Neuromyelitis optica without typical opticospinal phenotype

Neuromyelitis optica (NMO) is an inflammatory disease of the central nervous system (CNS) characterized by severe optic neuritis (ON) and acute myelitis (AM). NMO differs in many respects from multiple sclerosis (MS). NMO-IgG is an autoantibody exclusively detected in the sera of NMO, and is directed against aquaporin-4 (AQP4), a water channel richly expressed on astrocytes in the CNS. In most series of NMO, more than half of cases are positive for AQP4 antibody. In 2006, Wingerchuk et al. proposed the revised diagnostic criteria of NMO that incorporated NMO-IgG (AQP4 antibody) status. For definite NMO the criteria require (A) ON, (B) AM and (C) at least two of three supportive criteria: (1) contiguous spinal cord MRI lesion extending over >3 vertebral segments; (2) onset brain MRI not meeting Paty’s diagnostic criteria for MS; (3) NMO-IgG seropositive status. Since publication, the revised Wingerchuk et al. criteria have been widely used for the diagnosis of NMO.

In this issue of Multiple Sclerosis, two AQP4 antibody-positive cases of ‘NMO without typical opticospinal phenotype’ that did not meet the Wingerchuk et al. criteria are reported by two Asian groups, and the authors discuss the diagnostic problem and therapeutic implications. Tanaka et al. reported from Japan an AQP4 antibody-positive woman who developed multiple cerebral and brainstem lesions with impaired consciousness at onset and later a medullary lesion causing intractable hiccup. This 35-year-old patient had no ON or AM until the last follow-up. Since bilateral hypothalamic lesions were seen on the initial MRI, disturbance of consciousness in this patient might be attributable to low cerebrospinal fluid (CSF) hypocretin-1 level as reported previously in AQP4 antibody-positive patients. Intractable hiccup with a medullary lesion as the second exacerbation is typical of NMO. The authors stressed the importance of AQP4 antibody in the differential diagnosis including MS, and argued that AQP4-autoimmune syndrome is more appropriate than NMO as their patient’s diagnosis.

Kim et al. from Korea described a 51-year-old woman who had nausea and hiccough and subsequently developed progressive cervical myelopathy over the next 4 months that led to quadriplegia and respiratory arrest. MRI showed a longitudinal lesion extending from lower medulla to C7 which was centrally located and partially gadolinium-enhanced. These MRI features are commonly seen in NMO myelitis, but a slow progression is unusual for NMO. The patient was positive for AQP4 antibody and was diagnosed with a limited form of NMO. She did not respond to high-dose intravenous methylprednisolone, but was successfully treated with plasma exchange. The authors confirmed the diagnostic value of AQP4 antibody in their case and pointed out a possible misdiagnosis of primary progressive MS in the early stage, although the case was not completely typical of primary progressive MS. In a series of 96 cases of NMO seen at the Mayo Clinic, two cases (2.1%) developed secondary progressive cervical myelopathy. Based on these facts, Kim et al. emphasized that myelitis of NMO may not always be acute and AQP4 antibody-positive cases with progressive clinical worsening can also benefit from plasma exchange.

A number of clinical studies on AQP4 antibody-positive cases make it clear that brain lesions are not uncommon in NMO and that there are AQP4 antibody-seropositive patients not fulfilling the revised Wingerchuk et al. criteria. Some of them without previous history of ON or AM may develop brain lesions as onset events, as seen in the case of Tanaka et al. and previous reports. Pathological and CSF analyses have revealed severe astrocytic damage in NMO and recent experimental studies have demonstrated the pathogenicity of AQP4 antibody. Thus, it is reasonable to think that, first, AQP4 antibody probably plays a direct pathogenic role in the CNS lesions seen in AQP4 antibody-positive cases including those in NMO without typical opticospinal phenotype and, second, these two cases comprise part of the spectrum of an ‘anti-AQP4 syndrome’.

Neither of these two cases meet the revised Wingerchuk et al. criteria, and MS was a differential diagnosis in both. One serious diagnostic problem that could occur in Asia and other regions with higher ratios of NMO to MS is that some patients with unrevealed AQP4 antibody-seropositivity may be judged as ‘not NMO’ since they do not fulfill the revised Wingerchuk et al. criteria, and be misdiagnosed as ‘MS’ or another disease, especially in regions where the AQP4 antibody test is not available. It should be noted that Wingerchuk et al. proposed the revised criteria for the diagnosis of ‘definite NMO’ but not for
defining the whole spectrum of NMO or anti-AQ4P4 syndrome, and that they also stated mindfully in the article’s abstract that ‘CNS involvement beyond the optic nerve and spinal cord is compatible with NMO."

Since therapeutic response in NMO is different from that in MS, the differential diagnosis is critically important for patient management. Neurologists should suspect an NMO spectrum disorder or anti-AQ4P4 syndrome in patients with any clinical or MRI feature of the disease and, if possible, test for AQ4P4 antibody as was done in these two cases. In the future, we may need to discuss the most appropriate name for AQ4P4 antibody-associated neurological disease.

References

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