Neuromyelitis optica and anti-aquaporin-4 antibodies: widening the clinical phenotype

G Giovannoni

Presence of anti-aquaporin-4 antibodies in patients with neuromyelitis optica has wide implications

The phenotypic spectrum of the idiopathic inflammatory demyelinating disorders of the central nervous system (CNS) suggests that neuromyelitis optica (NMO), which includes Devic's disease, is a distinct clinical entity separate from classic or conventional multiple sclerosis.¹ NMO is also phenotypically similar to the opticospinal form of multiple sclerosis (OSMS) that occurs commonly in Asian populations with multiple sclerosis.² NMO and OSMS, by definition, involve the optic nerves and spinal cord. They tend to be severe diseases, typically causing complete transverse myelitis associated with longitudinally extensive lesions, as seen on magnetic resonance imaging (MRI), which may evolve to form a syrinx. An MRI of the brain is typically normal. NMO is often associated with a mild cerebrospinal fluid (CSF) pleocytosis, which is often polymorphonuclear in nature. Locally synthesised oligoclonal immunoglobulin G (IgG) bands are typically absent in NMO.¹ Pathologically, NMO is characterised by necrosis, eosinophilic and neutrophilic infiltrates, vascular proliferation, and hyalinisation and complement activation in a perivascular "rosette" pattern.^{1,3} These clinical and pathological features are uncommon in patients with multiple sclerosis.³

In 2004, the Mayo Clinic group, by using indirect immunofluorescence, reported a characteristic autoantibody staining pattern of CNS tissues with serum from cases with NMO; IgG was shown to outline CNS microvessels of the pia, subpia and Virchow–Robin spaces and co-localised with laminin.⁴ They aptly named this autoantibody NMO-IgG.⁴ The sensitivity and specificity of the NMO-IgG staining pattern in distinguishing cases of NMO and OSMS from related neurological disorders, including cases of conventional multiple sclerosis, were 73% (95% confidence interval (CI) 60 to 86) and 91% (95% CI 79 to 100) for NMO, and 58% (95% CI 30 to 86) and 100% (95% CI 66 to 100) for OSMS. More recently, they have

shown that NMO-IgG binds selectively to aquaporin (AQP)4,⁵ the predominant CNS water channel.

AQPs are a family of membrane-inserted water channel proteins providing a pathway for osmotically driven water transport through cell membranes. They have a vital role in the reabsorption of water from the renal tubular fluid.⁶ A failure to insert AQP molecules into renal tubular membranes causes nephrogenic diabetes insipidus.⁶ In the CNS, AQP1 is restricted to the apical domain of the epithelial cells of the choroid plexus. AQP4 is expressed on astrocytic foot processes and ependymocytes. AQP9 is localised in tanyocytes (hypothalamic bipolar cells bridging the CSF and the hypothalamic portal capillaries) and astrocytic processes.⁷ Messenger RNA expression of AQP3, AQP5 and AQP8 has also been reported to occur in cultured astrocytes.⁷ AQPs in the CNS have a role in osmoreception, potassium siphoning and CSF formation, and are strongly implicated in the pathogenesis of cerebral oedema.⁷

Involvement of the brain has been considered to be an exclusion criterion for the diagnosis of NMO.⁸ Abnormalities on MRI scans of the brain have, however, been described in patients with NMO^{9–11}; they are usually non-specific, but hypothalamic and periventricular lesions may be more specific for NMO.^{9–11} AQP4 expression is not restricted to the optic nerve and spinal cord: the hypothalamic and periventricular distribution of AQP4 seems to correspond with distribution of lesions as evident on the MRI of patients with NMO-IgG.¹²

In this issue, Nakashima *et al*¹³ (see p 1073) report that NMO-IgG was detected in 14 Japanese patients with multiple sclerosis; 12 (63%) had OSMS and 2 (15%) had conventional multiple sclerosis. Not unexpectedly, NMO-IgG-positive patients differed from those with conventional multiple sclerosis: longitudinally extensive spinal cord lesions and persistent visual loss (no

light perception) were more common in the NMO-IgG-positive patients.¹³ Importantly, the two NMO-IgG-positive patients with conventional multiple sclerosis had unusual brain lesions, but in other respects had features suggesting OSMS. This and other data support the supposition that OSMS and NMO are the same disease and widen the phenotype of NMO to include cases with brain involvement.

