy to establish the relationship between neuromyelitis optica and multiple sclerosis. Epidemiological studies performed during the second half of the 20th century show clearly that the typical form of demyelinating disease in Africa, Asia, the Far East and Aboriginal populations is neuromyelitis optica or optic-spinal multiple sclerosis. The relapsing-remitting phenotype, affecting many sites within the brain and spinal cord, is relatively uncommon by comparison with these features of multiple sclerosis in northern Europeans. Until recently, criteria for the diagnosis of neuromyelitis optica included: bilateral optic neuritis and acute myelitis with no evidence for clinical disease in other parts; a spinal lesion extending over ≥3 segments on MR imaging and without cerebral lesions; abnormal cerebrospinal fluid with >50 wbc or >5 neutrophils; and the course either monophasic or relapsing and remitting (Wingerchuk et al., 1999).

Meanwhile the neuropathology of human demyelinating disease was undergoing re-evaluation. Neuromyelitis optica is characterized by extensive demyelination with partial necrosis of the spinal cord white and grey matter, acute axonal injury, eosinophil and granulocyte inflammatory infiltrates, deposition of IgG and IgM, and perivascular complement activation (Lucchinetti et al., 2002). These features mimic those seen in some more typical cases of multiple sclerosis—the so-called pattern II that, alongside cases characterized by predominant T cell and macrophage infiltration (pattern I), hypoxia-like changes (pattern III) or primary damage to oligodendrocytes (pattern IV) supports the concept of ‘heterogeneity’ (Luchinetti et al., 2000). The gratifying response to plasma exchange in a proportion of patients with neuromyelitis optica or the pattern II neuropathology of multiple sclerosis suggests a primary pathogenic role for antibody and complement in these cases (Keegan et al., 2002; 2005).

A key step forward in this evolving story came with the description of a serum biomarker—IgG binding to mouse brain sections—in neuromyelitis optica (NMO-IgG), and its subsequent characterization as an anti-aquaporin (AQP) 4 autoantibody (Lennon et al., 2004; 2005). AQP4 is a homotetrameric integral plasma membrane protein, anchored in the astrocytic foot processes and therefore contacting endothelial cells and the pial surface, that acts as a water-channel protein in the central nervous system. Against this background, and the recognition that clinical and radiological features of neuromyelitis optica are not invariably confined entirely to the optic nerves and spinal cord, a revised definition of neuromyelitis optica includes optic neuritis and myelitis with ≥2 of three 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 (Wingerchuk et al., 2006). Can the NMO-IgG biomarker now be used to illuminate the relationship between neuromyelitis optica and multiple sclerosis. Four papers in the present issue address this question.

Toshiyuki Takahashi and colleagues (2007) from Tohoku and Sendai, Japan (p. 1235), compare assays that distinguish antibody directed against cells transfected with human AQP4 and the anti-murine NMO-IgG in 121 cases including those meeting the diagnostic criteria or considered high-risk for neuromyelitis optica, and others with multiple sclerosis, clinically isolated syndromes or miscellaneous diseases. The correlation between anti-AQP4 antibody and NMO-IgG is good, with high diagnostic sensitivity and specificity. The discordant cases and those with positive but low titres of anti-AQP4 antibody have the high-risk syndrome but lack spinal lesions extending over ≥3 segments; and, conversely, higher antibody titres—demonstrated using either assay—are associated with more extensive and severe optic nerve, cerebral and spinal disease. Takeshi Matsuoka and investigators (2007) from Kyushu, Japan (p. 1206) report on 113 patients with relapsing syndromes classified as optic-spinal or classical multiple sclerosis, each tested for anti-human AQP4 antibody and NMO-IgG: they find that discrepancies between these assays generally comprise negative tests for anti-AQP4 antibody in the presence of low titre NMO-IgG. Thus, within the spectrum of demyelinating disease,
anti-AQP4 antibody is an equally sensitive and highly specific biomarker for neuromyelitis optica and its high risk syndrome as MO-IgG.

Shanu Roemer and colleagues from the Mayo Clinics and National Institutes of Health (USA), Vienna (Austria) and Göttingen (Germany: p. 1194), report on neuropathological material from 36 individuals of whom 9 had neuromyelitis optica. First, they show that AQP4 is normally distributed in the optic nerves, brainstem and spinal cord—sites preferentially affected in neuromyelitis optica—and with relatively low expression in supratentorial structures. Staining is localized to astrocyte foot processes and the abluminal surface of blood vessels and has a meshed rim and rosette pattern. Whereas there is increased expression in active and recently remyelinated lesions, AQP4 is lost in the chronic lesions of multiple sclerosis. Conversely, AQP4 is not detectable in the antibody and complement rich optic nerve and spinal cord lesions of neuromyelitis optica irrespective of how much demyelination or astrocyte reactivity are present. These abnormalities differ from the pattern II lesions of multiple sclerosis both in the deposition and distribution of antibody and complement, and in the increased periplaque expression of AQP4 in association with reactive astrocytes and their foot processes. Tatsuro Misu and investigators (2007) from Sendai and Niigata, Japan, add to their previous case report (Misu et al., 2006), details of AQP4 deposition in a variety of clinical contexts (p. 1224). They also describe a normal distribution of AQP4 that matches the preferred lesion sites in neuromyelitis optica, and demonstrate that AQP4 is more or less invariably lost in the long and transverse necrotic and cystic cord lesions of neuromyelitis optica, along the perivascular sleeves rich in immune complex deposition, and often out to the pial surface of the cord, irrespective of the amount of inflammation and demyelination. Significantly, the loss of AQP4 matches that of glial fibrillary acidic protein (GFAP), a marker of reactive astrocytes some of which reveal antibody and complement laden swollen foot processes. Conversely, the lesions of multiple sclerosis (and also examples of brain infarction) show increased AQP4 and GFAP staining with integrity of the astrocyte foot processes.

