

Impact of anti-aquaporin-4 antibody on the diagnosis and management of idiopathic demyelinating diseases of the central nervous system

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Neuromyelitis optica (NMO), characterized by severe optic neuritis and transverse myelitis was first described over 100 years ago. Until recently, the controversy as to whether NMO is a distinct clinical entity or a subtype of multiple sclerosis (MS) is still unresolved. However, the discovery of NMO-IgG or anti-aquaporin-4 (AQP4) antibody has marked a significant milestone to foster better understanding of the devastating disease. This serum autoantibody clearly distinguishes NMO from MS. Moreover, recent studies have defined the spectrum of the disease including NMO's high risk syndrome and unique brain lesions and revealed the pathogenetic role of anti-AQP4 antibody, such as loss of AQP4 in the perivascular lesions of NMO and changes in antibody titres relative to disease activity. Anti-AQP4 antibody test has already become an indispensable laboratory examination in the differential diagnosis and management of patients with idiopathic demyelinating diseases of the central nervous system, since the antibody status directly influences choice of appropriate therapy. Anti-AQP4 antibody test is particularly important in Asian countries where NMO and its related syndrome are relatively common.

Previous studies emphasized that Japanese MS patients exhibited some unique features compared with the Western patients, and they were considered racial modifications of MS in Japan, which included (1) lower prevalence of disease, (2) severe optic-spinal involvement and (3) lower frequency of oligoclonal bands. But (2) and (3) were mainly due to high ratios of NMO to MS 30-50 years ago in Japan, and the ratios have become lower in recent years. Thus, 'genuine racial modification of Japanese MS' is (1) rather than (2) and (3), since even now the prevalence of MS in Japan is as low as 8-9/100,000. There are many clinical and laboratory differences between NMO and MS. NMO is rarely a progressive disease, and female preponderance is much higher than MS. The onset age is in the thirties, and brain magnetic resonance imaging (MRI) is often abnormal. The spinal cord lesions are often longer than 3 vertebral segments and oligoclonal bands are mostly negative. On axial view of spinal cord MRI, NMO lesions are located centrally, while MS lesions are located on the lateral and dorsal columns. NMO, like amyotrophic lateral sclerosis, shows higher concentration of cerebrospinal fluid neurofilament heavy chain compared to MS.¹ Ninety percent of NMO and 85% of high-risk syndrome are positive of serum anti-AQP4 antibody, while none of the patients with MS or clinically isolated syndrome or other central nervous diseases are seropositive.² There is also a direct and strong correlation between the serum titre of anti-AQP4 antibody and the length of spinal cord lesion. Periaqueductal and hypothalamic lesions are relatively unique to NMO, and patients with high anti-AQP4 antibody titers (>254x) often had extensive or large brain lesions..^{2,4} The anti-AQP4 antibody titer tends to be lower during relapse free period, especially during treatment with immunosuppressants such as azathioprine or corticosteroid.²

In a study by Nakashima⁴, 77 optic-spinal MS patients in Japan were divided into 2 groups, those with spinal cord lesions longer than 3 vertebral segments (n=51) and those without (n=26). Optic-spinal MS were defined as patients with recurrent optic neuritis and myelitis with or without mild brainstem signs in that study. The statistical significant differences between these two groups of patients include that the patients with long cord lesions were older (53 ± 15 versus 41 ± 15 years), had older onset age (38 ± 13 versus 28 ± 11 years), higher female to male ratio (16:1 versus 3.3:1), higher EDSS (median 6.0, range 1-10 versus median 2.0, range 0-8.5), higher proportion of transverse myelitis (71% versus 38%) and sustained severe optic neuritis (67% versus 23%), and serum anti-nuclear antibody (56% versus 24%), but lower proportion of periventricular ovoid lesions (12% versus 42%) and serum HLA-DRB1*1501 (27% versus 67%).

References

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