



Autoantibody Encephalitis: Presentation, Diagnosis, and Management

Eric Lancaster

Department of Neurology,
The University of Pennsylvania,
Philadelphia, PA, USA

Autoantibody encephalitis causes distinct clinical syndromes involving alterations in mentation, abnormal movements, seizures, psychiatric symptoms, sleep disruption, spasms, and neuromyotonia. The diagnoses can be confirmed by specific antibody tests, although some antibodies may be better detected in spinal fluid and others in serum. Each disorder conveys a risk of certain tumors which may inform diagnosis and be important for treatment. Autoantibodies to receptors and other neuronal membrane proteins are generally thought to be pathogenic and result in loss of function of the targets, so understanding the pharmacology of the receptors may inform our understanding of the syndromes. Patients may be profoundly ill but the syndromes usually respond to immune therapy, although there are differences in the types of immune therapy that are thought to be most effective for the various disorders.

Keywords antibody; encephalitis; paraneoplastic; cerebellar ataxia; anti-NMDAR encephalitis.

INTRODUCTION

Autoimmune encephalitis is a challenging diagnosis because patients may present with psychiatric symptoms, cognitive impairment, movement disorders, seizures, and diverse other manifestations. The differential diagnosis for these patients is accordingly complex, including intoxication, infections, primary psychiatric illness, and other processes. The discovery of specific antibodies to central nervous system (CNS) membrane proteins has revolutionized our understanding of autoimmune encephalitis and our ability to make precise diagnoses. These antibodies target important brain proteins, including neurotransmitter receptors, ion channels, and associated membrane proteins. The proliferation of new autoantibodies can be overwhelming to non-specialists. However, the great majority of patients have a few distinct syndromes that physicians can learn to recognize and treat. A broad testing approach using panels of antibody tests can assist with the diagnosis of other patients, but these panels can create false positive results.

When confronting a case of suspected autoimmune encephalitis, it is important to understand the basic principles underlying these diseases, and to recognize the main clinical syndromes. After a diagnosis is confirmed, more specific prognostic and treatment information can be reviewed for the specific disease.

SECTION 1. GENERAL PRINCIPLES

Specificity to subunits and dominant epitopes

Pathogenic CNS neuronal autoantibodies are specific for their antigens. In the case of pro-

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Received February 24, 2022

Revised April 22, 2022

Accepted April 22, 2022

Correspondence

Eric Lancaster, MD, PhD
Department of Neurology,
The University of Pennsylvania,
3400 Spruce St. Philadelphia,
PA 19104, USA

Tel +1-215-200-7646

Fax +1-215-349-5579

E-mail eric.lancaster@penmedicine.upenn.edu

teins targeting ionotropic receptors, there is generally a strong preference for specific subunits of the receptor. For examples, N-methyl D-aspartate receptor (NMDAR) autoantibodies target the GluN1 subunit, causing internalization of those receptors, but other types of NMDARs that lack this subunit would not be affected.¹ Similarly, gamma aminobutyric acid A (GABA-A) receptors and glycine receptors have a tremendous diversity of possible subunits and the known CNS autoantibody disorders target only those with specific subunits. The names of these disorders should therefore be regarded as a shorthand and simplification. Leucine-rich glioma-inactivated 1 (LGI1) is a single protein, but the autoantibodies have strong preference for that protein over the closely related proteins LGI2, LGI3, and LGI4. Similarly, contactin-associated protein-like 2 (Caspr2) antibodies have negligible reactivity to its closest homolog, Caspr.

The autoantibodies appear to target certain dominant epitopes on the relevant targets that are consistent across patients. For example, NMDAR antibodies target a specific part of N-terminal of the GluN1 subunit.¹ This same principle applies to alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPA) antibodies,² Caspr2 antibodies,³ glycine receptor antibodies,⁴ etc. This type of specificity is important to the pathogenicity of acetylcholine receptor antibodies associated with myasthenia gravis, which affect the peripheral nervous system (PNS).⁵ Pathogenic neuronal autoantibodies therefore consistently target similar parts of specific subunits of the relevant antigens.

Cell surface and intracellular epitopes

A distinction is often made between antibodies targeting cell surface proteins in or on the neuronal cell membrane and those targeting intracellular epitopes. Autoantibodies targeting synaptic proteins such as the NMDAR target domains exposed to the cytoplasm (cell surface epitopes). The antibodies can therefore bind to living neurons and plausibly exert physiological effects on antigen numbers, localization and/or function. The antigens in this category can be further subdivided into ionotropic receptors (NMDAR, AMPAR, GABA-A receptor, glycine receptor, kainate receptor), ion channels (dipeptidyl-peptidase-like protein-6 [DPPX], voltage-gated calcium channels [VGCCs]), metabotropic receptors (gamma aminobutyric acid B [GABA-B] receptor, metabotropic glutamate receptor 1 [mGluR1], mGluR5), and cell-adhesion or synaptic organizing proteins (Caspr2, LGI1). The true functions of some antigens (delta/notch-like EGF-related receptor [DNER]) are not clear.⁶ These diseases are thought to be mediated, at least in part, by direct effects of the antibodies. The symptoms often are similar to the types of symptoms one would expect with a loss of function of the target antigen. For

example, anti-NMDAR encephalitis has some resemblance to the symptoms caused by the NMDAR antagonist phencyclidine.⁷ And glycine receptor antibodies associate with a phenotype that resembles strychnine toxicity.^{8,9} These diseases tend to respond to immune therapies and prognosis is relatively favorable.

The classic paraneoplastic or onconeurological autoantibodies target intracellular neuronal epitopes are not thought to be directly pathogenic. These antibodies target diverse proteins that do not predict the associated neurologic symptoms. Hu (ANNA1) antibodies, for example, target a family of RNA binding proteins, particularly HuD.¹⁰ The antigen is expressed in neurons, and specifically in neurons that are affected by the anti-Hu immune response, but the functions of these proteins do not predict the neurologic syndromes associated with anti-Hu.¹¹ Autoantibodies to intracellular epitopes are not thought to bind their targets in living neurons and are not thought to cause disease. In the case of Hu antibodies, passive transfer experiments and animal immunization models do not result in disease.¹² Pathology studies have shown T cell-mediated cytotoxicity, which is thought to be the dominant pathogenic mechanism.¹³ The paraneoplastic intracellular autoantibodies are therefore best considered as markers of disease rather than pathogenic. There is, however, some evidence that Hu and Yo antibodies can enter neurons and exert some effects, but the true relevance of these findings to disease pathogenesis is unclear.¹⁴ The intracellular antibodies, particularly Hu, may exist in lower titers in patients with cancer who do not have the associated neurologic syndromes.

The differences between cell-surface and onconeurological antibodies have several important consequences. First, there is more variability in the clinical syndromes associated with some intracellular autoantibodies compared to cell-surface antibodies. For example, anti-Hu may be associated with a wide range of phenotypes including sensory neuronopathy, encephalomyelitis, and cerebellar degeneration.¹⁵ This contrasts with the much more specific phenotypes of NMDAR or LGI1 antibodies (see below). With other intracellular antibodies, such as Yo, the phenotypes are more consistent. Second, the outcomes tend to be worse with intracellular compared to cell-surface antibodies, possibly due to irreversible T cell-mediated neuronal loss. Third, treatments to reduce antibody production or activity may be better supported for cell-surface antibody diseases.

In the context of autoimmune encephalitis, cell-surface antibodies are much more common than informative intracellular antibody responses.

Mechanisms of CNS synaptic and cell membrane antibodies

Cell surface synaptic antibodies are thought, based upon variable levels of evidence, to be pathogenic, but the mechanisms may be different for each class of antigen. NMDAR antibodies have received the most study and are thought to act by cross-linking and internalizing synaptic NMDARs, resulting in loss of function.¹⁶ This effect of the antibodies has been studied in cell-culture models and also occurs in a passive transfer animal model.¹⁷ The passive transfer animal model has also been used to show that Ephrin B2 can inhibit this internalization, suggesting a novel therapy could be developed to ameliorate symptoms of the disease by preventing loss of NMDAR function.¹⁸ AMPAR antibodies and kainate receptor antibodies act similarly to NMDAR antibodies on cultured neurons, cross-linking and internalizing the target receptors.^{19,20} Similar mechanisms are possible with glycine receptor and GABA-A receptor antibodies, which also target inotropic receptors.

LGII represents a different type of antigen since it binds to other synaptic proteins (ADAM22 and ADAM23) to organize AMPA receptors and Kv1 type voltage-gated potassium channels. LGII antibodies disrupt the interactions of LGII with ADAM22 to reduce synaptic AMPA receptors.²¹ Since anti-LGII encephalitis is clinically distinct from anti-AMPA encephalitis, other mechanisms (such as effects on potassium channels) are also likely to occur. Caspr2 is a cell-adhesion molecule expressed in both the CNS and PNS, so it is unusual among the antigens associated with autoantibody encephalitis. However, antibodies to other cell-adhesion molecules associate with autoimmune neuropathies and myasthenia gravis (see below). Caspr2 antibodies are thought to act by blocking its interactions with other cell adhesion molecules.³

The relevance of IgG4 responses

The immunoglobulin genes undergo somatic DNA rearrangement during B cell development to generate diverse antibody proteins. After initial generation of a specific antibody, exposure to antigen can resume in expansion of the B cell clone with further somatic hypermutations. A competitive process among these B cells can result in increasing affinity over time. B cells may initially generate IgM type antibodies and then IgG type antibodies may be produced later. There are 4 specific subtypes of IgG in humans that may be expressed as B cells are influenced by cytokines and stimulation.

IgG4 is the least common subtype of IgG in human sera, comprising about 5% of total IgG (although this varies greatly among individuals) and has unique properties.²² IgG4 is not able to bind complement proteins, so probably acts by other mechanisms in both healthy immunity and in the autoimmune

context. IgG4 emerges last in the subtype maturation of B cells and IgG4 responses may have extremity high affinity for their antigens, having undergone rounds of somatic mutation and selective competition. IgG4s also undergo a unique process of exchanging Fab arms with other IgG4s. In this process each IgG4 antibody may change half of itself with another IgG4, leading to IgG4s that are functionally monovalent, having two completely different binding arms. The cross-linking of target antigens that occurs in anti-NMDAR encephalitis may therefore not be possible for IgG4 type responses such as those targeting LGII.

Most of the autoantibodies relevant to anti-NMDAR encephalitis are IgG1 and IgG3. And non-IgG4 responses are most common in autoimmunity to the receptor antigens in general. However, IgG4 responses predominate in anti-LGII encephalitis, where higher cerebrospinal fluid (CSF) IgG4 levels correlate with worse disease, and anti-Caspr2 encephalitis.^{3,23} IgG4 responses also are prominent in autoimmunity to Neurofascins and the caspr/contactin complex in the context of autoimmune neuropathy and to MUSK in myasthenia gravis.²⁴ DPPX responses involve a mixture of IgG1 and IgG4 so it is unclear how much each type of response contributes to the disease.²⁵ It is interesting that most of the antigens for IgG4 responses are cell adhesion molecules (Caspr2, neurofascins, caspr/contactin) or proteins that bind to cell adhesion molecules (LGII). Neurexin-3 α , however, is a synaptic cell adhesion molecule but the antibodies are predominantly IgG1.²⁶ In general, IVIG is thought to be less effective against IgG4 responses while rituximab may be effective.²⁷

While autoantibodies to NMDAR, AMPAR and most other ion channel antigens are an appropriate subtype to fix complement, pathologic studies do not show significant complement deposition or complement-mediated cytotoxicity, perhaps due to low levels of complement in CSF.²⁸ This difference in ability to fix complement may therefore be more important in the context of myasthenia gravis and autoimmune neuropathies than for autoimmune encephalitis. It should be noted that complement fixation is important in the context of aquaporin-4 (AQP4) antibodies in neuromyelitis optica (NMO), which target a CNS antigen just inside the blood-brain barrier, and treatments that inhibit the complement cascade is effective against that disorder.²⁹

While the pathogenic mechanisms of IgG4 to cell adhesion molecules has received less attention than the mechanism of autoantibodies to ion channels, there are some important differences. IgG4 probably do not cause antibody-mediated cross-linking and internalization because they are functionally monovalent. IgG4 may rather interfere with cell-cell interactions mediated by their targets.

