Neuromyelitis and more: the unfolding spectrum of aquaporin 4-related neurological diseases

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Since the seminal description by *Sir Thomas Clifford Allbutt* in Cambridge 1870 [1] and the systematic review by *Eugène Devic* and his student *Fernand Gault* in Lyon 1894 [2], neuromyelitis optica (NMO) or Devic's syndrome is regarded as a rare chronic disease of the central nervous system (CNS) that selectively and simultaneously affects the optic nerves and the spinal cord. In light of its chronic inflammatory nature, NMO was considered another variant of multiple sclerosis (MS), the most common inflammatory disorder of the CNS, although the quite exceptional manifestation, excluding other neurological systems such as the cerebellum, remained a puzzling issue. However, recent systematic clinical and pathological studies of this syndrome by researchers from the Mayo Clinic in Rochester suggested that NMO may represent a disease in its own right rather than a subtype of MS [3, 4]. Indeed, shortly thereafter, a serum autoantibody (called NMO-IgG) binding to CNS microvessels, pia, subpia, and Virchow-Robin spaces was identified in patients with NMO, using indirect immunofluorescence [5]. Very recently, the transfer of NMO-IgG from patients to sensitized rodents has been shown to induce pathologic CNS alterations similar to NMO [6]. The binding sites of this autoantibody were reported to co-localize with aquaporin 4 (AQP4), a water channel present on brain astrocytes [7]. After the first independent confirmation of these findings [8], AQP4 antibodies were recognized as a useful marker to differentiate NMO from MS [9, 10] and incorporated into the

revised diagnostic criteria for NMO [11]. Since then, we have witnessed enormous advances in the field, as the presence of a defined antigen facilitated the establishment of standardized detection assays and thus high throughput analysis of substantial sample numbers [12]. Within these activities, it turned out that NMO-IgG or antibodies against AQP4 can be detected in clinically limited forms as well, for example in recurrent optic neuritis or longitudinally extensive transverse myelitis (LETM). Early differentiation of NMO from MS and other inflammatory and demyelinating diseases of the CNS is highly desirable, as treatment options and prognoses differ widely, but so far has proven difficult or even impossible owing to overlap in clinical presentation, CSF and MRI findings [13]. Thus, further efforts are needed to characterize the occurrence and outcome not only of NMO, but also NMO-related neurological syndromes such as LETM and bilateral optic neuritis.

In the current issue, Bizzoco and colleagues report the combined clinical, radiological and serological findings from a patient cohort with demyelinating CNS disorders consecutively admitted to a regional neurological centre where they underwent standard diagnostic procedures including spinal cord MRI and CSF analysis [14]. Importantly, in contrast to similar retrospective studies recently published (e.g., [15]), this study included the NMO-IgG status, which was determined according to the initial description by Lennon and colleagues [5] by an indirect immunofluorescence assay. Based on the data of their unselected cohort of 850 individuals with suspected demyelinating inflammatory disease, Bizzoco and colleagues were able to identify and track patients with NMO or NMO-related syndromes. This study represents one of the largest cohorts reported so far which considered NMO-IgG status and thus gives valuable insights from the neurological bedside regarding the clinical course of this

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unfolding spectrum of disorders. Based on the revised NMO diagnosis criteria [11], the authors confirm earlier findings on the frequency of NMO and NMO-related syndromes as well as the rather guarded neurological outcome when compared to “typical” MS [3]. Importantly, their data indicate that the use of NMO-IgG as a biomarker allows identifying patients with NMO or NMO variants at early stages with limited CNS involvement. This is in line with the recent clinical experience that in the majority of cases, NMO starts with a monosymptomatic event, while the classic presentation with simultaneous bilateral optic neuritis and myelitis according to *Devic* is seen in only 10% of the patients [16]. The high specificity of NMO-IgG or AQP4 antibodies is of utmost clinical relevance, since NMO follows a relapsing-remitting course in the majority of cases, but it usually leads to more severe disability with impairment of functional vision or loss of ambulation compared to typical MS [3]. In this context, the limitations of this retrospective and open study have to be acknowledged. Ascertainment and referral biases may have influenced the results. Moreover, a major drawback is the NMO-IgG detection method used for the patient selection strategy: while showing a convincingly high specificity, the indirect immunofluorescence assay employed here has a relatively low sensitivity of only 30–45%, according to as-yet unpublished comparisons [14]. Thus, a considerable proportion of patients may have been missed and lost to follow-up. Clearly, future studies have to consider better cell-based or quantitative detection methods that utilize direct detection of AQP4 reactivity in order to identify patients at risk as early as possible [12]. The selection of such patients has immediate therapeutic consequences, since the recently reported relationship between AQP4 antibody response and clinical course [17] renders B lymphocytes an important target for treatment. Indeed, open trials reported that B lymphocyte-suppressing therapies such as the anti-CD20 monoclonal antibody rituximab or the immunosuppressant mitoxantrone prevent the occurrence of relapses [18, 19], while therapeutic experience with immunomodulatory treatments commonly used in MS such as interferon- β or glatiramer acetate is rather unsatisfactory [20, 21]. Taken together, the present study by Bizocco and colleagues highlights the importance of this syndrome as a differential diagnosis for inflammatory demyelinating diseases and hopefully encourages further attempts to investigate anti-AQP4 reactivity in longitudinal cohorts.

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