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Editors' Note: In reference to "Aquaporin-4 antibody–positive cases beyond current diagnostic criteria for NMO spectrum disorders," Blum et al. describe 2 cases of patients with neuromyelitis optica spectrum disorder detected by cell-based assay but negative on ELISA. Authors Sato et al. answer their questions about aquaporin-4 antibody testing. Verghese presents a case of myoclonus in a patient with type III Gaucher disease.

—Megan Alcauskas, MD, and Robert C. Griggs, MD

AQUAPORIN-4 ANTIBODY–POSITIVE CASES BEYOND CURRENT DIAGNOSTIC CRITERIA FOR NMO SPECTRUM DISORDERS

Stefan Blum, Bob Wilson, Kerri Prain, Richard Wong, David Gills, Brisbane, Australia: Sato et al.[1] described 13 cases of neuromyelitis optica spectrum disorder (NMO-SD) and 3 of those cases had brainstem involvement in which antibodies (Ab) to the M1 isoform of aquaporin-4 (AQP4) were detected by a cell-based assay (CBA) but not by an ELISA.

We saw 2 patients with NMO-SD who had lesions in the posterior pons adjacent to the floor of the fourth ventricle. Both had a similar clinical presentation of nystagmus and intranuclear ophthalmoplegia. One subject had further relapses with intractable nausea, hiccups, and gait ataxia and developed bilateral thalamic lesions. Neither had optic neuritis or spinal cord disease and both responded well to aggressive immunosuppressive therapy.

Similar to Sato et al., sera from these subjects were positive for AQP4-Ab on a commercial CBA (Euroimmun, Luebeck, Germany) but negative by indirect immunofluorescence on unfixed rodent brain tissue, indicating a lack of binding to the native protein. It is possible that these antibodies detected an epitope exposed on the cells transfected with M1 but not on native AQP4 or in the ELISA assay. Different structural arrangement of AQP4 in cell membranes could lead to a different epitope.[2,3]

Author Response: Douglas K. Sato, Toshiyuki Takahashi, Kazuo Fujihara, Sendai, Japan: We thank Blum et al. for their comments. Their 2 cases show that AQP4-Ab seropositivity is critical for the diagnosis of the NMO-SD without typical attacks of optic neuritis, longitudinally extensive myelitis, or both.

Blum et al. also questioned the AQP4 epitopes and differences on the assay sensitivities using nonhuman AQP4, human AQP4 isoforms, or fixed material. There are differences on the rodent and the human AQP4 proteins, so some patients' AQP4-Ab may not recognize rodent epitopes, providing negative results.[4] In addition, the human AQP4-M23 used in our CBA[1] was able to form orthogonal array of particles (OAP) in the cell membrane[5] that are not observed using either AQP4-M1 or linearized AQP4 (ELISA). These OAPs increased the assay sensitivity, as antibodies are more likely to recognize this large 3D structure. We have not seen a sample that has been positive on AQP4-M1 and not on AQP4-M23, and this has been confirmed.[6,7] Finally, fixation prior to exposure (commercial CBA) to human sera may reduce assay sensitivity.[7] In our study, the cells were only fixed after the secondary antibody.

1. Sato DK, Nakashima I, Takahashi T, et al. Aquaporin-4 antibody–positive cases beyond current diagnostic criteria for NMO spectrum disorders. Neurology 2013;80:2210–2216.
2. Jarius S, Wildemann B. AQP4 antibodies in neuromyelitis optica: diagnostic and pathogenetic relevance. Nat Rev Neurol 2010;6:383–392.
3. Furman CS, Gorelick-Feldman DA, Davidson KG, et al. Aquaporin-4 square array assembly: opposing actions of M1 and M23 isoforms. Proc Natl Acad Sci USA 2003;100:13609–13614.
4. Waters PJ, McKeon A, Leite MI, et al. Serologic diagnosis of NMO: a multicenter comparison of aquaporin-4-IgG assays. Neurology 2012;78:665–671.
5. Crane JM, Lam C, Rossi A, Gupta T, Bennett JL, Verkman AS. Binding affinity and specificity of neuromyelitis optica autoantibodies to aquaporin-4 M1/M23 isoforms and orthogonal arrays. J Biol Chem 2011;286:16516–16524.
6. Mader S, Lutterotti A, Di Pauli F, et al. Patterns of antibody binding to aquaporin-4 isoforms in neuromyelitis optica. PLoS One 2010;5:e10455.
7. Marignier R, Bernard-Valnet R, Giraudon P, et al. Aquaporin-4 antibody-negative neuromyelitis optica: distinct assay sensitivity-dependent entity. Neurology 2013;80:2194–2200.

THALAMIC GLUTAMATE/GLUTAMINE IN RESTLESS LEGS SYNDROME: INCREASED AND RELATED TO DISTURBED SLEEP

Iain Jordan, Declan Murray, Dublin: Allen et al.[1] reported elevated thalamic glutamate levels in restless

Aquaporin-4 antibody-positive cases beyond current diagnostic criteria for NMO spectrum disorders

Stefan Blum, Douglas K. Sato, Bob Wilson, et al.

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