CSF production and CSF testing

The selection of appropriate samples for testing and the optimal tests to use is complex. NMDAR antibodies are most sensitively detected in CSF, which is considered the gold standard.⁷ Serum testing is somewhat less sensitive and there may be rare false positives. GABA-B receptor antibodies are detected more readily in CSF than serum.³⁰ LGI1 antibodies, in contrast, may more readily be detected in serum, and patients with serum-only responses seem to have a similar disease to patients with both CSF and serum antibodies.³¹ Some commonly used commercial assays may have decreased sensitivity for AMPAR, GABA-B receptor, and LGI1 antibodies compared to research laboratory cell-based assays.^{32,33} A simple strategy is to test both CSF and serum in patients with suspected autoimmune encephalitis. When selecting test panels it is important to use those which contain the most relevant tests, and recognize that most panels are not truly comprehensive. Indeed, the very definition of comprehensive testing is frequently revised as new antigens are discovered. However, these new antigens tend to be much rarer, so it is unlikely that a disease as common as anti-NMDAR encephalitis awaits discovery.

Antibody responses to cell-surface antigens persist for months or years. The antibody responses should be continuously detected during active symptoms and reliable negative testing in the presence of symptoms should case doubt on the diagnosis. Antibody responses also tend to persist for months to years after clinical symptoms resolve, so positive antibody tests alone should not constitute a basis for immune therapy in the absence of symptoms. In patients with symptoms of possible relapse, testing again for antibodies (to determine if they persist) may be helpful, but this determination is mostly clinical.

Antibody titers have been studied in anti-NMDAR encephalitis.^{34,35} In these patients, CSF titers correlate with symptoms, being high at diagnosis, lower in remission, and higher again with relapse. Serum titers do not correlate with disease status. However, this correlation has only been demonstrated using repeat assays by the same method in the same laboratory. Each patient may only be compared to himself and not to others. Comparing values across laboratories may not be useful. Further, the correlation is only approximate. As noted above, CSF LGI1 antibodies associate with somewhat worse symptoms than serum-only responses, but the use of serial titers in treating individual patients has not been shown. The primary determination of immune therapy and relapses should be by clinical symptoms and not titers.

Cancer associations

Each form of autoimmune encephalitis has profile of cancer risk. For example, patients with anti-NMDAR encephalitis

have about 50% risk of ovarian teratoma, but GABA-B receptor antibodies convey a 50% risk of small cell lung cancer. LGI1 antibodies, in contrast, only rarely associate with cancer. When autoimmune encephalitis is suspected, a careful history and physical exam could be followed by imaging of the chest, abdomen, and pelvis while awaiting antibody test results. Breast cancer screening, pap smear, colonoscopy, and other age-appropriate studies should be brought up to date. Finding a specific cancer can guide antibody testing. Conversely, finding a specific antibody defines risk and allows for more focused cancer screening. Age and other patient demographics can also influence cancer screening. For example, an older male smoker with anti-NMDAR encephalitis might require broader cancer screening than a 14-year-old young woman with the same diagnosis, where careful testing for ovarian teratoma is by far the most useful testing. During follow-up evaluations, it is important to monitor for cancer since some tumors only become apparent later. Focused screening for 3–4 years after diagnosis is also reasonable, since tumors may not be detected at initial presentation despite appropriate testing. In general the clinical symptoms of patients and responses to treatment are remarkably similar between those with and without tumors. While it is not realistic to expect non-specialists to memorize the tumor associations of each antibody, it is important to review the literature for these associations when treating a patient with a given antibody.

If a cancer is present and chemotherapy is used, this can complicate immune therapy. It is important for the treating neurologist to communicate clearly with the oncologist in these situations. If cytotoxic chemotherapy is needed, this should usually be optimized to treat the specific tumor. Treatments such as IVIG, plasmapheresis, steroids, or rituximab generally do not conflict with cancer treatment, although plasmapheresis could remove monoclonal antibody treatments. Immune checkpoint inhibitors and other treatments designed to provoke an immune response against the tumor should generally be avoided in patients with known paraneoplastic disorders, since these could make the autoimmune disorder worse.

The relative frequency of disorders in adult and children

Since 2010, auto antigens associated with encephalitis have been discovered at a rate of 1–2 per year. The continuing discovery of new autoantibodies makes it challenging to properly test patients for all of the known immune mechanism. However, it is important to recognize that the antibodies have been discovered roughly in order of decreasing prevalence in patients. The average age of patients with NMDAR antibodies is about 20 years, and the average age of the other major antibodies (LGI1, Caspr2, GABA-B receptor) is closer to 60

years. NMDAR antibodies and LGI1 antibodies are significantly more common than the others. In children, NMDAR antibodies are much more common than all other antibodies of this type combined.³² The priority should be to test properly for the most likely antibodies and seek expanded testing in difficult cases when initial testing is negative.

Guidelines to empiric treatment in the context of autoimmune encephalitis and anti-NMDAR encephalitis

It is a common problem in clinical practice to treat patients with suspected encephalitis prior to having full antibody testing results. Patients may begin treatments with steroids, immune globulin or other treatments when only limited information is available. Expert guidelines have been published to aid these treatment decisions.³⁶ The criteria for possible autoimmune encephalitis are subacute working memory deficits, psychiatric symptoms or altered mental status. Patients must also have at least 1 supporting factor: new focal CNS deficits, new seizures, CSF pleocytosis, or MRI features of encephalitis. There should also be reasonable exclusion of alternative causes. Patients are considered to have definite autoimmune encephalitis if they have the appropriate symptoms, MRI changes, and at least one other supporting factor (CSF pleocytosis, EEG findings of epileptiform or slow wave activity in the temporal lobes).

Specific criteria for anti-NMDAR encephalitis have also been proposed.³⁷ The diagnosis is considered probable for patients with rapid progression of at least 4 the following 6 symptom clusters: abnormal behavior, cognitive dysfunction, abnormal movements, speech disruption, seizures, altered consciousness, decreased consciousness or hypoventilation. Patients must also have CSF pleocytosis or abnormal EEG. Alternative causes must be excluded.

While these criteria may be useful in considering the likelihood of autoimmune encephalitis, it is important to recognize that not every patient meeting these criteria will have the diseases, and not all patients with the diseases meet the criteria. Having specific antibody test results should cause a revision in how likely the diseases are considered. Negative testing in CSF for NMDAR antibodies makes the diagnosis of anti-NMDAR encephalitis very unlikely even if the diagnostic criteria for “probable anti-NMDAR encephalitis” were met. In these cases, other similar disorders, such as anti-AMPA encephalitis, should be considered.

General guidance on immune therapies

In addition to cancer treatment, patients with autoimmune encephalitis are treated with various immune therapies. Evidence to guide treatment of these disorders is limited, and

there appear to be some differences in how diseases respond to therapies. Patients are often initially treatment with steroids (solumedrol 1,000 mg daily for 3–5 days, followed by an oral steroid taper) and with either IVIG or plasmapheresis while awaiting antibody confirmation. A typical treatment with IVIG is 2 g/kg divided over 3–5 days. In the case of IgG4 responses such as LGI1 or Caspr2, treatment with very slow steroid tapers is used and IVIG may not be useful. In the case of NMDAR and other non-IgG4 responses, steroids are tapered off.

B cell depletion with rituximab is commonly used. This medication depletes circulating B cells within hours of the first dose, and the timing of subsequent doses is probably not important. A standard course will deplete CD19-positive/CD20-positive lymphocytes for 6–12 months. The medication can be removed by plasmapheresis, so additional doses may be needed if plasmapheresis is performed after rituximab. Since B cells are important as antigens presenting cells to T cells, rituximab may be useful in both B cell and T cell disorders. It is unclear how long this medication should be continued. In patients with good response, our center uses only a single course. But other centers might repeat therapy every 6 months for 1–2 years.

Cyclophosphamide can be used in monthly pulses (750 mg/m²) in cases that do not respond to other treatments. Treatment with gonadotropin-releasing hormone agonists can help preserve fertility in young female patients.³⁸ Due to its toxicity, the treatment can be stopped once the patient undergoes significant improvement.

It is unclear how to treat anti-NMDAR encephalitis or other disorders in this group in cases refractory to the above treatments. There are case reports or small case series describing bortezomib and tocilizumab treatment, but experience is limited (discussed below).

Some centers treat patients with multiple relapses or prolonged clinical course with mycophenolate mofetil or azathioprine. Pediatric series have reported that the treatments were usually tolerated but the efficacy is unclear.³⁹

SECTION 2. AUTOANTIBODY DISORDERS TARGETING CELL SURFACE PROTEINS

The autoantibody disorders targets neuronal membrane proteins are summarized in Table 1.

Anti-NMDAR encephalitis

Anti-NMDAR encephalitis is more common among females and the median age is 20 years. Young children and the elderly may be affected and some patients are male. The classic presentation of the disease involves psychosis with hallucinations

Table 1. CNS cell membrane autoantibodies

Antibody	Clinical features	Cancer associations
NMDAR	Psychosis, memory loss, seizures, dystonia, mutism, catatonia, autonomic instability, coma	Ovarian teratoma
LGI1	FBDS, other seizure types, memory impairment, impaired spatial navigation, hyponatremia	Tumors are rare (thymoma)
GABA-B-R	Encephalitis with severe seizures	Lung cancer
AMPA	Encephalitis, psychosis, abnormal movements	Lung, breast, thymus
Caspr2	Isaacs' syndrome Morvan syndrome Pain syndromes Encephalitis Potential overlap with myasthenia	Thymoma
mGluR5	Ophelia syndrome	Hodgkin lymphoma
DPPX	CNS and gastrointestinal hyper excitability, cerebellar symptoms	B cell neoplasms
GluK2	Cerebellar ataxia with cerebellar swelling, risk of CSF outflow obstruction	Thymoma, small cell lung cancer
Glycine receptor	PERM, hyperekplexia, abnormal eye movements	Thymoma, lymphoma
SEZ6L2	Cerebellar syndrome with extrapyramidal symptoms	Ovarian cancer (risk profile still unclear)
Neurexin-3 α	Confusion, seizures, decreased awareness	Evolving (so far low risk)

AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; Caspr2, contactin-associated protein-like 2; DPPX, dipeptidyl-peptidase-like protein-6; FBDS, faciobrachial dystonic seizures; GABA-B-R, gamma aminobutyric acid B receptor; GluK2, glutamate kainate receptor subunit 2; LGI1, leucine-rich glioma-inactivated 1; mGluR5, metabotropic glutamate receptor 5; NMDAR, N-methyl D-aspartate receptor; PERM, progressive encephalomyelitis with rigidity and myoclonus; SEZ6L2, seizure-related 6 homology 2.

and delusions. Initial consideration of primary psychiatric illness is common. Difficulty learning and remembering new information is also a common, if less dramatic, sign. Patients may present with seizures during any phase of the disease, including as the presenting sign, but these seizures usually remit after immune therapy takes effect and the other neurologic symptoms recover.⁴⁰ Persistent epilepsy is rare. As the disease process deepens, patients become less responsive and develop abnormal postures, dystonia, and may appear catatonic. In severe cases, patients are comatose and unresponsive to pain or external stimulation. While they are comatose, continuous biting, chewing, and other oral movements are characteristic. These movements may result in damage to the lips, teeth, or tongue. Dystonic posturing of the limbs may also occur in this phase of the disease. Patients may show profound instability of heart rate and blood pressure (autonomic instability) in the catatonic and comatose phases. Patients each progress through the phases of illness to a variable degree; some patients may have psychosis and memory loss but respond rapidly to treatment or spontaneously improve. Other patients may be comatose and unresponsive for months. As patients recover they may pass through the stages of illness in reverse order. For example, a patient may wake from coma and start responding slightly but still be mute and catatonic. As she improves further, the patient may start speaking but suffer a return of hallucinations, aggression, and other behavioral symptoms. It is important to note that this progression from coma to catatonia to psychosis reflects an overall improvement in the illness, not a treatment failure. As these symp-

toms in turn resolve the final stage is a slow increase in awareness and cognition. The ability to remember new information is the final step in recovery, often returning gradually over many months or years.

