A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis.

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Neuromyelitis optica (NMO) is a severe inflammatory demyelinating disease that tends to affect the optic nerves and spinal cord. This was the first study to show a specific biomarker for NMO, revolutionizing the diagnosis and treatment of NMO by (1) allowing for a clear distinction from multiple sclerosis (MS), a common early misdiagnosis, (2) allowing for early diagnosis of NMO, whose prognosis and therapeutic options are very different from MS, and (3) paving the way for future research trials which now have three FDA-approved treatments for NMO patients with this antibody. In this study, the authors assess the diagnostic accuracy of the newly-identified IgG autoantibody, called NMO-IgG at the time, which localizes to the blood-brain barrier (Note: subsequent studies of the NMO-IgG antibody revealed its target, the aquaporin-4 water (AQP4) channel, which we have come to know now in modern times).

Experimental design and statistics: The authors obtained serum from 3 groups of patients. Group 1 consisted of 102 North American patients who were clinically ascertained to have NMO or a syndrome with a high risk of conversion to NMO (see colored panel in Methods for NMO clinical criteria). Of the 102 patients in Group 1, 45 were clinically determined to have definite NMO, 35 were high-risk for NMO (either longitudinally extensive myelitis OR recurrent optic neuritis), and 22 cases were later felt to be more consistent with MS. They also included samples of control serum from patients with miscellaneous disorders including classic MS, myasthenia gravis with thymoma, paraneoplastic autoimmune disorders, neurosarcoidosis, etc. Group 2 consisted of 22 Japanese patients that were retrospectively clinically determined to have definite NMO (N=11), high-risk for NMO (N=1), typical MS as control patients (N=5), and only cerebral infarction as control patients (N=5). Group 3 consisted of 14 North American patients who were serologically ascertained by the incidental detection of a unique, unclassified, CNS-restricted autoantibody during their paraneoplastic autoantibody assessment and were retrospectively found to be NMO-IgG. For all 3 groups, serum specimens were assayed and scored as positive or negative without a knowledge of their clinical diagnosis. Serum samples were tested using indirect immunofluorescence assay.

Results: In the results section, the authors first report the immunohistochemical pattern of NMO-IgG, though clinical results are highlighted here. Of the 45 patients diagnosed with NMO in Group 1, N=33 (75%) were seropositive for NMO-IgG antibody. Of the 35 patients classified as high risk for NMO, 16 (46%) were seropositive for NMO-IgG. There were no NMO-IgG found in any patient with classic MS. There were no significant differences between seropositive and seronegative patients with respect to demographic factors, clinical status (e.g. occurrence of bilateral optic neuritis, presence of severe myelitis, number of attacks, or presence of co-existing autoimmune disease), MRI findings, or CSF abnormalities. A positive NMO-IgG result had a sensitivity of 73% and a specificity of 91% when used to discriminate patients with clinically defined NMO from those with optic neuritis or myelitis but not strict NMO criteria. In Group 2, none of the patients with a diagnosis of MS or cerebral infarction had positive NMO-IgG antibodies. They found a sensitivity of 58% and specificity of 100% for a positive NMO-IgG result in the Japanese cohort. In the Group 3 cohort, 12 of the 14 NMO-IgG positive patients met clinical criteria for the diagnosis of NMO (N=3) or high-risk syndrome (N=7 for longitudinally extensive myelitis and N=2 for recurrent optic neuritis).

Conclusions: Overall, the authors found that the NMO-IgG has a high specificity for NMO, detecting the antibody in almost ¾ of patients with this diagnosis and in nearly half of those at high risk of developing NMO. They did not detect NMO-IgG in any patients with classic MS. Thus, the study showed that the detection of NMO-IgG can enable early diagnosis of NMO, and the authors suggest that it even holds promise as a quantifiable biomarker to monitor disease progression and response to treatment.

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