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. 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 internuclear 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 CBA1 was able to form orthogonal array of particles (OAP) in the cell membrane4 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.

© 2014 American Academy of Neurology


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
legs syndrome (RLS) and their relation to disturbed sleep. Another prospective study of RLS and sleep and the involvement of the thalamus showed that zolpidem, which is known to reduce thalamic GABA, led to striking symptomatic improvement.

We saw 2 patients with medication-induced akathisia; the first patient took haloperidol and the other venlafaxine. Both patients showed marked response to zolpidem prescribed incidentally for insomnia. They elected to stay on their psychotropic medication due to the beneficial effect on their mental state.

Akathisia and RLS are clinically indistinguishable. The mainstay of treatment for akathisia is withdrawal of the offending agent. However, in some cases, the illness may be resistant to other medications and so the offending agent must be continued. Pharmacologic treatments for akathisia are of limited effectiveness and the evidence base is poor.

Together with the authors’ observations, these findings provide support for a broader model of akathisia and RLS, incorporating the thalamus and GABA/glutamate system.

SUBCORTICAL EPILEPSY?
Joe Verghese, Isabelle Rapin, Bronx, NY: Badawy et al. described the cerebellar origin of seizures and explored why experts disagree about seizure origin. It is clear that current findings lack detail, do not include determinations between myoclonus and epilepsy, and many cerebellar pathologies are outlined.

We described a case in which myoclonus correlated with selective dentate nucleus degeneration. We considered cerebellar seizures but offered an alternate explanation for previously described symptomatology. We followed this child from age 2 to her death at age 6. She had type III Gaucher disease with splenomegaly, stridor, ataxia, oculomotor apraxia, and disabling spontaneous and action myoclonus. She had myoclonic jerks causing falls and episodes of myoclonic status that superficially resembled generalized seizures but without alteration of consciousness or postictal state. Intelligence was preserved. Two EEGs and CT scans at ages 3 and 4 were normal. At autopsy, there was no neuronal, peryvascular, or meningeal storage but dentate nuclei neurons had degenerated without other brainstem abnormalities. The myoclonus may have resulted from selective toxic effects on dentate neurons of psychosine, a neurotoxin produced by an alternate pathway to the blocked glucosylceramide degradation. More detailed electrophysiologic study and well-defined neuropathology are needed before events are accepted as epileptic seizures arising from cerebellum.

Commenting Online is Easier Now with WriteClick™
Have a comment on a recent Neurology® article you would like to share? Now it is easier and more convenient. Neurology.org has launched WriteClick on the home page and sidebars of each article to encourage remarks and debate among users.

WriteClick is restricted to comments about studies published in Neurology within the last eight weeks.

Learn more at http://www.neurology.org/letters
Thalamic glutamate/glutamine in restless legs syndrome: Increased and related to disturbed sleep
Iain Jordan and Declan Murray
Neurology 2014;82;372-373
DOI 10.1212/01.wnl.0000443817.83968.a7

This information is current as of January 27, 2014

Updated Information & Services
including high resolution figures, can be found at:
http://n.neurology.org/content/82/4/372.2.full

References
This article cites 4 articles, 1 of which you can access for free at:
http://n.neurology.org/content/82/4/372.2.full#ref-list-1

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints
Information about ordering reprints can be found online:
http://n.neurology.org/subscribers/advertise

Neurology © is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2014 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.