About half of patients with the disorder are children. This is in contrast to the other synaptic autoantibody disorders, where the median ages are older and pediatric cases are very rarer.³² The symptoms in children are similar to those of adults, but there are a few notable differences.^{41,42} Hallucinations and delusions are still common but less often the presenting symptom. Children are more likely to present with abnormal movements such as dystonia compared to adults. Seizures are even more common in children than adults. Dragging a leg or unsteady gait, sometimes with leg pain, may occur as an early finding that is rarely observed in adults.⁴³ Speech regression or mutism may also be an early sign in children. Patients still tend to progress through similar phases of illness, with behavioral symptoms in the milder stages, and catatonia or coma in the more severe phases. In children there is more potential for long term disruption of cognitive development compared to adult patients, who are more likely to recover fully.⁴⁴ Careful attention to the cognitive, developmental, and rehabilitation needs of pediatric patients is needed.

Approximately half of patients have ovarian teratoma.⁴⁵ The tumors contain neuronal tissues, including NMDARs that can be recognized by the autoantibodies, and are plausible triggers for the immune response.²⁸ This association was important to the initial characterization of the disorder when cases with antibody reactivity to brain tissue and the charac-

teristic clinical syndrome were described prior to the identification of the specific NMDAR antibody.⁴⁶ The teratomas may not be detected on initial imaging studies, so follow up studies over the following three years may be useful. Other types of tumors are uncommon, although a small group of older patients have lung cancers and cases may have co-existing Hu immune responses.^{47,48} Tumors in children are uncommon, although cases with testicular seminoma/teratoma and lung cancer have been reported.⁴¹ In general, screening for tumors is advised on diagnosis. And follow-up studies for teratoma are reasonable in patients at risk for that tumor.

In most patients without ovarian teratoma, the precise trigger of the illness is unknown. Approximately 70% of patients have a prodromal illness 1–2 weeks prior to the onset of neurologic symptoms.⁴⁹ The prodrome may resemble an upper respiratory infection or diarrheal illness, and is generally mild and resolved before the neurologic symptoms occur. Numerous infections have been reported including EBV, influenza, hepatitis, HIV, HHV6, enteroviruses, etc.⁵⁰ The odds of each of these agents triggering anti-NMDAR encephalitis appear to be minimal for any given infection.

Herpes simplex virus (HSV) encephalitis is a special case, with a much higher risk of triggering anti-NMDAR encephalitis compared to other infections.^{51,52} These patients present with the typical symptoms of HSV encephalitis, including fever, altered sensorium, and seizures. They are HSV PCR positive on presentation and do not have NMDAR antibodies at that time. During recovery from the viral infection, usually 2–3 weeks later, patients have symptoms of anti-NMDAR encephalitis. The range of reported latencies is 7 days to 3 months. Interestingly, this group is particularly prone to have negative NMDAR antibody testing in serum (but positive in CSF) at diagnosis. These patients may be treated with immune therapy and recover from the symptoms of anti-NMDAR encephalitis. However, prognosis may be less favorable, especially in cases with substantial structural brain injury from the viral infection. Patients with such injuries may be more likely to have persistent cognitive deficits and persistent seizures compared to patients with regular anti-NMDAR encephalitis. Interestingly, prior oral or genital herpes virus infections (HSV-1) seem to be a low level risk factor for anti-NMDAR encephalitis.⁵³

Specific prognostic factors associate with good or poor outcomes in patients with anti-NMDAR encephalitis. One simple predictive tool is the Anti-NMDAR Encephalitis One Year Functional Status (NEOS) score.⁵⁴ The NEOS score can be calculated in the first 4 weeks of the course and consists of: need for ICU admission (1 point), no improvement within 4 weeks of treatment (1 point), no treatment within 4 weeks of symptom onset (1 point), and abnormal MRI (1 point). In

this study, patients with low scores (0–1) almost always had good functional recovery at 1 year. Patients with higher scores often had poor functional status at 1 year. It is important to note that even patients who are profoundly impaired at 1 year may improve further over time.

Ancillary testing can provide useful information in evaluating patients with suspected anti-NMDAR encephalitis. MRI of the brain is abnormal in about 33% of patients.⁴² The typical finding is increased T2 signal in the medial temporal lobes and other nearby brain regions. This pattern is not specific for anti-NMDAR encephalitis and could be seen with other types of autoimmune disorders and certain infections. As noted above, MRI abnormalities associate with a more severe course. The extreme delta brush pattern is a characteristic finding of anti-NMDAR encephalitis, but only seen in some patients and usually only when they are most impaired.⁵⁵ Lumbar puncture may show CSF pleocytosis, increased protein, oligoclonal bands, and/or elevated IgG index. However, other patients have normal studies aside from NMDAR antibodies. In one series, EEG was almost always abnormal (96%) during active disease, but the most common findings were focal or diffuse slowing, which are not specific for anti-NMDAR encephalitis.⁵⁶ But this was only present in a minority (11%) of patients. In this series, a normal posterior rhythm was associated with a good outcome, although patients without a normal posterior rhythm also usually had good outcomes. PET or SPECT scans are frequently abnormal, and may have certain patterns, but the reliability of these studies in differentiating anti-NMDAR encephalitis from other causes of encephalitis remains to be determined.^{57–59}

Anti-NMDAR encephalitis can rarely overlap with CNS demyelinating disorders such as the anti-myelin oligodendrocyte glycoprotein (MOG) syndrome, optic neuritis, or NMO spectrum disorders. In one large study 4.5%–7% of patients had co-existing autoantibodies to MOG, AQP4, glial fibrillary acidic protein (GFAP), or other CNS synaptic proteins.⁶⁰ Patients with MOG or AQP4 generally have prior, simultaneous or subsequent demyelinating disorders typically found with those antibodies. The implications of GFAP antibodies were less clear. Another large study found demyelinating disease in 3% of patients with anti-NMDAR encephalitis.⁶¹ The MOG and AQP4 associated syndromes were most common in these patients. Compared to other patients with anti-NMDAR encephalitis, they required longer immune therapy and had somewhat more deficits. Treatments should be selected that are effective against both disorders. Patients with co-existing demyelinating disorders were much less likely to have teratoma.

Several types of symptomatic therapies are used to treat anti-NMDAR encephalitis. Anti-psychotic medications are fre-

quently used to manage hallucinations, agitation, and aggression. Agents with strong dopamine antagonist properties, such as haloperidol, could worsen the movement disorders or catatonic-like symptoms. Anti-psychotic medications with weaker dopamine antagonism, such as quetiapine, may be tried instead. Benzodiazepines can help with managing agitation. The catatonic-like state seen in many patients probably has a different biochemical basis than the catatonia associated with psychiatric disorders. While some practitioners use benzodiazepines to try to improve the catatonia-like symptoms, it is unclear how beneficial this is, but benzodiazepines are usually well tolerated. Electroconvulsive therapy has also been used to treat these symptoms. Patients have occasionally been treated with NMDAR antagonists (such as ketamine) but there is no rational basis for this treatment and it could potentially worsen the disease by inhibiting the remaining NMDAR function in these patients.

Autonomic instability is a significant problem in the deepest stages of the illness. Tachycardia, fluctuations in blood pressure, and occasionally arrhythmias may occur. Cardiac monitoring is useful. Medications such as clonidine can help with blood pressure fluctuations. Glycopyrrolate or theophylline has been used for severe bradycardia. In extreme cases, pacemakers may be needed. Central respiratory failure is a common feature of the disease in the deeper stages, so patients should be monitored carefully. This is particularly important for patients with declining levels of awareness as the disease is worsening and becomes less of a danger in alert patients who are recovering.

Dystonia and abnormal movements may complicate care in several ways. Patients are at risk for limb injuries and dislocations from limb dystonia. Rhabdomyolysis may occur, especially in patients who receive dopamine receptor blockers.⁶² Abnormal orofacial movements may cause severe injuries to the lips, tongue, teeth, and jaw. In some patients the movements involve lip smacking or writhing of the lips, which is relatively harmless. However, the movements may also involve powerful biting movements which can damage endotracheal tubes and other care equipment, crack teeth and cause severe injuries. One option is focal use of botulinum toxin in the muscles of mastication. This can prevent injuries while the underlying disease process is treated.

Seizures occur in most patients with anti-NMDAR encephalitis. Status epilepticus can be a prominent feature and even the presenting feature. Various seizure medications are needed in these patients, although there is no clear evidence of one agent being superior in this disorder.⁶³ Levetiracetam may be associated with psychotic behavior, although it is frequently unclear how much this medication actually causes the symptom in these patients. Treatment of the underlying autoim-

mune problem generally results in remission of the seizures. Only a small group have persistent epilepsy after recovery.

Anti-NMDAR encephalitis generally involves prolonged attacks that last weeks to months. Patients may have a single event in their lifetime. However, relapses are a clear risk and a few patients have had 5 or more attacks spread out over decades. The degree of risk depends upon several factors and is strongly influenced by the type of immune therapy used during the first attack. Over the 3 years after an initial attack, patients who are not given immune therapy have about a 40% risk, those given IVIG, plasmapheresis, and/or steroids about 20%, and those given rituximab and/or cyclophosphamide about 10%.⁴² Patients without tumor had a higher risk of relapse. Relapses are in general milder than initial attacks and diagnosed more quickly. While the symptoms of anti-NMDAR encephalitis are diverse, patients often have relapse symptoms remarkably similar to the initial attack.

Patients are generally treated with a steroid pulse (solumedrol 1,000 mg/day for 3–5 days, followed by 2 week taper) and either IVIG (2 g/kg over 5 days) or plasmapheresis (5 exchanges).⁷ Rituximab is often started early in the disease course in patients with significant deficits (1 g × 2 dose separated by 2 weeks). Cyclophosphamide is given in monthly pulses (750 mg/m²) in patients who remain catatonic or comatose after the other treatments. This treatment can be stopped after significant improvement.

While most patients respond favorably to immune therapy within a few months, a subset of patients have more refractory and prolonged disease. These patients may remain comatose and critically ill for many months. It is unclear what treatments may benefit these refractory cases. Bortezomib has been used in case series.^{64,65} Tocilizumab has similarly been used for some refractory cases, and some centers have advocated for early use of this treatment as part of their protocol.⁶⁶ While some of these series report improvement, the patients have often been treated with multiple medications, which makes the precise benefit of each individual treatment hard to assess.

While Anti-LGI1 encephalitis is strongly associated with specific HLA types (see below), there are weaker associations for anti-NMDAR encephalitis.⁶⁷

Anti-LGI1 encephalitis

Anti-LGI1 encephalitis is the second most common of the CNS synaptic autoimmune disorders and affects mostly older adults (the median age is 60 years).⁶⁸ About 2/3 of patients are male. The primary symptoms are seizures and cognitive impairment. Compared to anti-NMDAR encephalitis, the onset may be more insidious, progressing over months in some cases. Diagnosis is often delayed as the cognitive symptoms may be misattributed to dementia.

