Published in final edited form as:

Semin Neurol. 2014 September ; 34(4): 458–466. doi:10.1055/s-0034-1390394.

Neuronal Surface Antibody-Mediated Autoimmune Encephalitis

Jenny J. Linnoila, MD, PhD¹, Myrna R. Rosenfeld, MD, PhD^{2,3,4}, and Josep Dalmau, MD, PhD^{3,4,5}

¹ Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts

² Department of Neurology, Hospital Clínic /Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Barcelona, Spain

³ Centre de Recerca Biomèdica CELLEX, Lab Neuroimmunologia P3A, Barcelona, Spain

⁴ Department of Neurology, University of Pennsylvania; Philadelphia, Pennsylvania

⁵ Institució Catalana de Recerca i Estudis Avançats (ICREA) at Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Barcelona, Spain

Abstract

In the past few years, many autoimmune encephalitides have been identified, with specific clinical syndromes and associated antibodies against neuronal surface antigens. There is compelling evidence that many of these antibodies are pathogenic and most of these encephalitides are highly responsive to immunotherapies. The clinical spectra of some of these antibody-mediated syndromes, especially those reported in only a few patients, are evolving. Others, such as anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, are well characterized. Diagnosis involves recognizing the specific syndromes and identifying the antibody in a patient's cerebrospinal fluid (CSF) and/or serum. These syndromes are associated with variable abnormalities in CSF, magnetic resonance imaging, and electroencephalography. Treatment is often multidisciplinary and should be focused upon neutralizing the effects of antibodies and eliminating their source. Overlapping disorders have been noted, with some patients having more than one neurologic autoimmune disease. In other patients, viral infections such as herpes simplex virus encephalitis trigger robust antineuronal autoimmune responses.

Keywords

autoimmune; limbic; encephalitis; neuronal antibodies

Encephalitis is commonly encountered in neurology.¹ When the etiology is unclear, the cause is typically labeled “viral” or “idiopathic.” In the past few years, it has become evident that many of these encephalitides are autoimmune in origin, and represent specific clinical syndromes associated with antibodies that target neuronal surface antigens.^{2–4} It has been

Address for correspondence Josep Dalmau, MD, PhD, Institució Catalana de Recerca i Estudis Avançats (ICREA) at Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Barcelona, Spain 08036 (jdalmau@clinic.ub.es)..

Conflicts

JD and MRR receive royalties from licensing fees to Euroimmun for a patent on the use of NMDAR as an autoantibody test.

demonstrated in vitro and in vivo that some of these cell surface-targeted antibodies are pathogenic and reversibly disrupt the structure and function of their target neuronal proteins.^{5–10} This in large part explains the responsiveness of patients' symptoms to immunotherapy. These syndromes have a variable association with cancer and may be confused with the classic antibody associated paraneoplastic neurologic disorders (PNDs).¹¹ However, in a classic PND of the central nervous system (CNS), the associated antibodies usually target intracellular neuronal proteins and are markers of paraneoplasia without being pathogenic. The neuronal damage in PNDs of the central nervous system (CNS) is T-cell mediated and mostly irreversible, resulting in the generally limited neurologic recovery of the patients, even with maximal treatment.¹²

As more autoimmune encephalitis (AE) with antibodies to neuronal cell surface antigens are identified, it can be difficult to keep track of newly described clinical associations and concepts that are still evolving. Because most of these syndromes are treatment responsive and if left undertreated can result in serious disability or death, it is important to promptly recognize and treat them. This review aims to provide a practical overview of the evaluation, diagnosis, and treatment of AE associated with antibodies against neuronal cell surface antigens.

Diagnosis

Recognizing Autoimmune Encephalitis

Diagnosing AE involves familiarizing oneself with the various syndromes that have been described in detail elsewhere,^{4,5,9,13–22} and thus are only briefly summarized below and in ►Table 1, with an emphasis on defining features. Many AE share overlapping clinical features, and knowing their characteristic or distinctive signs helps to differentiate them. However, there has been a growing tendency for some syndrome definitions to be used imprecisely. For instance, limbic encephalitis is a well-defined disorder characterized by subacute short-term memory loss, confusion, and mood/ behavioral changes, such as depression, irritability, and hallucinations, with or without seizures.^{23,24} In the literature, the term limbic encephalitis is frequently misused to describe any sort of autoimmune encephalopathy, which can misdirect the differential diagnosis.²⁵ Some AE have been described in only a few patients, and it is possible that their full clinical spectra remain to be defined. In contrast, other disorders, such as anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, have been comprehensively described,²⁶ and an atypical symptom could be unrelated or perhaps part of an overlapping but independent disorder, discussed further below.