Together, these two neuropathological studies suggest that, in contrast to multiple sclerosis where AQP4 expression varies directly with astrocyte reactivity, complement activating anti-AQP4 antibody binding the extracellular domain of the AQP4 water channel localized on the foot processes of astrocytes that define vascular and pial boundaries of the central nervous system initiates the lesions of neuromyelitis optica. Evidently, these events precede the development of inflammation, demyelination, necrosis and cavitation. Perhaps what happens is transient functional impairment of the normal astrocytic control of water flux that follows the initial binding of IgG to AQP4—an effect that may be compensated where tissue is richly endowed with AQP4 and not resulting in any pathological changes under these circumstances.

Given these differences in the neuropathology, and high sensitivity and specificity of the anti-AQP4 and NMO-IgG assays, one turns to the clinical descriptions of Matsuoka et al., (2007), cataloguing details of their 113 patients with relapsing–remitting disorders categorized as the optic-spinal or conventional form of multiple sclerosis, expecting confirmation that these disorders are neatly segregated. Much hinges on the status of the long (≥3 segments) cord lesions demonstrated by MR imaging during either the acute or chronic stages. Commonly observed in neuromyelitis optica, these are generally rare in Western multiple sclerosis but observed not infrequently in patients from Asia otherwise meeting diagnostic criteria for multiple sclerosis. As expected, the commonest phenotype in cases with anti-AQP4 antibody is optic-spinal multiple sclerosis. But by no means all such patients are sero-positive, and several combinations appear counter-intuitive. The group of sero-positive individuals with the conventional phenotype of multiple sclerosis and optic-spinal individuals without NMO-IgG/anti-AQP4 antibody are often older-onset females with high relapse rates and severe disability who nevertheless do not enter the secondary progressive phase; over and above the defining features of conventional and optic-spinal multiple sclerosis, respectively, they have a high frequency of episodes manifesting as optic neuritis and myelitis; and their cerebrospinal fluid is more active but with a lower frequency of oligoclonal bands. Some differences in the number, distribution and shape of cerebral MR abnormalities are seen in this mixed group by comparison with sero-negative conventional multiple sclerosis and sero-positive optic-spinal cases. But more revealing are the spinal cord appearances. Almost one-third of sero-positive cases with conventional multiple sclerosis have long thoracic spinal lesions involving the central grey matter—features that differ from sero-negative optic-spinal disease in whom the cord is more diffusely involved, both in the transverse and longitudinal dimensions. In order to offset the possibility that lumping neuromyelitis optica with optic-spinal multiple sclerosis has confounded matters, the authors consider cases meeting the new criteria for neuromyelitis optica with the remaining examples of sero-negative optic-spinal multiple sclerosis having long spinal lesions. Whilst the distinctions from conventional multiple sclerosis are preserved for both groups, individuals with neuromyelitis optica are invariably female, older at onset and with a higher relapse rate. They have more brain MR lesions but slightly shorter spinal MR abnormalities, and less active cerebrospinal fluid.

Matsuoka et al. (2007) return to the debate of whether neuromyelitis optica is fundamentally different from conventional multiple sclerosis. First, they hedge their bets by proposing that since AQP4 sero-positivity sits uncomfortably with any one clinical or radiological
phenotype, the term ‘autoimmune aquaporinopathy’ might be used. But in debating why long spinal lesions may occur in conventional Japanese multiple sclerosis—patients who, in all other respects, match multiple sclerosis as seen in Europeans—and notwithstanding the possibility that the long lesions are merely coalesced multiple areas of abnormality, the authors then come to the nub of the matter. These may be cases that are intermediate between sero-positive neuromyelitis optica and sero-negative multiple sclerosis—the optic-spinal phenotype and long spinal lesions marking such transitional cases. They list the many features that seem to straddle the polar groups of neuromyelitis optica and regular multiple sclerosis: periventricular ovoid lesions defined radiologically representing sharply defined histological areas of acute demyelination; no difference in frequency of atypical brain lesions observed in sero-positive neuromyelitis optica across the three groups; and occasional long lesions in anti-AQP4 negative conventional multiple sclerosis. Perhaps the most telling link between these putatively different conditions is the switch in clinical phenotype from optic-spinal to conventional multiple sclerosis in Japan (Kira et al., 1999), coinciding with changes in industrialization, and in the French West Indies with patterns of migration (Cabre et al., 2005).

We have suggested elsewhere that neuromyelitis optica is an original and 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 resulting in the phenotype of relapsing remitting multiple sclerosis (Compston, 2004; Cox et al., 2005). On a shorter timescale cultural changes may expose the intrinsic vulnerability of individuals at risk of demyelinating disease encountering infections at a crucially altered phase of maturation in their immune repertoire. The description of intermediate cases revealed by stratification around a biomarker likely to reflect early events in the pathogenesis of the disorder described 113 years ago by Eugene Devic strengthens the case for an evolutionary formulation on the origins of multiple sclerosis, and one that is testable using the matrix of informative populations, genetic markers, and discrete clinical syndromes now defined.

Alastair Compston
Department of Clinical Neurosciences
University of Cambridge Clinical School
Cambridge, CB1 2QQ, UK
E-mail: alastair.compston@medschl.cam.ac.uk

References