The characteristic seizures associated with the disorder are faciobrachial dystonic seizures (FBDS).⁶⁹ FBDS involve rapid unilateral movements of the arm, shoulder and face. Each event is very brief, lasting a few seconds. In my experience, brief extension movements of the hand/arm are most common and movements extending to the shoulder and face are less common. Some patients have a sensory equivalent, reporting abnormal sensations extending up the arm to the jaw. Patients may progress to having hundreds of FBDS per day. Although each individual event is unilateral, patients generally progress to having events on both sides. FBDS may precede other symptoms of anti-LGI1 encephalitis. Recognition of the diagnosis in these patients and immune therapy prior to any cognitive deficits may be associated with a particularly good outcome. While FBDS are most common, patients may have diverse other seizure types including partial seizures with unawareness or generalized convulsions. Seizure medications are generally ineffective or only transiently effective for FBDS, and have only limited effects on other seizure types. In one analysis, seizures were unlikely to be controlled solely by seizure medications (without immune therapy) and carbamazepine was associated with better seizure control than levetiracetam.⁶³ Seizures respond rapidly to immune therapy, particularly steroids.^{70,71} It is common for FBDS to be dramatically reduced within 1 week of beginning a pulse of intravenous steroids, and typical for seizures to be completely controlled by immune therapy. Seizure medications may generally be tapered off after several months in patients responding to immune therapy. Seizures, like other symptoms, may recur if immune therapy is tapered too rapidly. Return of seizures in a patient with anti-LGI1 encephalitis whose seizures were previously controlled should be regarded as an indication of relapse.

About 60% of patients have hyponatremia, having characteristics similar to syndrome of inappropriate antidiuretic hormone secretion (SIADH), at some point during the illness.⁶⁸ This is usually mild and limited to the acute stages of illness, but can rarely persist for several months. The hyponatremia may occasionally be mistaken as the cause of symptoms rather than just one symptom of the disorder. Correction of the hyponatremia usually does not result in improvement of neurologic symptoms.

Anti-LGI1 encephalitis does not generally have an identifiable cause such as an infection or relevant tumor. While 5%–10% of patients may be found to have various cancers, most commonly thymoma, the great majority do not have relevant cancers.⁷² Anti-LGI1 encephalitis is strongly associated with HLA types DR7 (found in 88% of patients compared to 20% of controls) and DRB4 (found in 100% of patients and 46.5% of controls) in a Dutch population.⁷² Another study in a South

Korean population similarly found strong associations with HLA types DRB*07:01-DQB1*02:02 (91%), B*44:03 (73%) and C*07:06 (64%).⁷³ This study interestingly found no significant differences in HLA types of anti-NMDAR encephalitis patients and controls. A study from China also linked anti-LGI1 encephalitis with HLA-DRB1*03:01 and HLA-DQB1*02:01, and similarly found no associations with anti-NMDAR encephalitis.⁶⁷ A recent study in a multi-ethnic cohort found strong associations with HLA-DRB*07:01 and a lesser association with HLA-DRB1*04:02.⁷⁴ While these HLA types are significant risk factors, only a tiny fraction of individuals with these HLA types develop anti-LGI1 encephalitis. A study of prognostic features for anti-LGI1 encephalitis found that patients with CSF antibodies (as opposed to having antibodies only detected in serum) had more severe disease.³¹ Patients without HLA-DRB1*07:01 were more likely to be female and younger. However, HLA types were not independent predictors of disease severity in this study.

We do not have randomized controls to guide treatment but do have data from retrospective analyses. In one study of 118 patients with anti-LGI1 encephalitis, steroid treatment was significantly more likely to cause remission of FBDS and improvement of mRS scores compared to IVIG treatment.⁷¹ In this study the differences were stark, with IVIG appearing to have a much more modest effect. Another smaller series also showed a strong effect of steroids on clinical symptoms and LGI1 titers.⁷⁵ Steroid treatment with pulses of IV solumedrol often causes a dramatic decrease in FBDS within days. Cognitive symptoms tend to improve more slowly over several weeks to many months. Patients may require prolonged steroid therapy with slow tapers over many months. Rapid tapers may lead to relapse of symptoms.

Rituximab may also be a useful treatment option in patients with anti-LGI1 encephalitis.^{75,76} This option may be particularly useful in patients with severe disease, those who cannot tolerate the necessary doses of steroids, and those who relapse during steroid taper.

Patients typically have substantial improvement in seizures and cognitive symptoms. However, in one large series, residual memory symptoms and mild difficulty with spatial navigation was common two years later.⁷⁰ Some patients develop medial temporal sclerosis. About 35% of patients have relapses. These relapses can take two forms. First, patients may have worsening symptoms if immune suppression (particularly steroids) is tapered too rapidly. If recognized early, increasing steroids rapidly control these events. Patients may also have relapses even after being in remission for months or years off immune therapy. These relapses can be treated similarly to original attacks.

Anti-AMPA receptor encephalitis

AMPA antibodies are associated with a form of autoimmune encephalitis with similarities to anti-NMDAR encephalitis, but also important differences.^{77,78} Symptoms of confusion, memory loss, seizures, and agitation are common. Psychiatric symptoms are also typical, particularly psychosis with hallucinations and delusions. Hyponatremia is common at presentation. Hemiparesis and/or spasticity affects a significant fraction of patients. Abnormal movements or speech disruption may occur. Patients do not tend to have autonomic instability or characteristic movements seen in coma or catatonia to the degree that anti-NMDAR encephalitis patients do. The average age is much older than anti-NMDAR encephalitis, 60 years. Anti-AMPA encephalitis is much rarer than anti-NMDAR encephalitis and is particularly uncommon in children.

Lumbar puncture may show mild lymphocytic pleocytosis, and MRI may show increased T2 signal in the medial temporal lobes and other brain regions. The tumor profile is different than anti-NMDAR encephalitis with most patients have a tumor of the lung, breast, thymus, or other tissue, although a few have an ovarian teratoma. The response to immune therapy is somewhat worse on average. Patients may have other co-existing paraneoplastic antibodies or paraneoplastic syndromes.

Anti-GluK2 (kainate-receptor) encephalitis

Glutamate kainate receptor subunit 2 (GluK2) has recently been identified as an autoantigen.²⁰ Patients with GluK2 IgG1 antibodies most often have cerebellitis, but may have symptoms of confusion, delusions, memory loss, myoclonus, cognitive deficits and/or seizures. Hydrocephalus is surprisingly common with this antibody, a finding distinct from the other synaptic autoantibodies. GluK2 antibodies appear to be rarer than AMPA antibodies and much rarer than NMDAR antibodies. Cancer associations are still uncertain but one patient with Hodgkin lymphoma has been reported.

Although the data on antibody effects is limited compared to NMDAR antibodies, the antibodies do cause internalization of the receptor on cultured neurons, which results in loss of signaling at affected synapses. This mechanism therefore applies to all three types of glutamate ionotropic receptor antibodies.

GluK2 antibodies may be found at lower levels in a small group of patients with anti-AMPA encephalitis or anti-NMDAR encephalitis.

Anti-glycine receptor syndrome

Glycine receptor antibodies associate with the clinical syndrome of Progressive Encephalomyelitis with Rigidity and

Myoclonus (PERM).^{9,79} Patients are most often middle-aged adults, although pediatric cases occur. PERM patients have stiffness of the axial muscles and limbs, exaggerated startle responses, tremulousness, and alterations in mentation. Disabling muscle spasms and falls are common. Eye movement abnormalities such as ptosis and diplopia can be an important clue to the diagnosis. Seizures occur in a subset of patients and may co-exist with spasms and tremulousness. A subset of patients have thymoma, lymphoma or other tumors. Antibody responses to GAD65 or other antigens may co-exist with glycine receptor antibodies. MRI studies and EMG/NCS are most commonly normal.

The glycine receptor antibody syndrome has some resemblance to the stiff-person syndrome associated with GAD65 antibodies, and some patients may be clinically classified as having stiff person syndrome. However, patients with glycine antibodies have more rapid progression (although cases with insidious onset occur), higher likelihood of eye movement abnormalities, more pronounced startle responses, and more frequent cognitive impairments. Conversely, the glycine receptor antibody syndrome patients can have robust responses to immune therapy and may show dramatic recoveries, which is not typical of GAD65 antibody stiff-person syndrome. Relapses have been reported in some patients.

Anti-GABA-A receptor encephalitis

Autoantibodies to the GABA-A receptor are associated with a characteristic form of encephalitis characterized by particularly severe seizures and distinctive brain lesions on MRI.⁸⁰ This disease affects children and adults with a median age of 22 years and broad distribution. Patients commonly have diverse seizure types and many have epilepsy partialis continua (continuous focal motor seizures) or other forms of status epilepticus. Seizures tend to be refractory to treatment until the underlying autoimmune problem is treated. Patients may also appear to have stiff-person syndrome or opsoclonus-myoclonus. Brain lesions are characteristic areas of increased T2 signal involving cortical and subcortical areas. These lesions tend to appear and fade spontaneously until patients are given immune therapy. Large areas of cortical signal abnormality may occur with surprisingly few focal deficits. Patients tend to respond, at least partially, to immune therapy. The brain lesions generally resolve after immune therapy is effective.

Anti-Caspr2 syndromes

Caspr2 is an axonal membrane protein that strongly associates with Kv1 type potassium channels, organizing these channels in specific domains flanking nodes of Ranvier called juxtaparanodes.⁸¹ Autoantibodies to Caspr2 may bind to both

CNS and PNS axons, causing hyperexcitability of peripheral nerve axons and/or the CNS.⁸² Patients with Caspr2 antibodies may present with encephalitis similar to anti-LGI1 encephalitis but without the distinctive dystonic movements. Like anti-LGI1 encephalitis, the disease affects patients with a median age of 60 years and the presentation tends to be somewhat mildly and more insidious than anti-NMDAR encephalitis. Caspr2 antibody patients may present with Isaacs' syndrome, a form of peripheral nerve hyperexcitability causing cramps, fasciculations, hyperhidrosis, and characteristic neuromyotonic discharges on needle electromyography. Patients may have both symptom clusters: the combination of neuromyotonia, pain, hyperhidrosis, hallucinations, agitated delirium, and severe insomnia is called Morvan syndrome or Morvan fibrillary chorea.⁸³ In addition to these primary phenotypes, patients may alternatively (or in addition) present with pain syndromes (sometimes resembling painful peripheral neuropathy) or autonomic manifestations (such as Adie's pupil).

A subset of Caspr2 antibody patients (about 10%) have tumors, most typically thymoma. Patients with thymoma, especially, may have co-existing myasthenia gravis.⁸⁴ The combination of bulbar weakness (from myasthenia) and diffuse fasciculations may result in a presentation that mimics motor neuron disease (amyotrophic lateral sclerosis).

There is less data on treatment compared to the LGI1 syndrome, but steroids may be effective and rituximab may be helpful for difficult cases. Patients may have relapses of the illness even years after recovery, so ongoing monitoring is useful.

Anti-DPPX encephalitis

Autoantibodies to DPPX are associated with a syndrome of CNS and gastrointestinal hyperexcitability.^{25,85} Patients are mostly middle-aged men or women. A gastrointestinal prodrome with severe diarrhea and weight loss is typical. The CNS symptoms occur later and include agitation, confusion, tremors, and myoclonus. Some patients have brainstem or cerebellar symptoms. There may be exaggerated startle responses similar to those seen in glycine receptor antibody patients. Most patients have significant improvement with immune therapy. There is some risk of B cell neoplasms.

Anti-GABA-B receptor encephalitis with or without co-existing KCTD16 antibodies

Autoantibodies to GABA-B receptor associate with limbic encephalitis with severe seizures.⁸⁶ Patients tend to be middle-aged to older adults, and half of patients have small cell lung cancer (This disorder is the leading cause of autoimmune encephalitis in the setting of lung cancer). Some patients, particularly the ones with lung cancer may have co-existing Hu antibodies. The autoimmune disorder responds to immune

therapy in most cases, but the overall prognosis depends to a large degree on oncologic considerations.

