Anti-AMPA receptor encephalitis

The family of glutamatergic autoencephalitides further expands

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Discovered shortly after anti-NMDAR encephalitis, anti–α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) encephalitis remains rare. Patients develop antibodies against AMPA-type ionotropic glutamate receptors, the major brain excitatory neurotransmitter receptors. First described in 2009 in a cohort of 10 patients with limbic encephalitis,[1] only 6 patients have subsequently been described. In contrast, hundreds of patients have been reported with anti-NMDAR encephalitis.[2] Anti-AMPAR encephalitis appears less prevalent, although it may be underdiagnosed because the typical clinical presentation remains unclear. In this issue of *Neurology*®, a study by Höftberger et al.[3] more than doubles the number of described patients, complementing and extending the findings of the initial case series.

To identify 21 patients, the authors screened >10,000 samples from patients with diverse suspected neuroimmune disease. Screening a broad repository reduces bias, but this cohort still likely underrepresents atypical disease for which advanced neuroimmune testing was not pursued—for example, isolated epilepsy or psychiatric disease. Extending the known association of anti-AMPAR antibodies with classic limbic encephalitis, the authors note presentation of 2 patients with hyponatremia, and nearly 30% of patients with prominent psychiatric symptoms, including one patient with isolated psychosis, which suggests that anti-AMPAR encephalitis is a potential mimic of new-onset psychiatric disease. However, similar to anti-NMDAR encephalitis,[2] additional neurologic symptoms develop with time; it seems unlikely that this disorder causes chronic isolated psychiatric disease.

Interestingly, the authors note a high prevalence of associated autoantibodies (7/21 patients), which in some cases drive the disease phenotype. For example, they report a patient with co-occurring anti-NMDAR antibodies who developed typical psychosis and dyskinesias. This raises the question of whether anti-AMPAR antibodies are always pathogenic. These antibodies could arise following encephalitic neuronal damage, and therefore be a marker of more generalized synaptic or antineuronal autoimmunity. Arguing against this possibility, these antibodies target antibody-accessible surface epitopes and have profound effects on AMPAR synaptic localization, AMPAR-mediated currents, and neuronal excitatory/inhibitory balance.[1,4–6] Further, in paired CSF and serum examination, all CSF samples were positive, but 4 out of 14 serum samples were negative, suggesting that CSF autoantibodies are more likely disease-causing, particularly when they target surface antigens.[7] Clearly, it is important to obtain CSF if there is suspicion of autoimmune encephalitis, as almost 30% of these patients would have been missed by serum testing alone.

In addition to coloring the clinical presentation, the associated autoantibodies have prognostic importance. Patients with associated tumors, but without additional paraneoplastic autoimmunity, had similar survival to those patients without associated tumors. However, patients with tumor and additional paraneoplastic autoimmunity had very high mortality (6/7 patients vs 2/17 with cancer and isolated AMPAR antibodies). It is not clear if this increased mortality is due to more aggressive tumor types, greater severity of neuroimmune disease, or additional associated medical comorbidities.

Overall, anti-AMPAR encephalitis is highly treatable. The authors present a cautionary example of a patient with refractory seizures requiring pharmacologic coma, and extensive MRI abnormalities, who was deemed too severely affected for treatment. However, after initiation of appropriate therapy, he made a good recovery and is currently home and seizure-free. Treating neurologists must use extreme caution in opining a poor prognosis, refusing more aggressive therapies, or considering withdrawal of care. Although potent immune suppression carries the risk of potentially serious side effects,[8] as these disorders carry substantial morbidity and mortality, it is usually possible to justify the use of rituximab or other immunosuppressive drugs.

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Further paralleling anti-NMDAR encephalitis, aggressive treatment may reduce the risk of relapse. All reported relapses have been in patients who did not receive aggressive therapy with agents such as rituximab or cyclophosphamide. Although these data are from uncontrolled, retrospective studies that may be subject to bias in diagnosis, treatment, and follow-up, this apparent effect of immunotherapy suggests that the threshold for treatment with aggressive agents should be low. Additional prospective studies regarding the presentation, natural history, and treatment of this rare disease are needed, which will improve recognition and treatment.

More broadly, the work by Höftberger et al. furthers our understanding regarding the generation of CNS-targeted autoimmunity. Autoantibody-associated CNS disorders have many similarities, but there are key differences among different autoantibody syndromes. Better understanding of the reasons for these similarities and differences could help answer the question of why autoimmunity occurs. Some syndromes have clear racial predilections; for example, teratoma-associated anti-NMDAR encephalitis is more common in black and Asian populations.[2] Some are limited to older adults (such as anti-LGI1 encephalitis),[7] whereas others (such as anti-NMDAR encephalitis) predominantly affect the young.[2] The trigger of autoimmunity can be tumors expressing neural tissue; however, in young children with anti-NMDAR encephalitis and most adults with anti-LGI1 encephalitis, there is no paraneoplastic association.[2,7] A recent important piece of the puzzle is the discovery in 2012 that anti-NMDAR encephalitis may occur weeks after confirmed herpes simplex virus (HSV) encephalitis.[9] Interestingly, these patients sometimes have CSF anti-NMDAR immunoglobulin G only 2 weeks after HSV encephalitis (rather than immunoglobulin M)[10]; this mature autoimmune response suggests that patients harbored autoreactive anti-NMDAR clones before HSV encephalitis, and that the inflammatory response to HSV caused a loss of immune tolerance. Such loss of tolerance is a central theme of why autoimmunity occurs. Recently, pediatric non-tumor-associated anti-NMDAR encephalitis was reported as seasonal, suggesting that other infections besides HSV may play a similar role.[11]

Further complicating the picture are the varied pathologic features of autoimmune encephalitides, which differ according to the associated autoantibody, with some appearing more reversible than others both in vitro and in patients.[7,12] Finally, therapeutic requirements may differ among syndromes; for example, there is clearly a role for rituximab in anti-NMDAR encephalitis,[2] whereas in anti-LGI1 encephalitis steroids remain the mainstay of treatment.[7,13]

The current study adds to our understanding of the spectrum of anti-AMPAR encephalitis, thereby improving our understanding of why autoimmunity occurs, and demonstrating that collaborative efforts are essential to improve understanding of these rare diseases.

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