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Anti-aquaporin 4 antibody test in a large series of Japanese optic-spinal multiple sclerosis and neuromyelitis optica

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Anti-aquaporin 4 antibody (AQP4-Ab) is detected specifically with high sensitivity in optic-spinal form of multiple sclerosis (OSMS)/neuromyelitis optica (NMO). We established the immunofluorescence detection system of NMO-IgG and AQP4 antibody (AQP4-Ab) using human AQP4 cDNA-transfected HEK 293 cells and examined NMO-IgG/AQP4-Ab in a large series of Japanese OSMS/NMO patients since 2006.

As for NMO-IgG detection, we used cryostat sections from rat cerebrum and cerebellum with indirect immunofluorescence detection system. For AQP4-Ab detection, we cloned human AQP4-cDNA from human brain total RNA. The cDNA was then inserted into expression vector, and HEK 293 cells were transfected with this vector. The cells were then fixed with 4% paraformaldehyde/PBS, incubated with the patients' sear or CSF, and finally with FITC-conjugated anti-human IgG.

We tested AQP4-Ab in 2,076 samples with Japanese OSMS/NMO patients and found 569 AQP4-Ab positive cases. Among them, 450 of AQP4-Ab positive sera/CSF were from women (79.1%). AQP4-Ab positive group showed higher age of onset, higher percentages of blind or bed-ridden patients, higher EDSS scores; 75% of them showed long spinal cord lesions of more than three vertebrate segments on spinal MRI (Table 1).

Those with AQP4-Ab negative contained heterogeneous group of patients, so we compared the clinical features between AQP4-Ab positive or negative group among those with long spinal cord lesions.

Higher percentage of AQP-Ab positive patients with long spinal cord lesions were associated with Sjögren syndrome and frequently detected autoantibodies such as ANA or SS-A and SS-B. Our study with large series confirmed the characteristic features of AQP4-Ab positive group with strong

Table 1: Clinical features in AQP4-Ab (+) optic-spinal multiple sclerosis/neuromyelitis optica patients

Study parameter	AQP4-Ab (+)
Number (men/women)	569 (119/450) (women: 79.1%)
Age at onset in years	47.2±16.3
Relapsing remitting/secondary progressive/primary progressive in percent	75.8/8.1/1.3
EDSS score	6.2±2.1
Wheel chair bound/bed ridden	85/138 (38.1%)
Severe visual loss (blind)	99/116 (46.0%)
First lesion (Optic nerve/spinal cord/brainstem/cerebrum) in percent	43.9/41.0/8.1/7.0
MRI (cerebrum/cerebellum/brainstem) in percent	35.9/4.8/22.3
MRI long cord lesion (+/–) in percent	74.1/7.6
Oligoclonal band (+)/MBP (+) in percent	10.4/57.4

co-relations to female preponderance, higher age at onset, long spinal cord lesions, severe optic and spinal symptoms and other autoimmune diseases.

However, certain amount of overlap was seen between AQP4-Ab positive and negative patients. It is not yet clear that AQP4-Ab is the essential pathognomonic factor or diagnostic marker, but the certain clinical features seen in the AQP4-Ab positive cases are clearly differed from classic MS. Those with AQP4-Ab negative group might be heterogeneous with those having low titer AQP4-Ab which could not be detected by the present assay system.

To clarify the significance of AQP4-Ab, we need to show the direct role of AQP4-Ab for NMO.

References

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