Should NMO-IgG/or anti-AQP4 antibody positivity be included as part of the diagnostic criteria for NMO? Until the NMO-IgG and anti-AQP4 antibody assays are validated and made widely available, and these findings are confirmed by independent groups, it would be wise to consider anti-AQP4-associated neurological disorders to be an emerging clinical entity. It would also be premature to refine the diagnostic criteria for NMO. As soon as a specific biomarker for a well-defined disease is described, the clinical phenotype associated with the biomarker widens—that is, the so-called phenotypic spread. This is already occurring; involvement of the brain, particularly the hypothalamus and periaqueductal grey matter, is already considered to be part of the clinical spectrum of NMO.^{9–11,14} I suspect that cases of idiopathic relapsing myelitis¹⁵ and chronic relapsing inflammatory optic neuropathy¹⁶ will also have to be included in the wider phenotype.

Distinguishing between NMO-IgG-positive patients and those with other inflammatory CNS disorders—for example, multiple sclerosis—will be important, as there will be therapeutic implications. NMO tends to be severe, has a strong tendency to relapse and seems to respond to immunosuppressive strategies. At present, long-term immunosuppression with a combination of azathioprine and corticosteroids is recommended.¹⁷ Similarly, NMO-IgG-positive syndromes may prove to be responsive to therapeutic plasma exchange.¹⁸

What are the wider implications of NMO-IgG or anti-AQP4 antibodies? It is tempting to speculate that anti-AQP4 antibodies are functionally relevant and are responsible for the clinical presentation of NMO. Results of passive transfer animal experiments and in vitro functional AQP4 experiments are eagerly awaited. It will also be important to establish an appropriate animal model. This emerging clinical entity raises the question of whether other, possibly non-immune-mediated, reversible AQP4 channelopathies exist. Obvious candidates include pre-eclampsia, eclampsia, posterior reversible encephalopathy syndrome, cyclosporin-associated encephalopathy and other causes of cerebral

oedema, such as that associated with fulminant hepatic failure.

J Neurol Neurosurg Psychiatry 2006;**77**:1001–1002.

doi: 10.1136/jnnp.2006.090944

Correspondence to: G Giovannoni, Department of Neuroinflammation, Institute of Neurology, University College London, Queen Square, London, UK; G.Giovannoni@ion.ucl.ac.uk

Published Online First 17 May 2006

REFERENCES

- 1 Weinshenker BG. Neuromyelitis optica: what it is and what it might be. *Lancet* 2003;**361**:889–90.
- 2 Weinshenker B. Western vs optic-spinal MS: two diseases, one treatment? *Neurology* 2005;**64**:594–5.
- 3 Lucchinetti CF, Mandler RN, McGovern D, et al. A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. *Brain* 2002;**125**:1450–61.
- 4 Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet* 2004;**364**:2106–12.
- 5 Lennon VA, Kryzer TJ, Pittock SJ, et al. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *J Exp Med* 2005;**202**:473–7.
- 6 Bedford JJ, Leader JP, Walker RJ. Aquaporin expression in normal human kidney and in renal disease. *J Am Soc Nephrol* 2003;**14**:2581–7.
- 7 Lehmann GL, Gradilone SA, Marinelli RA. Aquaporin water channels in central nervous system. *Curr Neurovasc Res* 2004;**1**:293–303.
- 8 Wingerchuk DM, Hogancamp WF, O'Brien PC, et al. The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology* 1999;**53**:1107–14.
- 9 Poppe AY, Lapierre Y, Melancon D, et al. Neuromyelitis optica with hypothalamic involvement. *Mult Scler* 2005;**11**:617–21.
- 10 Nakamura M, Endo M, Murakami K, et al. An autopsied case of neuromyelitis optica with a large cavitory cerebral lesion. *Mult Scler* 2005;**11**:735–8.
- 11 Misu T, Fujihara K, Nakashima I, et al. Intractable hiccup and nausea with periaqueductal lesions in neuromyelitis optica. *Neurology* 2005;**65**:1479–82.
- 12 Pittock SJ, Weinshenker B, Lucchinetti CF, et al. MRI brain lesions characteristic of neuromyelitis optica (NMO) colocalize with sites of high aquaporin protein concentrations. *Neurology* 2006;**S22**:004.
- 13 Nakashima I, Fujihara K, Miyazawa I, et al. Clinical and MRI features of Japanese MS patients with NMO-IgG. *J Neurol Neurosurg Psychiatry* 2006;**77**:1073–5.
- 14 Pittock SJ, Lennon VA, Krecke K, et al. Brain abnormalities in neuromyelitis optica. *Arch Neurol* 2006;**63**:390–6.
- 15 Chan KH, Tsang KL, Fong GC, et al. Idiopathic severe recurrent transverse myelitis: a restricted variant of neuromyelitis optica. *Clin Neurol Neurosurg* 2005;**107**:132–5.
- 16 Kidd D, Burton B, Plant GT, et al. Chronic relapsing inflammatory optic neuropathy (CRION). *Brain* 2003;**126**(Pt 2):276–84.
- 17 Wingerchuk DM, Weinshenker BG. Neuromyelitis Optica. *Curr Treat Options Neurol* 2005;**7**:173–82.
- 18 Keegan M, Pineda AA, McClelland RL, et al. Plasma exchange for severe attacks of CNS demyelination: predictors of response. *Neurology* 2002;**58**:143–6.