A recent paper has reported that some patients may present with rapidly progressive dementia rather than encephalitis.⁸⁷ This same study showed that a majority of patients with GABA-B receptor antibodies also have antibodies to KCTD16 (potassium channel tetramerization domain containing 16), which is a protein that associates with GABA-B receptors. KCTD16 was nearly universal among patients with lung cancer, but also occurred in about 1/3 of patients without tumor.

Ophelia syndrome with mGluR5 antibodies

Ophelia syndrome was first described by Ian Carr and consists of a dissociative state (disconnected in space and time) in the setting of Hodgkin lymphoma.⁸⁸ Treatment of the lymphoma would result in improvement of the neurologic disorder. Autoantibodies to mGluR account for at least some of these cases, and other patients with a similar form of encephalitis, but without detectable lymphoma, have also been described.⁸⁹ The primary concern in these cases is a careful search for the relevant tumor and coordination with the treating oncologist for patients with tumor.

SEZ6L2 (seizure-related 6 homology 2) antibody syndrome

Autoantibodies to the brain membrane protein SEZ6L2 have been recently reported in a small number of patients with a cerebellar syndrome (ataxia, dysarthria) with extrapyramidal symptoms (bradykinesia, hypomimia, postural instability).⁹⁰ SEZ6L2 antibodies are predominantly IgG4 and do not cause internalization of their target antigen on cultured neurons.

Neurexin-3 α autoimmunity

Autoantibodies to neurexin-3 α have been reported in a small number of patients with confusion, seizures, and decreased awareness.²⁶ Patients may have mild orofacial dyskinesias. Some patients require respiratory support. The disease can be fatal but patients may respond to immune therapy. No tumors were reported in the initial small case series.

Neurexin-3 α is a presynaptic cell adhesion molecule and the antibodies deplete the target antigen, and decrease the number of synapses on neurons. Autoantibodies were mostly of the IgG1 subtype.

SECTION 3. ONCONEURONAL ANTIBODIES AS MARKERS OF ENCEPHALITIS

The onconeural antibody disorders are summarized in Table 2.

Anti-Hu (ANNA-1) syndromes

Anti-Hu are most strongly associated with sensory neuronopathy, which causes disabling sensory ataxia due to loss of primary somatosensory neurons.^{15,91} Patients may also (or alternatively) have cerebellar ataxia, encephalitis, or encephalomyelitis. Other phenotypes include enteric neuropathy, which involves destruction of the enteric nervous system with severe gastrointestinal dysmotility. Hu antibodies are much more common than the associated paraneoplastic disorders among patients with lung cancer, particularly at lower titer, so the presence of the antibodies by itself is not definitive of the diagnosis in the absence of appropriate symptoms and findings.⁹² The association with small cell tumors, especially small cell lung cancer is strong.

Since Hu antibodies target a group of intracellular antigens, they are not believed to be pathogenic and passive transfer experiments did not produce symptoms in animals.

Anti-Ri (ANNA-2) syndromes

Anti-Ri is associated with a brainstem syndrome (sometimes including paraneoplastic opsoclonus-myoclonus ataxia), cerebellar syndrome, myelopathy, neuropathy or other syndromes.⁹³ This antibody is strongly associated with tumors of the breast, lung or other organs.

Anti-Ma and anti-Ma2 syndromes

Ma2 antibodies, in isolation, are most commonly found in

men with testicular tumors.^{94,95} An encephalitis with prominent brainstem involvement and eye movement abnormalities is most typical.

When Ma and Ma2 antibodies are both present, the patients are more likely to be female and have other tumors. These patients more often show ataxia as part of their phenotype.

SECTION 4. CEREBELLAR SYNDROMES

The autoantibodies most relevant to autoimmune cerebellar syndromes are summarized in Table 3. Autoimmune cerebellitis, also known as paraneoplastic cerebellar degeneration, is a difficult diagnosis due to the diversity of rare causes. The likelihood of an autoimmune or paraneoplastic cause is relatively high for this presentation (a cerebellar disorder progressive over weeks to months without any obvious cause on brain imaging) compared to other phenotypes (such as new onset epilepsy or progressive memory loss).

The symptoms can be divided into 4 categories. 1) Ocular ataxia, nystagmus and misalignment. This symptom usually causes nausea and vertigo, which can be very disabling. Saccades may be hypermetric or hypometric. There may be ocular misalignment. 2) Limb ataxia with mis-reaching, incoordination, and tremors. Patients may also have head tremor, which can be debilitating. 3) Dysarthria. Speech is often harsh, strained, and difficult to understand. The staccato dysarthria seen with other types of cerebellar injuries is less common.

Table 2. Onconeuroal autoantibodies

Antibody	Clinical features	Cancer associations
Hu (ANNA1)	Sensory neuronopathy, encephalomyelitis, cerebellar syndromes, enteric neuropathy	Lung cancer (high risk) and other small cell tumors
Ri (ANNA2)	Brainstem syndrome, opsoclonus-myoclonus ataxia, cerebellar syndrome, myelopathy, neuropathy	Lung, breast, and other cancer
Ma2	Brainstem syndrome, encephalitis	Testicular cancer, other tumors

Table 3. Antibodies associated with autoimmune cerebellar syndromes

Antibody	Clinical features	Cancer associations
DNER	Cerebellar ataxia	Hodgkin lymphoma
Yo (PCA-1)	Cerebellar ataxia	Breast, ovarian, other female-specific tumors (high risk)
GAD65	Cerebellar ataxia, stiff person syndrome, type 1 diabetes, encephalitis, refractory epilepsy	Rare
mGluR1	Cerebellar ataxia	Lymphoma
Gluten ataxia	Cerebellar ataxia, possible overlap with celiac disease	Low risk
VGCC	Cerebellar ataxia, overlap with Lambert-Eaton syndrome	Lung cancer
GluK2	Cerebellar ataxia with cerebellar swelling, risk of CSF outflow obstruction	Thymoma, small cell lung cancer
SEZ6L2	Cerebellar syndrome with extrapyramidal symptoms	Ovarian cancer (risk profile still unclear)
KLHL11	Cerebellar and brainstem syndrome	Strong association with testicular seminoma

CSF, cerebrospinal fluid; DNER, delta/notch-like EGF-related receptor; GluK2, glutamate kainate receptor subunit 2; Kelch-like protein 11 (KLHL11); mGluR1, metabotropic glutamate receptor 1; SEZ6L2, seizure-related 6 homology 2; VGCC, voltage-gated calcium channels.

4) Gait ataxia with unsteadiness and difficulty timing and coordinating walking movements. This symptom can be disproportionately severe compared to limb ataxia tested in the sitting position. The relative severity of each symptom cluster varies from patient to patient even when the same autoimmune cause is present.

Patients tend to have progression of disability and response to immune therapy is often poor regardless of whether the associated antibody targets a cell-surface antigen or intracellular target. The goal is often to stabilize symptoms rather than to achieve the large improvements seen with autoimmune limbic encephalitis.

While there are diverse autoantibodies associated with cerebellar degeneration, the most common include anti-Yo (PCA-1) and anti-GAD65. However, there are a large and increasing number of other antigens associated with cerebellar ataxia, leading one group to use the apt term “Medusa head ataxia” to reflect the diverse immune mechanisms and other reported antibodies.⁹⁶⁻⁹⁸

Yo antibodies are very strongly associated with female-specific tumors, particularly breast and ovarian cancers.⁹⁹ Thorough evaluation for breast cancer (with mammogram and then breast MRI), ovarian tumors (pelvic MRI), cervical cancer (pap smear), and other rarer tumors is critical. The antibodies target an intracellular epitope, although some researchers believe they may still exert pathogenic effects. Patients have a relatively pure cerebellar phenotype and progression to significant disability.

GAD65 antibodies target the intracellular synaptic protein glutamic acid decarboxylase-65kD, which is responsible for producing GABA for synaptic release in neurons.¹⁰⁰ GAD65 antibodies associate with several distinct phenotypes including type 1 diabetes, stiff person syndrome, severe epilepsy, limbic encephalitis, and cerebellar ataxia.^{101,102} A recent paper has shown, however, that other patients with cerebellar ataxia have autoantibodies restricted to the GAD67 isoform.¹⁰³ The antibodies probably are not directly pathogenic since they cannot readily access the target on living neurons. GAD65 responses may be seen in some normal individuals or in persons with prior encephalitis. Patients with the neurologic disorders have strong GAD65 responses in both CSF and serum. The ataxia patients usually present with a pure cerebellar syndrome. However, some patients may also show signs of stiff person syndrome or develop signs of the other GAD65 associated disorders (type 1 diabetes, etc.). Tumors are uncommon in GAD65 disorders in general. One recent study has suggested that patients with GAD65 antibodies and cerebellar ataxia may benefit from a gluten-free diet.¹⁰⁴

DNER antibodies (previously known as anti-Tr) target a brain membrane protein of uncertain function that is expressed

in cerebellum.⁶ Patients with DNER present with an acute or subacute cerebellar syndrome.^{105,106} DNER autoimmunity is strongly associated with Hodgkin lymphoma, so treatment of the cancer itself typically involves powerful immune suppression and should not be delayed. Autoantibodies to mGluR1 have also been reported in patients with cerebellar degeneration (some with Hodgkin lymphoma) and antibodies to Homer-3, which organizes mGluR1 at synapses, have also been reported.^{97,107}

Kelch-like protein 11 (KLHL11) antibodies associate with a cerebellar and brainstem syndrome that is strongly linked to testicular seminoma.^{108,109} Some patients may have hearing loss or seizures. KLHL11 is an intracellular protein, so the antibodies are unlikely to be pathogenic. It should be noted that Ma2 antibodies also associate with testicular tumors and a similar phenotype.

As discussed above, GluK2 (kainate) receptor antibodies are associated with an autoimmune cerebellar syndrome that is distinct due to the high risk of severe cerebellar edema and obstruction of CSF outflow, a phenomenon that would be highly unusual in the other disorders.

VGCC antibodies are most strongly associated with Lambert-Eaton myasthenic syndrome (LEMS), a disorder of muscle fatigue and weakness. LEMS is a neuromuscular junction disorder and has characteristic findings on nerve conduction studies (very low amplitude motor responses and marked facilitation with exercise among other characteristics). However, some patients with VGCC antibodies may have cerebellar ataxia.⁹⁶ The cerebellar findings could present along with the neuromuscular disorder, or in isolation, or separated in time from the neuromuscular presentation. These syndromes involve a significant risk of lung cancer.

The diagnosis of gluten ataxia should also be considered as an underdiagnosed potential cause of autoimmune cerebellar ataxia. These patients have characteristics more similar to non-celiac gluten sensitivity than the celiac disease.¹¹⁰

Guidelines have been proposed for diagnosing primary autoimmune cerebellar ataxia in cases without informative antibodies.¹¹¹ The diagnostic criteria require an acute or subacute cerebellar syndrome, normal MRI (or MRI showing vermin atrophy), exclusion of alternative causes, and 2 of the following 3 items: 1) family or personal history of autoimmunity, 2) CSF inflammation, or 3) other autoantibodies that are not directly diagnostic but supportive of a tendency to autoimmunity.