Initial Studies in the Workup of Autoimmune Encephalitis

The initial workup for autoimmune encephalitis is similar to that for other encephalitides, including standard bloodwork, routine cerebrospinal fluid (CSF) analysis with IgG index and oligoclonal bands (OCBs), magnetic resonance imaging (MRI) of the brain, and electroencephalography (EEG). The CSF, MRI, and EEG results can be variable for the different AE,¹³ as noted below. Some of the variability relates to the point in the clinical course that the studies are done. For instance, a normal or low CSF white blood cell count

may represent either a very early point in the disease course or a later time, when the pleocytosis has resolved. An elevated IgG index and OCBs in the CSF may indicate intrathecal antibody synthesis,²⁷ but they can be normal. Seizures may confound interpretation of the MRI, as they can produce T2 fluid attenuation inversion recovery (FLAIR) hyperintensities, contrast enhancement, and even diffusion restriction.²⁸ Some studies have reported brain positron emission tomography (PET) findings that may aid in making the diagnosis of autoimmune encephalitis, but further analyses remain to be done with larger numbers of patients.²⁹ The EEG can have obvious abnormalities but sometimes findings may be subtle,³⁰ so the interpreting physician should be made aware of the clinical picture and the suspicion of autoimmune encephalitis.

Autoimmune Encephalitis Syndromes

The most common and first described autoimmune encephalitis syndrome is anti-NMDA receptor encephalitis.¹⁵ This disorder is most common in females with a median age of 21 years (range 0.6–85). In adults, the syndrome often starts with a viral prodrome progressing to psychiatric/behavioral changes and insomnia, usually followed by decreased consciousness, seizures, unusual movements, and autonomic instability that may result in central hypoventilation. As patients recover, symptoms typically resolve in the reverse order.²⁶ The syndrome in children is similar, but the first symptoms are often behavioral changes, seizures, or movement disorders.^{26,31,32} The CSF often shows a lymphocytic pleocytosis ± OCBs. Only about a third of patients have brain MRI findings, usually FLAIR hyperintensity in cortical or subcortical regions, or in the cerebellum and/or brainstem. Approximately 30% of patients have an EEG pattern known as “extreme delta brush.”³³ There is an age-related association with tumors, almost always ovarian teratomas, with a tumor found in 46% of all females, but in only 6% of those younger than 12 years.²⁶

The next syndrome to be described was associated with antibodies against the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor.⁵ These patients are almost all women, with a median age of 60 (range 38–87), who present with the subacute onset of limbic encephalitis, sometimes with isolated psychiatric symptoms.^{34,35} Relapses are common, occurring in approximately half of the patients. Analysis of the CSF often shows a lymphocytic pleocytosis ± OCBs. Most patients have mesiotemporal FLAIR abnormalities on their brain MRIs. Less than half of the patients have seizures. About 70% of the patients have malignancies (thymomas, lung, or breast cancer) and approximately 50% have concurrent systemic autoimmune diseases, including Hashimoto thyroiditis and Raynaud disease, as well as antithyroperoxidase (TPO), glutamic acid decarboxylase (GAD), and antinuclear (ANA) autoantibodies.

Patients with antibodies against the gamma-aminobutyric acid (GABA)_B receptor^{17,36} are equally men and women, with a median age of 62 (range 24–75). These patients present subacutely with limbic encephalitis associated with early and refractory seizures. Most patients have a CSF lymphocytic pleocytosis ± OCBs. Patients often have mesiotemporal FLAIR hyperintensity on their brain MRIs. As with patients with anti-AMPA receptor encephalitis, about half of these patients have other systemic autoimmune diseases, and approximately 60% of cases are related to malignancies, most often small cell lung cancer.