Ganglioside complexes in MFS

Ganglioside complexes as targets for antibodies in Miller Fisher syndrome

H J Willison

The specificity of Miller Fisher syndrome sera for ganglioside complexes may influence its pathogenesis

In the early 1990s, Kusunoki's group^{1,2} showed, in two seminal papers, that antibodies directed against the ganglioside GQ1b were present in the acute-phase sera of patients with Miller Fisher syndrome (MFS). Since then, numerous studies have been published which show that anti-GQ1b antibodies and closely related anti-GT1a antibodies have a central role in MFS pathogenesis.³ In the latest paper from Kusunoki's group by Kaida *et al*⁴ (see page 1043), another fundamental issue surrounding anti-GQ1b antibodies has been uncovered, which confounds several issues and adds an intriguing layer of complexity to this highly charged subject.

Gangliosides are a large family of glycosphingolids that are concentrated in the nervous system. In Schwann cells and neuronal plasma membranes of peripheral nerves, gangliosides reside in clusters in specialised microdomains termed as lipid rafts. Here, their extracellular carbohydrate moieties are readily accessible to act as landing pads for

circulating autoantibodies, which then mediate inflammatory injury to the membrane. Autoantibodies to around 20 individual ganglioside species have been reported in Guillain-Barré syndrome (GBS) and related disorders, and many studies attest to their clinical and pathological significance.⁵

In 2004, Kusunoki's group⁵ observed that GBS-associated autoantibodies occasionally preferred to bind to mixtures of gangliosides rather than to a highly purified single-ganglioside species. By carrying out immunodetection studies in which gangliosides (GM1, GD1a, GD1b and GT1b) were admixed in varying proportions, they determined the optimum ratio of ganglioside mixtures to effect maximum binding for a range of different anti-ganglioside antibody-containing GBS sera. Most importantly, they identified some GBS sera that entirely failed to react with single-ganglioside species, but nevertheless reacted strongly with ganglioside complexes. In this study, they extended this approach to investigate a similar

phenomenon in MFS sera. Thus, anti-antibody reactivity with GQ1b or GT1a can be enhanced by the presence of additional gangliosides, including GM1, GD1a and GT1b. Furthermore, they identified one MFS serum that failed to react with either GQ1b or GT1a, yet reacted strongly with GQ1b/GM1 and GT1a/GM1 complexes, thereby accounting for at least some of the occasional MFS cases that are apparently anti-GQ1b antibody negative. Although it is too early to draw firm conclusions from the small sample size in this study, the specificity of MFS sera for GQ1b, GT1a and their respective complexes may influence the pattern of clinical features seen in this already diverse spectrum of anti-GQ1b antibody-associated disorders.

Kusunoki's studies have to date concentrated on the identification of ganglioside complexes under artificial immunoassay conditions. One crucial pathophysiological issue is the extent to which these clusters exist in the natural membrane environment of the peripheral nerve and, if so, whether they can act as stable targets for autoantibodies. A second issue that requires study is the mechanism by which antibodies to ganglioside complexes are formed, as the prediction from Kusunoki's studies is that carbohydrate complexes should be present on the bacterial and viral surfaces that trigger GBS. Various models can be proposed to support this possibility.⁶ These fascinating studies lead us towards new vistas in carbohydrate recognition by antibodies and other sugar-binding proteins (lectins), which will greatly enrich this field from both clinical and basic perspectives.