SECTION 5. SPECIAL SITUATIONS

Autoimmune epilepsy and new onset refractory status epilepticus

New onset refractory status epilepticus (NORSE) is a syndrome with diverse causes. Autoimmune causes have drawn particular interest due to the increasing recognition that specific CNS autoantibody diseases can present with status epilepticus. In a series of 130 NORSE patients, Gaspard et al.¹¹² found autoimmune and paraneoplastic cases in 19% and 18% of cases, accounting for 70% of cases where an etiology could be found. However, it is not clear whether all of the antibodies found indicate a true autoimmune mechanism, and certain tests, such as GABA-B receptor antibodies, were done only in small subsets of patients. While testing patients with NORSE for autoimmune causes is reasonable, the true yield is unclear. It is unclear what empiric immune therapy is appropriate for patients with NORSE without defined autoimmune disorders.¹¹³

While patients with the CNS synaptic autoimmune disorders are at risk for sudden onset refractory epilepsy and status epilepticus, it is unclear how often an immune mechanism may be present in patients with chronic epilepsy. GAD65 antibodies have drawn particular attention in this setting. One series found a very low rate of GAD65 antibodies in patients with epilepsy (<1%) overall.¹¹⁴ However, another study focusing on patients with therapy-resistance epilepsy found a higher rate.¹¹⁵

Several predictive scores, including APE2 and RITE2, have been proposed to predict which patients with NORSE may be more likely to have autoimmune causes.¹¹⁶ In one study, patients with prodromal fever, absence of behavioral/memory problems prior to seizures, absence of dyskinesia during impaired alertness, and symmetric T2 MRI changes were more likely to have cryptogenic NORSE and less likely to have autoimmune causes.¹¹⁷

Schizophrenia and new-onset psychosis

It is controversial how commonly patients with schizophrenia or new onset psychosis may have autoantibodies to synaptic antigens, especially NMDAR. Several studies report NMDAR antibodies in up to 10%–15% of patients with schizophrenia, and have considered whether these antibodies may relate to pathogenesis (for a review see¹¹⁸). However, the methods used are not the standard autoantibody tests employed in anti-NMDAR encephalitis, and others have cast doubt on the relevance of these findings.¹¹⁹ The papers reporting the highest levels of antibodies rely on low titer serum responses of the IgA or IgD or IgM subtype.¹²⁰ These papers do not provide evidence of a response to immune therapy or other

evidence of brain autoimmunity (CSF inflammation, brain MRI changes, etc.). The rate of the IgG antibodies associated with anti-NMDAR encephalitis in new onset psychosis patients may <1%.¹²¹ In a study of 387 patients with first episode of psychosis, 3.9% were found to be seropositive for NMDAR antibodies using a live cell-based assay.¹²² However, other confirmatory studies to support actual anti-NMDAR encephalitis were not reported and the patients responded similarly to seronegative patients to antipsychotic medications. Another study of 621 patients with new onset psychosis, schizophrenia, schizoaffective disorder and related diagnoses found a very low incidence of weak serum antibody responses in patients, similar to controls.¹²³ These responses were not accompanied by reactivity to brain sections or neurons and were thought to not be significant. While NMDAR encephalitis and related disorders should always be considered in the evaluation of new onset psychosis, the likelihood of these diagnoses is low.

Encephalitis after immune checkpoint inhibitor therapy

Immune checkpoint inhibitors, particularly PD-1 and PD-L1 inhibitors, have increasingly been used to treat a variety of cancers. Autoimmunity is a risk of these treatments and can affect many organ systems including the thyroid gland, muscle and the nervous system. A wide range of neurologic autoimmune diseases have been reported, including myositis, autoimmune neuropathies, Lambert-Eaton syndrome, myasthenia gravis, encephalitis, cerebellar ataxia, and brainstem encephalitis.^{47,124,125} While the associations of specific tumors with specific neurologic disorders are maintained to some degree, the probability of autoimmune disorders occurring seems markedly increased after these therapies. In a patient with a suspected autoimmune or paraneoplastic disorder, it is important to consider whether these treatments have been given and to avoid using them further. A prior history of an autoimmune or paraneoplastic disorder may be a relative contraindication to using these treatments.

Critical analysis of laboratory testing

The expansion of antibody testing panels that are used in patients with autoimmune encephalitis can result in false-positive results. These results can disrupt care by resulting in inappropriate cancer screening tests, biopsies, and unnecessary immune therapy. One analysis of 500 sequently paraneoplastic panels found that a majority of positive results were false positives.¹²⁶ Certain tests, such as the ganglionic acetylcholine receptor antibody test, the voltage-gated potassium channel antibody test, and the VGCC antibody test may have low titer false positives. False positive results for cell-based assays

for the synaptic antibodies (NMDAR, AMPAR, etc.) are uncommon, especially in CSF. When faced with such results it is important to consider whether the test result is a plausible fit for the disease in question. It is also important to consider the specificity of the result at the reported titer. Repeating such tests at another laboratory can be helpful, since irreproducible results are unlikely to be significant. However, the persistence of a result does not guarantee clinical relevance.

CONCLUSIONS

Autoantibody encephalitis involves distinct clinical syndromes that can be recognized in many cases. In other patients, cancer screening and rational antibody testing can lead to a precise diagnosis. Our knowledge about the optimal treatments is still hampered by the lack of randomized treatment trials, but new information from retrospective studies has provided important new information on treatment of anti-LGI1 and anti-NMDAR syndromes. In selecting treatments it is important to understand the underlying disease mechanisms and the evidence supporting treatment. There will almost certainly be additional autoantibody syndromes discovered in the coming year. Each disease teaches us about the neuroscience of the target antigens. It is not reasonable to expect a general neurologist to memorize the associations of each new antibody. Rather, the goal should be to read and review the cancer associations and treatment guidance for a specific antibody when encountering a case.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

ORCID iD

Eric Lancaster <https://orcid.org/0000-0001-6131-2698>

Conflicts of Interest

The author has no potential conflicts of interest to disclose.

Funding Statement

None

REFERENCES

- Gleichman AJ, Spruce LA, Dalmau J, Seeholzer SH, Lynch DR. Anti-NMDA receptor encephalitis antibody binding is dependent on amino acid identity of a small region within the GluN1 amino terminal domain. *J Neurosci* 2012;32:11082-11094.
- Gleichman AJ, Panzer JA, Baumann BH, Dalmau J, Lynch DR. Antigenic and mechanistic characterization of anti-AMPA receptor encephalitis. *Ann Clin Transl Neurol* 2014;1:180-189.
- Olsen AL, Lai Y, Dalmau J, Scherer SS, Lancaster E. Caspr2 autoantibodies target multiple epitopes. *Neurol Neuroimmunol Neuroinflamm* 2015;2:e127.
- Rauschenberger V, von Wardenburg N, Schaefer N, Ogino K, Hirata H, Lillesaar C, et al. Glycine receptor autoantibodies impair receptor function and induce motor dysfunction. *Ann Neurol* 2020;88:544-561.
- Lindstrom J, Luo J. Myasthenogenicity of the main immunogenic region. *Ann N Y Acad Sci* 2012;1274:9-13.
- Greene M, Lai Y, Pajcini K, Bailis W, Pear WS, Lancaster E. Delta/Notch-Like EGF-related receptor (DNER) is not a Notch ligand. *PLoS One* 2016;11:e0161157.
- Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011;10:63-74.
- Makarovsky I, Markel G, Hoffman A, Schein O, Brosh-Nissimov T, Tashma Z, et al. Strychnine--a killer from the past. *Isr Med Assoc J* 2008;10:142-145.
- Carvajal-González A, Leite MI, Waters P, Woodhall M, Coutinho E, Balint B, et al. Glycine receptor antibodies in PERM and related syndromes: characteristics, clinical features and outcomes. *Brain* 2014;137(Pt 8):2178-2192.
- Szabo A, Dalmau J, Manley G, Rosenfeld M, Wong E, Henson J, et al. HuD, a paraneoplastic encephalomyelitis antigen, contains RNA-binding domains and is homologous to Elav and Sex-lethal. *Cell* 1991;67:325-333.
- Okano HJ, Darnell RB. A hierarchy of Hu RNA binding proteins in developing and adult neurons. *J Neurosci* 1997;17:3024-3037.
- Sillevis Smitt PA, Manley GT, Posner JB. Immunization with the paraneoplastic encephalomyelitis antigen HuD does not cause neurologic disease in mice. *Neurology* 1995;45:1873-1878.
- Bernal F, Graus F, Pifarré A, Saiz A, Benyahia B, Ribalta T. Immunohistochemical analysis of anti-Hu-associated paraneoplastic encephalomyelitis. *Acta Neuropathol* 2002;103:509-515.
- Greenlee JE, Clawson SA, Hill KE, Wood BL, Tsunoda I, Carlson NG. Purkinje cell death after uptake of anti-Yo antibodies in cerebellar slice cultures. *J Neuropathol Exp Neurol* 2010;69:997-1007.
- Graus F, Keime-Guibert F, Reñe R, Benyahia B, Ribalta T, Ascaso C, et al. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. *Brain* 2001;124:1138-1148.
- Moscato EH, Jain A, Peng X, Hughes EG, Dalmau J, Balice-Gordon RJ. Mechanisms underlying autoimmune synaptic encephalitis leading to disorders of memory, behavior and cognition: insights from molecular, cellular and synaptic studies. *Eur J Neurosci* 2010;32:298-309.
- Planagumà J, Leypoldt F, Mannara F, Gutiérrez-Cuesta J, Martín-García E, Aguilar E, et al. Human N-methyl D-aspartate receptor antibodies alter memory and behaviour in mice. *Brain* 2015;138(Pt 1):94-109.
- Planagumà J, Haselmann H, Mannara F, Petit-Pedrol M, Grünewald B, Aguilar E, et al. Ephrin-B2 prevents N-methyl-D-aspartate receptor antibody effects on memory and neuroplasticity. *Ann Neurol* 2016;80:388-400.
- Peng X, Hughes EG, Moscato EH, Parsons TD, Dalmau J, Balice-Gordon RJ. Cellular plasticity induced by anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor encephalitis antibodies. *Ann Neurol* 2015;77:381-398.
- Landa J, Guasp M, Míguez-Cabello F, Guimaraes J, Mishima T, Oda F, et al. Encephalitis with autoantibodies against the glutamate kainate receptors GluK2. *Ann Neurol* 2021;90:101-117.
- Ohkawa T, Fukata Y, Yamasaki M, Miyazaki T, Yokoi N, Takashima H, et al. Autoantibodies to epilepsy-related LGI1 in limbic encephalitis neutralize LGI1-ADAM22 interaction and reduce synaptic AMPA receptors. *J Neurosci* 2013;33:18161-18174.
- Davies AM, Sutton BJ. Human IgG4: a structural perspective. *Immunol Rev* 2015;268:139-159.
- Gadoth A, Zekeridou A, Klein CJ, Thoreson CJ, Majed M, Dubey D, et al. Elevated LGI1-IgG CSF index predicts worse neurological outcome. *Ann Clin Transl Neurol* 2018;5:646-650.

