Short Commentary for “Features of anti-aquaporin 4 Antibody-Seronegative Thai Patients with Neuromyelitis Optica Spectrum Disorders: A Comparison with Seropositive Cases”

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Neuromyelitis optica (NMO) is an inflammatory CNS syndrome distinct from multiple sclerosis (MS) in their pathogenesis, clinical manifestations and neuroimaging findings [1]. According to the recent international consensus on diagnostic criteria for neuromyelitis optica spectrum disorders (NOMS) 2015, the new criteria combine “definite NMO” and “NOMSD” into one term “NMOSD”. NMOSD was stratified further by serologic testing into NMOSD with or without presence of AQP4-antibody together with the 6 core clinical symptoms including clinical syndromes or MRI findings associated with optic nerve, spinal cord, area postrema, other brainstem, diencephalic, or cerebral manifestations. More stringent clinical criteria with MRI findings compatible with those seen in NMOSD are required for a diagnosis of seronegative NMOSD [2].

To identify patients with seronegative NMOSD is a challenge for clinical practice. Several considerations are needed. Firstly, method used for AQP4-antibody detection is crucial to confirm the seronegativity. At present, cell-based assay (CBA) is the best available method with high sensitivity and specificity. The time of blood samples taken is also important and is best done during relapses and before treatment either with steroids, immunosuppressants or plasmapharesis as treatments can lower antibody titer to the undetectable level [3,4]. Serial monitoring of AQP4-antibody is warranted in seronegative cases highly suspicious of NMOSD. Secondly, many studies including ours demonstrated that seronegative NMOSD differs from seropositive NMOSD in several aspects: having less lengthy TM, more favorable visual outcome, lower number of attacks, lower annualized relapse rate and less female predominance. [5-8] Notably, in seronegative NMOSD, bilateral optic neuritis (ON) was frequently detected as an initial presentation, and there was a trend of having fewer patients with spinal cord involvement over 3 vertebral segments (VBS). Moreover they can have mild CSF pleocytosis and presence of CSF oligoclonal bands (OCB) similar to findings in MS (5-6).

There were reports that in seronegative NMOSD with non-MS phenotype, anti-MOG-antibody was found in approximately 20 percent [9-12]. Recent studies showed that optic nerve involvement associated with both anti-MOG and anti-AQP4 were commonly bilateral and lengthy, but the former had a better visual recovery [9-12].

ON in seropositive NMOSD was at the posterior optic pathway and chiasmatic involvement was more frequent. On the contrary, in seronegative NMOSD, involvement was anterior, similar to those found in MS, with sparing of the optic chiasma [9-12]. Other cerebral lesions, e.g., ADEM-like MRI findings, were also reported [13]. In general, MOG-associated seronegative NMOSD can have clinical presentations resembling NMO (having ON, more commonly bilateral, or myelitis, either with short segments or as longitudinally extensive transverse myelitis) as well as MS (positive CSF-OCB and brain lesions).

Therefore it is hard to classify patients presenting with equivocal clinical manifestations, typical in parts for MS and NMO, especially in seronegative NMOSD. Further biomarker testing may be needed for those with the overlapping clinical spectrum. Patients with anti-MOG present in both serum and CSF showed an increase in MBP but not GFAP [14]. This implies that the autoimmune process might cause CNS demyelination rather than astrocytopathy as observed in cases with seropositive AQP4-antibody and probably contributed to the good functional recovery in anti-MOG-positive patients. Further studies are needed to determine the specific role of anti-MOG antibody in the pathogenesis. Whether the seropositive and seronegative NMOSD are two separate disease entity or a spectrum of one condition remains to be clarified.

Based on previous studies showing that NMOSD patients with AQP4-antibody positive who present with ON or TM are at risk of having future attacks. Since disability in NMOSD is attack-related, starting treatment with immunosuppressant early to prevent future attacks is recommended [15]. In contrast, it is still unclear how to manage patients with seronegative NMOSD. Although the chance of getting a second attack is lower compared to seropositive group, but some patients can still have relapsing form. In addition, they might exhibit severe brainstem syndrome or high cervical cord involvement with respiratory insufficiency. Decision to start immunosuppressants early to prevent future relapses can be reached after thorough discussion about risks and benefits of the treatment between the patient and the physician.

In conclusion some seronegative NMOSD patients may have clinical syndrome indistinguishable from MS or AQP4-antibody positive NMOSD, but their course and prognosis seem to be different. Future studies together with researches on biomarkers in each patient group may answer these issues.

References

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Received September 29, 2015; Accepted October 19, 2015; Published October 26, 2015


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