

**Growing Excellence in Multiple Sclerosis Symposium  
8– 9 September 2007, Taipei, Taiwan**

**Editor: HT Chong**

**Aquaporin-4 IgG among Japanese multiple sclerosis patients**

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*Background and Objective:* Optic-spinal multiple sclerosis (MS) in Asians has similar features to relapsing-remitting form of neuromyelitis optica (NMO). Asian optic-spinal MS seems to be the same as NMO based on the frequent detection of NMO-IgG. The molecular target of NMO-IgG was recently identified as aquaporin-4 (AQP4) water channel protein, and we have established human cell lines stably expressed human AQP4 protein to detect the antibody against AQP4 in the sera. We report here the positive rates of anti-AQP4 antibodies in a group of Japanese MS patients and discuss the clinical implication of this antibody.

*Methods:* Full length human AQP4 cDNA was cloned into pcDNA-DEST53 vector to fuse GFP to the N-terminus of AQP4 protein. Human embryonic kidney HEK-293T cells were stably transfected with this GFP-AQP4 fusion protein expression vector using FuGENE6 Transfection Reagent according to the manufacturer's instructions. Sera from 113 consecutive Japanese patients with clinically definite MS, based on the Poser criteria, were assayed for anti-AQP4 antibodies by immunofluorescence using HEK-293T cells expressing GFP-AQP4 fusion protein.

*Results:* The sensitivity of the anti-AQP4 antibody assay was 83.3% and the specificity was 100%, using sera predetermined for the NMO-IgG status by Mayo clinic. The anti-AQP4 antibody positivity rate was 27.1% (13/48) in optic-spinal MS patients, and 5.6% (3/54) in conventional MS patients. None of the 11 brainstem-spinal MS patients, 52 other neurological diseases and 35 healthy controls gave positive results. Of the 4 idiopathic recurrent transverse myelitis patients, only 1 (25%) was seropositive. The antibody positivity rate was highest in optic-spinal MS patients with longitudinally extensive spinal cord lesions (LESCLs) extending over three vertebral segments and Barkhof's brain lesions (55.6%). The anti-AQP4 antibody was exclusively found in females. Multiple logistic analysis revealed that anti-AQP4 antibody was positively associated with the numbers of exacerbations and optic-spinal MS and negatively associated with the HLA-DRB1\*0405 allele. Although there were many common clinical features between anti-AQP4 antibody-positive MS and antibody-negative optic-spinal MS with LESCLs, the LESCLs in anti-AQP4 antibody-positive patients were preferentially located at the upper-to-middle thoracic cord, while those in anti-AQP4 antibody-negative optic-spinal MS patients appeared throughout the cervical-to-mid-thoracic cord. On axial planes, the latter more frequently exhibited the holocord involvement pattern, while the former more frequently showed the central gray matter pattern. LESCLs were observed in 29.4% (15/51) of anti-AQP4 antibody-negative conventional MS patients during entire disease course. Anti-AQP4 antibody-positive MS patients fulfilling definite NMO criteria showed a greater frequency of brain lesions fulfilling either Barkhof or Paty criteria than antibody-negative optic-spinal MS patients with LESCLs.

*Conclusion:* There are cases of anti-AQP4 antibody-positive MS/NMO and anti-AQP4 antibody-negative optic-spinal MS with LESCLs but few brain lesions in Japanese. This indicates that the mechanisms producing LESCLs in optic-spinal MS patients are heterogeneous, i.e. both anti-AQP4 antibody related and unrelated.