24. Huijbers MG, Querol LA, Niks EH, Plomp JJ, van der Maarel SM, Graus F, et al. The expanding field of IgG4-mediated neurological autoimmune disorders. *Eur J Neurol* 2015;22:1151-1161.
25. Hara M, Ariño H, Petit-Pedrol M, Sabater L, Titulaer MJ, Martínez-Hernández E, et al. DPPX antibody-associated encephalitis: main syndrome and antibody effects. *Neurology* 2017;88:1340-1348.
26. Gresa-Arribas N, Planagumà J, Petit-Pedrol M, Kawachi I, Katada S, Glaser CA, et al. Human neurexin-3α antibodies associate with encephalitis and alter synapse development. *Neurology* 2016;86:2235-2242.
27. Dalakas MC. IgG4-mediated neurologic autoimmunities: understanding the pathogenicity of IgG4, ineffectiveness of IVIg, and long-lasting benefits of anti-B cell therapies. *Neurol Neuroimmunol Neuroinflamm* 2022;9:e1116.
28. Tüzün E, Zhou L, Baehring JM, Bannykh S, Rosenfeld MR, Dalmau J. Evidence for antibody-mediated pathogenesis in anti-NMDAR encephalitis associated with ovarian teratoma. *Acta Neuropathol* 2009; 118:737-743.
29. Pittock SJ, Lennon VA, McKeon A, Mandrekar J, Weinschenker BG, Lucchinetti CF, et al. Eculizumab in AQP4-IgG-positive relapsing neuromyelitis optica spectrum disorders: an open-label pilot study. *Lancet Neurol* 2013;12:554-562.
30. Höftberger R, Titulaer MJ, Sabater L, Dome B, Rózsás A, Hegedus B, et al. Encephalitis and GABAB receptor antibodies: novel findings in a new case series of 20 patients. *Neurology* 2013;81:1500-1506.
31. Muñoz-Castrillo S, Haesebaert J, Thomas L, Vogrig A, Pinto AL, Picard G, et al. Clinical and prognostic value of immunogenetic characteristics in anti-LGI1 encephalitis. *Neurol Neuroimmunol Neuroinflamm* 2021;8:e974.
32. McCracken L, Zhang J, Greene M, Crivaro A, Gonzalez J, Kamoun M, et al. Improving the antibody-based evaluation of autoimmune encephalitis. *Neurol Neuroimmunol Neuroinflamm* 2017;4:e404.
33. Ruiz-García R, Muñoz-Sánchez G, Naranjo L, Guasp M, Sabater L, Saiz A, et al. Limitations of a commercial assay as diagnostic test of autoimmune encephalitis. *Front Immunol* 2021;12:691536.
34. Gresa-Arribas N, Titulaer M, Leypoldt F, Rosenfeld MR, Graus F, Dalmau J. Sensitivity of antibody testing, clinica-titer correlations, and epitope repertoire in anti-NMDAR encephalitis. *Ann Neurol* 2013; 74:S25.
35. Gresa-Arribas N, Titulaer MJ, Torrents A, Aguilar E, McCracken L, Leypoldt F, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol* 2014;13:167-177.
36. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016;15:391-404.
37. Graus F, Delattre JY, Antoine JC, Dalmau J, Giometto B, Grisold W, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry* 2004;75:1135-1140.
38. Clowse ME, Behera MA, Anders CK, Copland S, Coffman CJ, Lepert PC, et al. Ovarian preservation by GnRH agonists during chemotherapy: a meta-analysis. *J Womens Health (Larchmt)* 2009;18: 311-319.
39. Nosadini M, Gadian J, Lim M, Sartori S, Thomas T, Dale RC. Mycophenolate mofetil in paediatric autoimmune or immune-mediated diseases of the central nervous system: clinical experience and recommendations. *Dev Med Child Neurol* 2019;61:458-468.
40. Titulaer MJ, Dalmau J. Seizures as first symptom of anti-NMDA receptor encephalitis are more common in men. *Neurology* 2014;82: 550-551.
41. Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol* 2009;66:11-18.
42. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol* 2013;12:157-165.
43. Yeshokumar AK, Sun LR, Klein JL, Baranano KW, Pardo CA. Gait disturbance as the presenting symptom in young children with anti-NMDA receptor encephalitis. *Pediatrics* 2016;138:e20160901.
44. Gordon-Lipkin E, Yeshokumar AK, Saylor D, Arenivas A, Probasco JC. Comparative outcomes in children and adults with anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis. *J Child Neurol* 2017;32:930-935.
45. Titulaer M, McCracken L, Cuellar IG, Martínez-Hernández E, Graus F, Balice-Gordon R, et al. Clinical features, treatment, and outcome of 500 patients with anti-NMDA receptor encephalitis. *Neurology* 2012;78(1 Supplement):PL01.001.
46. Ances BM, Vitaliani R, Taylor RA, Liebeskind DS, Voloschin A, Houghton DJ, et al. Treatment-responsive limbic encephalitis identified by neuropil antibodies: MRI and PET correlates. *Brain* 2005; 128(Pt 8):1764-1777.
47. Gill A, Perez MA, Perrone CM, Bae CJ, Pruitt AA, Lancaster E. A case series of PD-1 inhibitor-associated paraneoplastic neurologic syndromes. *J Neuroimmunol* 2019;334:576980.
48. Kobayashi Y, Sato M, Kinoshita M, Kakizawa M, Higuchi K, Yamada M, et al. An elderly case of paraneoplastic anti-NMDA receptor encephalitis associated with small-cell lung cancer expressing NR1 subunits. *Intern Med* 2020;59:2307-2309.
49. Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007;61:25-36.
50. Deng S, Qiu K, Liu H, Wu X, Lei Q, Lu W. Clinical characteristics and short-term prognosis of autoimmune encephalitis: a single-center cohort study in Changsha, China. *Front Neurol* 2019;10:539.
51. Armangué T, Leypoldt F, Málaga I, Raspall-Chaure M, Martí I, Nichter C, et al. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. *Ann Neurol* 2014;75:317-323.
52. Höftberger R, Armangué T, Leypoldt F, Graus F, Dalmau J. Clinical neuropathology practice guide 4-2013: post-herpes simplex encephalitis: N-methyl-D-aspartate receptor antibodies are part of the problem. *Clin Neuropathol* 2013;32:251-254.
53. Salovin A, Glanzman J, Roslin K, Armangué T, Lynch DR, Panzer JA. Anti-NMDA receptor encephalitis and nonencephalitic HSV-1 infection. *Neurol Neuroimmunol Neuroinflamm* 2018;5:e458.
54. Balu R, McCracken L, Lancaster E, Graus F, Dalmau J, Titulaer MJ. A score that predicts 1-year functional status in patients with anti-NMDA receptor encephalitis. *Neurology* 2019;92:e244-e252.
55. Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology* 2012;79:1094-1100.
56. Sonderer AV, Arends S, Tavy DLJ, Bastiaansen AEM, Bruijn MAAM, Schreurs MWJ, et al. Predictive value of electroencephalography in anti-NMDA receptor encephalitis. *J Neurol Neurosurg Psychiatry* 2018; 89:1101-1106.
57. Kerik-Rotenberg N, Diaz-Meneses I, Hernandez-Ramirez R, Muñoz-Casillas R, Reynoso-Mejia CA, Flores-Rivera J, et al. A metabolic brain pattern associated with anti-N-methyl-D-aspartate receptor encephalitis. *Psychosomatics* 2020;61:39-48.
58. Probasco JC, Benavides DR, Ciarallo A, Sanin BW, Wabulya A, Berggey GK, et al. Electroencephalographic and fluorodeoxyglucose-positron emission tomography correlates in anti-N-methyl-d-aspartate receptor autoimmune encephalitis. *Epilepsy Behav Case Rep* 2014;2: 174-178.
59. Probasco JC, Solnes L, Nalluri A, Cohen J, Jones KM, Zan E, et al. Abnormal brain metabolism on FDG-PET/CT is a common early finding in autoimmune encephalitis. *Neurol Neuroimmunol Neuroinflamm* 2017;4:e352.
60. Martínez-Hernández E, Guasp M, García-Serra A, Maudes E, Ariño H, Sepulveda M, et al. Clinical significance of anti-NMDAR concur-

- rent with glial or neuronal surface antibodies. *Neurology* 2020;94:e2302-e2310.
61. Titulaer MJ, Höftberger R, Iizuka T, Leypoldt F, McCracken L, Cellucci T, et al. Overlapping demyelinating syndromes and anti-N-methyl-D-aspartate receptor encephalitis. *Ann Neurol* 2014;75:411-428.
 62. Lim JA, Lee ST, Kim TJ, Moon J, Sunwoo JS, Byun JI, et al. Frequent rhabdomyolysis in anti-NMDA receptor encephalitis. *J Neuroimmunol* 2016;298:178-180.
 63. de Bruijn MAAM, van Sonderen A, van Coevorden-Hameete MH, Bastiaansen AEM, Schreurs MWJ, Rouhl RPW, et al. Evaluation of seizure treatment in anti-LGI1, anti-NMDAR, and anti-GABABR encephalitis. *Neurology* 2019;92:e2185-e2196.
 64. Wang T, Wang B, Zeng Z, Li H, Zhang F, Ruan X, et al. Efficacy and safety of bortezomib in rituximab-resistant anti-N-methyl-d-aspartate receptor (anti-NMDAR) encephalitis as well as the clinical characteristics: an observational study. *J Neuroimmunol* 2021;354:577527.
 65. Scheibe F, Prüss H, Mengel AM, Kohler S, Nümann A, Köhnlein M, et al. Bortezomib for treatment of therapy-refractory anti-NMDA receptor encephalitis. *Neurology* 2017;88:366-370.
 66. Lee WJ, Lee ST, Shin YW, Lee HS, Shin HR, Kim DY, et al. Teratoma removal, steroid, IVIG, rituximab and tocilizumab (T-SIRT) in anti-NMDAR encephalitis. *Neurotherapeutics* 2021;18:474-487.
 67. Hu F, Liu X, Zhang L, Chen C, Gong X, Lin J, et al. Novel findings of HLA association with anti-LGI1 encephalitis: HLA-DRB1*03:01 and HLA-DQB1*02:01. *J Neuroimmunol* 2020;344:577243.
 68. Lai M, Huijbers MG, Lancaster E, Graus F, Bataller L, Balice-Gordon R, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. *Lancet Neurol* 2010;9:776-785.
 69. Irani SR, Michell AW, Lang B, Pettingill P, Waters P, Johnson MR, et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. *Ann Neurol* 2011;69:892-900.
 70. van Sonderen A, Thijs RD, Coenders EC, Jiskoot LC, Sanchez E, de Bruijn MA, et al. Anti-LGI1 encephalitis: clinical syndrome and long-term follow-up. *Neurology* 2016;87:1449-1456.
 71. Rodriguez A, Klein CJ, Sechi E, Alden E, Basso MR, Pudumjee S, et al. LGI1 antibody encephalitis: acute treatment comparisons and outcome. *J Neurol Neurosurg Psychiatry* 2022;93:309-315.
 72. van Sonderen A, Roelen DL, Stoop JA, Verdijk RM, Haasnoot GW, Thijs RD, et al. Anti-LGI1 encephalitis is strongly associated with HLA-DR7 and HLA-DRB4. *Ann Neurol* 2017;81:193-198.
 73. Kim TJ, Lee ST, Moon J, Sunwoo JS, Byun JI, Lim JA, et al. Anti-LGI1 encephalitis is associated with unique HLA subtypes. *Ann Neurol* 2017;81:183-192.
 74. Peris Sempere V, Muñoz-Castrillo S, Ambati A, Binks S, Pinto AL, Rogemond V, et al. Human leukocyte antigen association study reveals DRB1*04:02 effects additional to DRB1*07:01 in anti-LGI1 encephalitis. *Neurol Neuroimmunol Neuroinflamm* 2022;9:e1140.
 75. Irani SR, Gelfand JM, Bettcher BM, Singhal NS, Geschwind MD. Effect of rituximab in patients with leucine-rich, glioma-inactivated 1 antibody-associated encephalopathy. *JAMA Neurol* 2014;71:896-900.
 76. Brown JW, Martin PJ, Thorpe JW, Michell AW, Coles AJ, Cox AL, et al. Long-term remission with rituximab in refractory leucine-rich glioma inactivated 1 antibody encephalitis. *J Neuroimmunol* 2014;271:66-68.
 77. Lai M, Hughes EG, Peng X, Zhou L, Gleichman AJ, Shu H, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. *Ann Neurol* 2009;65:424-434.
 78. Höftberger R, van Sonderen A, Leypoldt F, Houghton D, Geschwind M, Gelfand J, et al. Encephalitis and AMPA receptor antibodies: novel findings in a case series of 22 patients. *Neurology* 2015;84:2403-2412.
 79. Hutchinson M, Waters P, McHugh J, Gorman G, O'Riordan S, Connolly S, et al. Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. *Neurology* 2008;71:1291-1292.
 80. Petit-Pedrol M, Armangue T, Peng X, Bataller L, Cellucci T, Davis R, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. *Lancet Neurol* 2014;13:276-286.
 81. Horresh I, Poliak S, Grant S, Bredt D, Rasband MN, Peles E. Multiple molecular interactions determine the clustering of Caspr2 and Kv1 channels in myelinated axons. *J Neurosci* 2008;28:14213-14222.
 82. Lancaster E, Huijbers MG, Bar V, Boronat A, Wong A, Martinez-Hernandez E, et al. Investigations of Caspr2, an autoantigen of encephalitis and neuromyotonia. *Ann Neurol* 2011;69:303-311.
 83. Irani SR, Pettingill P, Kleopa KA, Schiza N, Waters P, Mazia C, et al. Morvan syndrome: clinical and serological observations in 29 cases. *Ann Neurol* 2012;72:241-255.
 84. Fleisher J, Richie M, Price R, Scherer S, Dalmau J, Lancaster E. Acquired neuromyotonia heralding recurrent thymoma in myasthenia gravis. *JAMA Neurol* 2013;70:1311-1314.
 85. Boronat A, Gelfand JM, Gresa-Arribas N, Jeong HY, Walsh M, Roberts K, et al. Encephalitis and antibodies to dipeptidyl-peptidase-like protein-6, a subunit of Kv4.2 potassium channels. *Ann Neurol* 2013;73:120-128.
 86. Lancaster E, Lai M, Peng X, Hughes E, Constantinescu R, Raizer J, et al. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. *Lancet Neurol* 2010;9:67-76.
 87. van Coevorden-Hameete MH, de Bruijn MAAM, de Graaff E, Bastiaansen DAEM, Schreurs MWJ, Demmers JAA, et al. The expanded clinical spectrum of anti-GABABR encephalitis and added value of KCTD16 autoantibodies. *Brain* 2019;142:1631-1643.
 88. Carr I. The Ophelia syndrome: memory loss in Hodgkin's disease. *Lancet* 1982;1:844-845.
 89. Lancaster E, Martinez-Hernandez E, Titulaer MJ, Boulos M, Weaver S, Antoine JC, et al. Antibodies to metabotropic glutamate receptor 5 in the Ophelia syndrome. *Neurology* 2011;77:1698-1701.
 90. Landa J, Guasp M, Petit-Pedrol M, Martínez-Hernández E, Planagumà J, Saiz A, et al. Seizure-related 6 homolog like 2 autoimmunity: neurologic syndrome and antibody effects. *Neurol Neuroimmunol Neuroinflamm* 2021;8:e916.
 91. Dalmau J, Graus F, Rosenblum MK, Posner JB. Anti-Hu--associated paraneoplastic encephalomyelitis/sensory neuronopathy. A clinical study of 71 patients. *Medicine (Baltimore)* 1992;71:59-72.
 92. Dalmau J, Furneaux HM, Gralla RJ, Kris MG, Posner JB. Detection of the anti-Hu antibody in the serum of patients with small cell lung cancer--a quantitative western blot analysis. *Ann Neurol* 1990;27:544-552.
 93. Luque FA, Furneaux HM, Ferziger R, Rosenblum MK, Wray SH, Schold SC Jr, et al. Anti-Ri: an antibody associated with paraneoplastic opsoclonus and breast cancer. *Ann Neurol* 1991;29:241-251.
 94. Dalmau J, Graus F, Villarejo A, Posner JB, Blumenthal D, Thiessen B, et al. Clinical analysis of anti-Ma2-associated encephalitis. *Brain* 2004;127(Pt 8):1831-1844.
 95. Hoffmann LA, Jarius S, Pellkofer HL, Schueller M, Krumbholz M, Koenig F, et al. Anti-Ma and anti-Ta associated paraneoplastic neurological syndromes: 22 newly diagnosed patients and review of previous cases. *J Neurol Neurosurg Psychiatry* 2008;79:767-773.
 96. Jarius S, Wildemann B. 'Medusa head ataxia': the expanding spectrum of Purkinje cell antibodies in autoimmune cerebellar ataxia. Part 2: anti-PKC-gamma, anti-GluR-delta2, anti-Ca/ARHGAP26 and anti-VGCC. *J Neuroinflammation* 2015;12:167.
 97. Jarius S, Wildemann B. 'Medusa-head ataxia': the expanding spectrum of Purkinje cell antibodies in autoimmune cerebellar ataxia. Part 1: anti-mGluR1, anti-Homer-3, anti-Sj/ITPR1 and anti-CARP VIII. *J Neuroinflammation* 2015;12:166.
 98. Jarius S, Wildemann B. 'Medusa head ataxia': the expanding spec-

