"The more we know"

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*Neurol Neuroimmunol
Neuroinflamm*
2015;2:e112; doi: 10.1212/
NXI.0000000000000112

Almost half of the articles in this issue of *Neurology*[®] *Neuroimmunology & Neuroinflammation* (N2) are focused on disorders related to autoantibodies against well-defined antigens expressed by astrocytes (aquaporin-4 [AQP4]), oligodendrocytes (myelin oligodendrocyte glycoprotein [MOG]), or neurons, either synaptic receptors (NMDA receptor, dipeptidyl-peptidase-like protein-6 [DPPX]) or intracellular proteins (glutamic acid decarboxylase [GAD], collapsing response-mediator protein 5 [CRMP-5]). Although these disorders are already known, a common theme of the current N2 articles is that when atypical syndromes occur, additional mechanisms or the presence of concurrent autoantibodies should be carefully investigated. This is particularly relevant when the involved autoantibodies are known to be unambiguously pathogenic in cultured cells (astrocytes, oligodendrocytes, or neurons) or in animal models.^{1–3} Indeed, if, after hundreds of patients are reported with a specific antibody-associated syndrome, one encounters a patient with atypical manifestations, it is more reasonable to search for an additional pathogenic mechanism than to label the case as an "expansion" of the syndrome.

These cases add a new level of complexity to the differential diagnosis of antibody-associated encephalitis, as exemplified by 3 articles in the current issue. Orengo et al.⁴ describe a patient with simultaneous AQP4 and NMDA receptor (NMDAR) antibodies whose symptoms are not typical of the syndromes associated with either of these antibodies but could be explained by a combination of both. Rossel et al.⁵ report a patient with a history of Sjögren syndrome who developed transverse myelitis (likely related to AQP4 antibodies) followed by a diagnosis of colon cancer; retrospective assessment of the patient's serum showed the presence of AQP4 antibodies prior to the presentation of myelitis, without other signs of neuromyelitis optica spectrum disorder (NMOSD). Feyissa et al.⁶ report the differential diagnosis of a patient with new-onset seronegative NMO and acute

peripheral neuropathy with past history of Churg-Strauss syndrome; the new symptoms developed while tapering the dose of tacrolimus, suggesting that immune reconstitution mechanisms might have been pathogenically involved.

These clinical complexities, along with the growing number of cell surface neuronal antigens, require practitioners to have knowledge of the clinical syndromes and of the relevance of specific autoantibodies. A diagnosis that depends solely on antibody results without careful consideration of the syndrome may not be correct, as some antibody testing may be falsely negative or may be positive for an antibody unrelated to the actual disease. This is a potential problem of using antibody panels if the results prevail over the clinical assessment.⁷

For "autoimmune encephalitis," the number of nonspecific antibody associations is notable, especially when techniques such as radioimmunoassays or immune precipitation (voltage-gated calcium channel, voltage-gated potassium channel complex antibodies) are used,⁸ but also when cell-based assays with only serum are used.⁹ Two of the patients with anti-NMDAR encephalitis included in this issue of N2 had antibodies detectable in only CSF,^{4,10} a problem previously reported in a large series of patients with anti-NMDAR encephalitis whose paired serum and CSF samples were available for testing.¹¹ Moreover, some CSF antibodies are highly syndrome-specific (e.g., NMDAR; leucine-rich, glioma inactivated 1 [LGI1]), whereas others are more promiscuous and found in a variety of syndromes (e.g., GAD65 and stiff person syndrome, cerebellar ataxia, or limbic encephalitis) or with nonspecific syndromes. In this case, the accompanying comorbidities or prodromal symptoms may suggest the diagnosis. An example is DPPX-antibody-associated encephalitis. This disorder results in neuropsychiatric symptoms, CNS hyperexcitability (tremor, myoclonus, and seizures, among others), and frequent hyperekplexia, which may suggest the diagnosis; however, it is the

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Funding information and disclosures are provided at the end of the editorial. Go to Neurology.org/nn for full disclosure forms.

