

## **IS THE ASIAN OPTICO-SPINAL MS A DISTINCT ENTITY OR PART OF THE NMO SPECTRUM?**

**Kazuo Fujihara**

*Department of MS Therapeutics, Tohoku University School of Medicine, Sendai, Japan*

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system. Although the prevalence of MS in Asia is lower than the figures in Western countries, the number of MS cases has been constantly increasing in this region. Neuromyelitis optica (NMO) has been described as a disease clinically characterized by severe optic neuritis and transverse myelitis. The relationship between NMO and MS, that is, whether NMO is a variant of MS (optic-spinal MS, OSMS) or a distinct clinical entity, has been debated.

We can divide the history of MS and NMO in Japan into three periods. I) Before 1950s, there had been few cases of MS, while some autopsy cases with features of NMO were reported. II) Since 1960s, Japanese neurologists started to find and recognize MS in the country and then the number of MS cases in Japan increased gradually. Comparative studies of Japanese and other Asian MS and Western MS consistently showed that the proportions of cases clinically characterized by severe optic neuritis and transverse myelitis were much larger in Asian MS than in Western patients, and thus OSMS was considered a unique feature of "Asian MS" as compared with Western MS. In Japan, the term "NMO" and Devic's disease were used only for monophasic opticomyelitis at that time probably because the single autopsied case reported by Eugene Devic in 1894 followed such a clinical course. III) However, after NMO-IgG, an NMO-specific autoantibody, was reported in 2004, and the target antigen was identified as aquaporin (AQP)-4, that is NMO-IgG = anti-AQP4 antibody, the recognition of NMO has grown remarkably in Japan. Meanwhile, "OSMS" has been used far less these days.

Before the wide recognition of NMO, MS had often been classified into two subtypes based on lesion distribution in Asia. Conventional MS (CMS) represented MS with brain lesions, and OSMS was defined as MS with optic neuritis and myelitis alone. But whether minor or a small number of brain lesions were acceptable for OSMS or not was unresolved. To look into this issue further, we analyzed "pure OSMS" defined by the following three criteria, (i) clinically selective involvement of the optic nerves and spinal cord, (ii) normal brain MRI, and (iii), longer than 5 years of follow-up. As a result, 10 out of 118 patients met the criteria. Female preponderance and negative oligoclonal IgG bands were the common features, but the clinical disabilities ranged from mild to severe and mild cases were often positive for DRB1\*1501, an HLA type relatively common in Western MS.

More than a few Japanese studies clearly demonstrated that the proportions of cases with optic neuritis and transverse myelitis to those with brain lesions have been steadily declining in the last 30 ~ 50 years, suggesting so-called OSMS is no longer the unique feature of Japanese MS. We conducted a collaborative survey of 77 cases of "OSMS" defined by the Kira's criteria [(i) clinically estimated main lesions are confined to the optic nerve and spinal cord, (ii) neither cerebellar nor cerebral symptoms, (iii) minor brainstem signs are acceptable, and (iv) at least one relapse]. We found two subtypes of OSMS, 1) cases with longitudinally extensive spinal cord lesions (LESL) (n=51) had features of NMO and 2) those without LESL (n=26) were similar to MS in many respects. Another interesting finding was that cases resembling MS have increased recently while those with NMO-like disease remain constant.

The discovery of NMO-IgG (anti-AQP4 antibody) (Lennon et al, Lancet 2007) was truly a milestone in the field. In this collaborative study, the autoantibody highly specific to NMO was detected in 73% of North American NMO patients and 58% of Japanese OSMS patients, but we enrolled Japanese patients who fully met the Wingerchuk's 1999 Criteria (optic neuritis, acute myelitis and no demyelinating evident beyond optic nerve and spinal cord) as OSMS, and those who completely fulfilled the McDonald Criteria including the MRI criteria as CMS because we thought that enrolling both NMO-like and MS-like "OSMS" in the study would be problematic and make data interpretation difficult. Various assays to detect anti-AQP4 antibody have been developed, and the sensitivities vary from one assay to another while the specificities are very high. Human AQP4-transfected cell-based assays are the most sensitive.

The subsequent studies using anti-AQP4 antibody delineated a number of clinical, MRI, laboratory and pathological features of the NMO spectrum, and they strongly suggest that NMO is a clinical entity distinct from MS. More than half of the seropositive patients develop brain lesions, and some of the lesions appear to be diagnostic. Thus, cases with brain lesions can be either MS or NMO, and the same is true of cases with optic neuritis and myelitis alone. In other words, the lesion site-based classification of MS is not valid any more. The 2010 revisions to the McDonald Criteria of MS clearly stated that NMO should be separated from MS.

In conclusion, "typical Asian" OSMS corresponds to NMO and "all" OSMS is an admixture of NMO and MS.