- trum of Purkinje cell antibodies in autoimmune cerebellar ataxia. Part 3: anti-Yo/CDR2, anti-Nb/AP3B2, PCA-2, anti-Tr/DNER, other antibodies, diagnostic pitfalls, summary and outlook. *J Neuroinflammation* 2015;12:168.
99. Peterson K, Rosenblum MK, Kotanides H, Posner JB. Paraneoplastic cerebellar degeneration. I. A clinical analysis of 55 anti-Yo antibody-positive patients. *Neurology* 1992;42:1931-1937.
 100. Tian N, Petersen C, Kash S, Baekkeskov S, Copenhagen D, Nicoll R. The role of the synthetic enzyme GAD65 in the control of neuronal gamma-aminobutyric acid release. *Proc Natl Acad Sci U S A* 1999;96:12911-12916.
 101. McKeon A, Robinson MT, McEvoy KM, Matsumoto JY, Lennon VA, Ahlskog JE, et al. Stiff-man syndrome and variants: clinical course, treatments, and outcomes. *Arch Neurol* 2012;69:230-238.
 102. Pittock SJ, Yoshikawa H, Ahlskog JE, Tisch SH, Benarroch EE, Kryzer TJ, et al. Glutamic acid decarboxylase autoimmunity with brainstem, extrapyramidal, and spinal cord dysfunction. *Mayo Clin Proc* 2006;81:1207-1214.
 103. Guasp M, Solà-Valls N, Martínez-Hernández E, Gil MP, González C, Brieva L, et al. Cerebellar ataxia and autoantibodies restricted to glutamic acid decarboxylase 67 (GAD67). *J Neuroimmunol* 2016;300:15-17.
 104. Hadjivassiliou M, Sarrigiannis PG, Shanmugarajah PD, Sanders DS, Grünewald RA, Zis P, et al. Clinical characteristics and management of 50 patients with anti-GAD ataxia: gluten-free diet has a major impact. *Cerebellum* 2021;20:179-185.
 105. de Graaff E, Maat P, Hulsboom E, van den Berg R, van den Bent M, Demmers J, et al. Identification of delta/notch-like epidermal growth factor-related receptor as the Tr antigen in paraneoplastic cerebellar degeneration. *Ann Neurol* 2012;71:815-824.
 106. Greene M, Lai Y, Baella N, Dalmau J, Lancaster E. Antibodies to Delta/notch-like epidermal growth factor-related receptor in patients with anti-Tr, paraneoplastic cerebellar degeneration, and Hodgkin lymphoma. *JAMA Neurol* 2014;71:1003-1008.
 107. Coesmans M, Smitt PA, Linden DJ, Shigemoto R, Hirano T, Yamakawa Y, et al. Mechanisms underlying cerebellar motor deficits due to mGluR1-autoantibodies. *Ann Neurol* 2003;53:325-336.
 108. Dubey D, Wilson MR, Clarkson B, Giannini C, Gandhi M, Cheville J, et al. Expanded clinical phenotype, oncological associations, and immunopathologic insights of paraneoplastic Kelch-like protein-11 encephalitis. *JAMA Neurol* 2020;77:1420-1429.
 109. Mandel-Brehm C, Dubey D, Kryzer TJ, O'Donovan BD, Tran B, Vazquez SE, et al. Kelch-like protein 11 antibodies in seminoma-associated paraneoplastic encephalitis. *N Engl J Med* 2019;381:47-54.
 110. Rodrigo L, Hernández-Lahoz C, Lauret E, Rodríguez-Peláez M, Soucek M, Ciccocioppo R, et al. Gluten ataxia is better classified as non-celiac gluten sensitivity than as celiac disease: a comparative clinical study. *Immunol Res* 2016;64:558-564.
 111. Hadjivassiliou M, Graus F, Honnorat J, Jarius S, Titulaer M, Manto M, et al. Diagnostic criteria for primary autoimmune cerebellar ataxia—guidelines from an International Task Force on Immune-Mediated Cerebellar Ataxias. *Cerebellum* 2020;19:605-610.
 112. Gaspard N, Foreman BP, Alvarez V, Cabrera Kang C, Probasco JC, Jongeling AC, et al. New-onset refractory status epilepticus: etiology, clinical features, and outcome. *Neurology* 2015;85:1604-1613.
 113. Iizuka T, Kanazawa N, Kaneko J, Tominaga N, Nonoda Y, Hara A, et al. Cryptogenic NORSE: its distinctive clinical features and response to immunotherapy. *Neurol Neuroimmunol Neuroinflamm* 2017;4:e396.
 114. Tizazu E, Ellis CA, Reichert J, Lancaster E. Low rate of glutamic acid decarboxylase 65 (GAD-65) antibodies in chronic epilepsy. *Seizure* 2020;80:38-41.
 115. Peltola J, Kulmala P, Isojärvi J, Saiz A, Latvala K, Palmio J, et al. Autoantibodies to glutamic acid decarboxylase in patients with therapy-resistant epilepsy. *Neurology* 2000;55:46-50.
 116. Husari KS, Dubey D. Autoimmune epilepsy. *Neurotherapeutics* 2019;16:685-702.
 117. Yanagida A, Kanazawa N, Kaneko J, Kaneko A, Iwase R, Suga H, et al. Clinically based score predicting cryptogenic NORSE at the early stage of status epilepticus. *Neurol Neuroimmunol Neuroinflamm* 2020;7:e849.
 118. Pollak TA, McCormack R, Peakman M, Nicholson TR, David AS. Prevalence of anti-N-methyl-D-aspartate (NMDA) receptor [corrected] antibodies in patients with schizophrenia and related psychoses: a systematic review and meta-analysis. *Psychol Med* 2014;44:2475-2487.
 119. Titulaer MJ, Dalmau J. Antibodies to NMDA receptor, blood-brain barrier disruption and schizophrenia: a theory with unproven links. *Mol Psychiatry* 2014;19:1054.
 120. Lancaster E, Leypoldt F, Titulaer MJ, Honnorat J, Waters PJ, Reindl M, et al. Immunoglobulin G antibodies to the N-methyl-D-aspartate receptor are distinct from immunoglobulin A and immunoglobulin M responses. *Ann Neurol* 2015;77:183.
 121. Cullen AE, Palmer-Cooper EC, Hardwick M, Vaggers S, Crowley H, Pollak TA, et al. Influence of methodological and patient factors on serum NMDAR IgG antibody detection in psychotic disorders: a meta-analysis of cross-sectional and case-control studies. *Lancet Psychiatry* 2021;8:109-120.
 122. Pollak TA, Vincent A, Iyegbe C, Coutinho E, Jacobson L, Rujescu D, et al. Relationship between serum NMDA receptor antibodies and response to antipsychotic treatment in first-episode psychosis. *Biol Psychiatry* 2021;90:9-15.
 123. Hoffmann C, Zong S, Mané-Damas M, Molenaar PC, Losen M, Titulaer MJ, et al. Absence of autoantibodies against neuronal surface antigens in sera of patients with psychotic disorders. *JAMA Psychiatry* 2020;77:322-325.
 124. Graus F, Dalmau J. Paraneoplastic neurological syndromes in the era of immune-checkpoint inhibitors. *Nat Rev Clin Oncol* 2019;16:535-548.
 125. Vogrig A, Muñoz-Castrillo S, Joubert B, Picard G, Rogemond V, Marchal C, et al. Central nervous system complications associated with immune checkpoint inhibitors. *J Neurol Neurosurg Psychiatry* 2020;91:772-778.
 126. Ebright MJ, Li SH, Reynolds E, Burke JF, Claytor BR, Grisold A, et al. Unintended consequences of Mayo paraneoplastic evaluations. *Neurology* 2018;91:e2057-e2066.