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accompaniment of prodromal gastrointestinal dysfunction, diarrhea, and weight loss (not cancer-related) that commonly leads to the diagnosis.¹² The patient presented in this issue by Stoeck et al.¹³ had diarrhea and dramatic weight loss; she was undiagnosed for 1.5 years yet still responded to immunotherapy with azathioprine and steroids. This outcome is in contrast to that of classic paraneoplastic syndromes, which rarely respond to therapy. However, Hampton et al.¹⁴ describe a 23-year-old man with anti-CRMP-5–associated cerebellar ataxia, longitudinally extensive transverse myelitis (LETM), and demyelinating peripheral neuropathy who responded to treatment of the underlying tumor, a mediastinal seminoma. The good outcome of this patient, likely related to his young age and treatment-responsive tumor, indicates that even patients with classic paraneoplastic syndromes can recover if therapy is promptly instituted.

The spectrum of antibody-associated autoimmune encephalitis in children is also expanding, but the repertoire of syndromes and initial manifestations of some disorders are different from those of adults. Bigi et al.¹⁰ report their experience at the Hospital for Sick Children in Toronto. Among 169 children with inflammatory brain disorders, 16 (10%) had an antibody-associated encephalitis. The other patients had primary or secondary vasculitis, CNS vasculopathies, or a heterogeneous group of diseases (Rasmussen encephalitis or granulomatous diseases). Among the antibody-positive patients, 9 had anti-NMDAR encephalitis, 4 had AQP4-related syndromes, 2 had Hashimoto encephalitis, and 1 had anti-GAD65 encephalitis. The study emphasizes the difficulty of differentiating among subtypes of encephalitis at early stages of the disease (encephalopathy, seizures, and nonfocal symptoms for NMDAR, Hashimoto, and GAD antibody-related symptoms vs lack of seizures and more focal symptoms for AQP4 antibody-related symptoms). One in 4 children had function-limiting residual deficits, emphasizing the importance of prompt diagnosis and treatment. In children, AQP4 autoimmunity frequently presents with symptoms other than optic neuritis or transverse myelitis, and recent reports in this¹⁵ and other journals¹⁶ have highlighted that in this population (probably more than in adults), NMOSD and acute demyelinating encephalomyelitis (ADEM) may be associated with MOG antibodies.¹⁷ In fact, Morris et al.¹⁸ describe an adult patient with MOG antibodies and a syndrome compatible with either NMOSD or ADEM; the authors favored the diagnosis of NMOSD because the patient presented with severe LETM and mild encephalopathy. It is interesting that the antibody testing was negative using the short-length form of MOG but the antibodies were eventually demonstrated with

the full-length form; the patient improved with steroids and plasma exchange. To optimize the sensitivity and specificity of the MOG assay, Waters et al.¹⁹ examined 1,109 sera sent for AQP4 antibody testing. Of these, 180 were antibody positive for the full-length form of MOG (21 for the short-length form), but the specificity for demyelinating diseases was limited given that 48% of patients with epilepsy (controls) also had these antibodies. The assay substantially gained in specificity (optic neuritis, AQP4 antibody-negative NMOSD, ADEM) when it was adjusted to detect IgG1 antibodies.

Sleep dysfunction is frequent among patients with autoimmune encephalitis, although few studies have addressed this problem. Song et al.²⁰ examined 33 patients with NMOSD (2007 Wingerchuk criteria) who showed a marked disruption in sleep architecture, including decrease of sleep efficiency, non-REM stage N3, and arousal index, and increase of REM sleep. Periodic leg movements were also higher than in the healthy controls. This study enlarges the list of antibody-associated brain disorders with sleep dysfunction (anti-LGI1 REM sleep behavior disorder,²¹ IgLON5,²² Morvan syndrome,²³ anti-NMDAR encephalitis⁷).

It appears that the more we know the more complex things appear. My impression is that the more we know the more we see.

DISCLOSURE

J. Dalmau is the editor of *Neurology: Neuroimmunology & Neuroinflammation*; is on the editorial board for *Neurology UpToDate*; holds patents for and receives royalties from Ma2 autoantibody test, NMDA receptor autoantibody test, GABA(B) receptor autoantibody test, GABA(A) receptor autoantibody test, DPPX autoantibody test, and IgLON5 autoantibody test; and received research support from Euroimmun, NIH, and Fondo de Investigaciones Sanitarias de la Seguridad Social (Spanish Government). Go to Neurology.org/nn for full disclosure forms.

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Neurol Neuroimmunol Neuroinflamm 2015;2;

DOI 10.1212/NXI.0000000000000112

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