Petit-Pedrol et al. has identified another new autoantibody syndrome to GABA-A receptors leading to encephalitis and refractory status epilepticus. The syndrome was identified via two index patients out of a cohort of 140 patients with similar symptoms. The two index cases had serum and CSF reactivity against an unknown rat brain neuropil antigen. The antigen was identified as the β3 subunit of the GABA-A receptor. CSF and serum were positive for the specific antibody. A total of four patients from a sample of 140 patients with encephalitis and two from disease control patients with autoantibodies against GABA-B receptors were identified with high titers against the GABA-A receptor antigen. An autoantibody syndrome to the GABA-B receptor—a G-protein coupled receptor—has been previously identified and seems clinically different. Early seizures associated with limbic encephalitis are typical, and 50% of patients have associated small cell lung cancer (1).
From the remaining sample of the 416 disease control patients with other suspected autoantibody disease, the authors identified another 12 patients with GABA-A reactivity but with lower titers (<1:160). Of those 12 patients with low titers, six had encephalitis with seizures, four had stiff person, and two had opsoclonus-myoclonus. CSF samples in three patients were negative for autoantibodies to GABA-A receptors in this group, and autoantibodies were present only in serum.

All of the six patients with high titers against GABA-A receptors had some form of status epilepticus, encephalopathy, and an abnormal MRI. In the three patients in whom CSF was available, titers were positive in CSF and serum. CSF findings were mixed with inconsistently elevated protein, pleocytosis, and oligoclonal banding. Half of the patients were children. All of the patients seemed to go through a prolonged prodromic phase with altered cognition before the onset of seizures. One patient was diagnosed with a malignant thymoma postmortem, and the authors conclude that the syndrome is not associated with a malignancy. Two patients died, and four had partial or total recovery. The four who survived had a quite functional outcome with returning to work or school.

The MRI findings are quite dramatic (Figure 4 of original paper). In one index patient, those findings seemed to improve, although in another, they seemed to persist. Unfortunately, the progression of the MRI findings in other patients was not presented. In the discussion, it is questioned whether the MRI findings were merely a result of seizure activity; however, frequently in status epilepticus, there are no MRI findings despite prolonged seizures. This finding would support that the MRI findings could be related to the underlying disease and may even be typical. It is well possible that in the past, similar images may have been interpreted as acute demyelinating encephalomyelitis, especially in children.

Other autoantibody syndromes, such as anti NMDA receptor encephalitis, often show no MRI abnormalities, and antibody syndromes associated with AMPA, GABA-B, or LGI1 receptors show predominant involvement of the hippocampus (2, 3).

The authors elegantly show that the presence of the antibodies does not decrease the overall number of GABA-A receptors but leads to loss of GABA-A receptors at the synapse with relocation at the dendrites. This could be an important mechanism for autoimmune-mediated seizures. The loss of GABA-A receptors at the synapse leads to seizures and certainly reinforces status epilepticus. It also suggests that some treatments, such as barbiturates and benzodiazepines, may be ineffective as they bind to the GABA-A receptor.

As more and more autoimmune-mediated seizures and syndromes are described, they can be classified into those that are associated with autoantibodies to plasma membrane receptors or to intraneuronal antigens (Table 1). While the intraneuronal targets seem to evoke a T cell-mediated response, plasma membrane antigens (such as NMDA receptors) become internalized in plasma membrane associated syndromes and may explain reversibility (4). Loss of synaptic receptors adds another possible mechanism. These underlying mechanisms may also explain the greater responsiveness of neural plasma membrane associated syndrome to immunosuppressive therapy. A recent study of 29 patients reports a response rate to immunosuppression and IV-IG of 87.5% in patients with syndromes associated with plasma membrane antigens, 33% with intraneuronal targets (GAD-65), and 33% with negative antibody screening (5). Internalization of the receptors without neuronal cell death or relocation of the receptors from the synapse to the dendrite, as demonstrated by Petit-Pedrol et al., may additionally explain the reversibility of some of the syndromes (4).

There was cross-reactivity with other autoantibodies in the patient cohort. In the group with high serum titers, there was reactivity with thyroid peroxidase antibodies and GAD-65 antibodies. In the group with low serum titers, there was cross-reactivity with GAD-65 and NMDA receptor antibodies. GAD-65 and thyroid peroxidase are intraneuronal antigens as compared to GABA-A or NMDA, which are plasma membrane receptors. As there was cross-reactivity, encephalitis with autoimmunity to the GABA-A receptor could be easily misidentified as a syndrome with autoimmunity against intraneuronal targets, which may have important treatment implications.
In addition, the cross-reactivity of autoimmune antibodies raises the question of whether the autoantibody production presents an epiphenomena of an underlying immunologic process or whether it is the underlying pathophysiology. The demonstration of loss of synaptic GABA-A receptors could certainly explain some of the pathophysiology regarding seizures. The underlying process of inflammatory processes and central nervous system immunity certainly warrants further attention, as there is also ample evidence that epileptogenesis is related to microglial activation (6). Their relationship to humoral processes needs to be explored in more depth.

Autoantibodies to neuronal antigens have been demonstrated in new and established epilepsy in 10% of patients (7). Clearly, disease-relevant antibody titers need to be identified. A sample of 74 normal controls in the Petit-Pedrol et al. study showed no reactivity to GABA-A at all, which certainly supports the pathologic value of the autoantibody. However, with the identification of more autoantibody syndromes, studying false positives in normal and other neurologic disease populations becomes more and more imperative.

Over the last decade, a multitude of autoimmune antibodies have been identified, and it seems that autoimmune encephalitis has become the new neurologic epidemic. Out of desperation, several immunosuppressive agents are often given to such patients. There is some collective clinical experience with anti-NMDA receptor encephalitis in regard to treatment (8), but we do not know the true risk–benefit ratio. It
needs to be studied systematically to identify which treatment is most effective and which underlying immune process is the most efficient to modulate. Typically given immunosuppression—such as with steroids, IV-IG, or cyclophosphamide—may not target the appropriate underlying mechanism and could cause more harm than good (4). Identifying underlying pathophysiology, as attempted in this paper, will get us a step further to this goal, and establishing close collaborations with oncological researchers who have made strides in targeting specific underlying immune processes can only guide this process along.

by Barbara C. Jobst, MD

References
Disclosure of Potential Conflicts of Interest

Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. **Identifying information.**
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

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   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. **Relevant financial activities outside the submitted work.**
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2. First Name  Barbara   Last Name Jobst  Degree MD

3. Are you the Main Assigned Author?  Yes    No

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4. Manuscript/Article Title:

5. Journal Issue you are submitting for:  14.5

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<th>Money to Your Institution*</th>
<th>Name of Entity</th>
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* This means money that your institution received for your efforts on this study.
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<td>13. Other (err on the side of full disclosure)</td>
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