ARE MS AND AQUAPORIN-4 POSITIVELY MUTUALLY EXCLUSIVE? YES

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There is little remaining controversy that neuromyelitis optica (NMO) is a different condition than MS[1]. Although the primary clinical features of NMO, transverse myelitis and optic neuritis, overlap with those that occur in prototypic MS, they tend to be more severe in NMO than in MS, and are very commonly associated with longitudinally extensive lesions in the corresponding affected CNS structures, which are rare radiological findings in prototypic MS. Interferon beta treatment and natalizumab are both beneficial for patients with MS, but both appear to exacerbate NMO[2].

Aquaporin-4 (AQP4) autoantibodies are specific to NMO[3]. However, are these autoantibodies so specific that we can diagnose NMO spectrum disorder and exclude MS from consideration whenever they are detected? Most studies evaluating the specificity of AQP4 autoantibodies have been conducted retrospectively in patients clinically classified as having either NMO or MS. Historically, performance of biomarkers is optimal in typical cases and less good when patients are studied prospectively. Increasing experience with prospective evaluation of NMO-IgG has suggested that specificity, while high (>90%), is not perfect. However, is the imperfect specificity primarily due to imperfection of the biomarker or imperfection of the clinical definition of NMO and distinction from MS and other mimics?

The phenotype of NMO has been proposed to be broader than previously recognized. The recognition of an extended phenotype of NMO ("NMO spectrum disorders") was based on the association of certain phenotypes with AQP4 autoantibodies. Initially, these phenotypes were restricted to partial phenotypes of NMO (recurrent myelitis and recurrent optic neuritis). Subsequently, the spectrum has been extended to include phenotypes with certain brain lesions accompanied by AQP4 autoantibodies. In fact, some "NMO typical" brain lesions, especially those targeting area postrema and hypothalamus, have been classified as NMO spectrum disorders even when they occur in the absence of the NMO signature syndromes of optic neuritis and transverse myelitis.

Some argue that this extension of the NMO syndrome beyond previously accepted historical boundaries that distinguish NMO from MS based on the presence of AQP4 autoantibodies indicates that AQP4 autoantibodies lack specificity. In a recent study from Thailand (coauthored by my opponent in this debate), approximately 16 of 53 patients who were seropositive for AQP4 autoantibodies (over half of the inflammatory demyelinating disease cases in this Thai series) did not meet the criteria of either NMO or NMO spectrum disorder, but were classified on purely clinical grounds as having conventional MS, "opticospinal MS", or clinically isolated syndrome[4]. Nonetheless, as the authors point out, in each misclassified case but one, clinical clues were present that should have indicated that the patients had NMO rather than MS. Based on final global analysis of the patient's diagnosis, AQP4 autoantibodies "trumped" the clinical criteria when applied in rote fashion based on dogma.

We are too early in our experience with AQP4 autoantibodies to conclude 100% specificity of the antibody. My opponent has reported that the antibody was retrospectively present in patients who later developed definitive symptoms of NMO[5], so an apparent "false positive" result could indicate preclinical disease, which is not something that one should regard as false positive.

Few if any autoantibodies, including highly specific and pathogenic antibodies such as AQP4 autoantibodies or acetylcholine receptor (AchR) autoantibodies are entirely specific. AchR autoantibodies, which are highly specific for and pathogenic in myasthenia gravis, may be seen as indicator of paraneoplastic autoimmunity even in the absence of clinical myasthenia gravis[6]. It is likely that some patients with AQP4 autoantibodies may harbor these antibodies as indicators of autoimmunity, paraneoplastic or otherwise. But, these occurrences would be very rare occurrence. In screening large numbers of patients with systemic lupus erythematosus and Sjogren's syndrome, we found none who were seropositive for AQP4 autoantibodies aside from those with clinical history of optic neuritis, transverse myelitis or both[7].

This is a time of continuing modification and optimization of assays for AQP4 autoantibodies. With each new method, optimization and setting of cutoffs must occur, and there is potential for

false positive results with one or other method. Using an immunoprecipitation technique, the Mayo Clinic neuroimmunology laboratory reported that some individuals had false positive results by virtue of having autoantibodies to green fluorescent protein, a fusion partner in the recombinant protein used as antigen in the assay[8]. This and other similar technical glitches will preclude perfect specificity of the assay. However, this is different than saying that AQP4 autoantibodies are nonspecific; it merely indicates that the detection of the antibodies may be subject to false positive results with some assays.

Multiple studies conducted worldwide have documented high specificity of AQP4 autoantibodies. In the recent Thai study in which consecutive patients with a variety of inflammatory demyelinating diseases were studied, seropositivity for AQP4 autoantibodies "trumped" the clinical definitions of inflammatory demyelinating disease syndromes applied by rote, though clinical judgment applying what has been recently learned about NMO syndromes led to near perfect agreement with AQP4 autoantibody seropositivity.

Should one automatically diagnose NMO in a patient who is seropositive for AQP4 autoantibodies and exclude MS? No. But, one should have a healthy respect for a positive result for AQP4 autoantibodies, and be aware that the spectrum of NMO is broader than previously suspected. Without doubt, we will continue to learn and expand the spectrum of this emerging disease.

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