The identification of anti-contactin-associated protein-like 2 (CASPR2) and antileucine-rich glioma inactivated-1 (LGI1) encephalitis^{18,19} was significant because these patients were previously considered to have antibodies to the voltage gated potassium channel³⁷ (VGKC; e.g., many of the cases reported before 2010 with typical limbic encephalitis and VGKC antibodies were likely related to LGI1 antibodies). Anti-LGI1 is the second most common autoimmune encephalitis after anti-NMDA receptor encephalitis.¹³ Patients with antibodies targeting LGI1 and CASPR2 are predominantly men, with a median age of 60 years (range 30–80 in LGI1, 46–77 in CASPR2). Anti-LGI1 patients usually present with limbic encephalitis, seizures, and sleep disruptions.^{19,38} Some patients also have brief myoclonic-like seizures, called faciobrachial dystonic or tonic seizures, that may occur during or prior to the memory changes.^{39,40} Approximately 60% of the patients have hyponatremia. Less than half of patients have an abnormal CSF profile, although many have mesiotemporal FLAIR abnormalities on their MRIs. Patients with anti-CASPR2 antibodies usually present with Morvan syndrome (encephalitis with sleep dysfunction, dysautonomia, and neuromyotonia) or less frequently with isolated neuromyotonia. Only about a quarter of patients with anti-CASPR2 antibodies have abnormal CSF profiles and less than half have MRI FLAIR hyperintensities, usually in the mesiotemporal lobes. More than half of patients have seizures. Relapses of encephalitis are common in anti-CASPR2 encephalitis. The true frequency of malignancy in patients with LGI1 or CASPR2 antibodies is unknown; less than 10% of patients with anti-LGI1 antibodies have a thymoma, and depending on the series, 0% to 40% with anti-CASPR2 antibodies have a thymoma (patients with Morvan's syndrome seem to be prone to having a thymoma).^{41,42}

Antibodies against the metabotropic glutamate receptor 5 (mGluR5)^{20,43} were identified in the CSF of a woman and two men (46, 15, and 35 years old, respectively) with Hodgkin disease and limbic encephalitis, otherwise known as Ophelia syndrome. The first two patients also had myoclonus, seizures, and CSF lymphocytic pleocytosis. The third patient had mononuclear cells in his CSF. All of the patients had FLAIR hyperintensities on brain MRI (mesiotemporal lobe in the first, mesiotemporal lobe with more extensive involvement of the cortex in the second, and pons in the third).

Glycine α (Gly α) receptor autoantibodies have been found in some patients with progressive encephalomyelitis with rigidity and myoclonus (PERM),¹⁶ stiff-person syndrome,⁴⁴ and less frequently, patients with seizures, limbic encephalitis, cerebellar ataxia, and optic neuropathy.^{44–48} As with the clinical presentations, the CSF profiles, MRI findings, and EEG abnormalities associated with anti-Gly α receptor antibodies are variable.

The most recently characterized autoimmune encephalitis syndromes are those associated with anti-dipeptidyl-peptidase-like protein-6 (DPPX),²¹ anti-GABA_A receptor,⁹ and antiimmunoglobulin-like family member 5 (IgLON5)²² antibodies. Dipeptidyl-peptidase-like protein-6 is a regulatory subunit of the Kv4.2 potassium channel. Anti-DPPX antibodies were initially described in four patients, equally men and women, aged 45 to 76 years old, who presented with encephalitis associated with tremor, myoclonus, nystagmus, seizures, and sometimes hyperekplexia.²¹ Three of the four patients had prominent diarrhea that resulted in an initial diagnosis of a primary gastrointestinal disorder, leading to a delay in the neurologic diagnosis. Most of the patients had a lymphocytic pleocytosis $\pm$ OCBs in their

CSF. The MRI abnormalities were mostly nonspecific T2 hyperintensities. None of the patients had tumors. Recently, four patients with anti-DPPX antibodies were reported who presented with PERM,⁴⁹ so it is likely that the clinical spectrum for this AE has not yet been fully elucidated.

Patients with high titer serum and CSF anti-GABA_A receptor antibodies (median age 22, range 3–63; five-sixths male) developed a rapidly progressive encephalopathy, beginning with behavioral or cognitive changes, leading to refractory seizures and highly abnormal brain MRIs with multifocal lesions.⁹ Most of these patients had CSF with lymphocytic pleocytosis ± OCBs. None had tumors, although one had a history of Hodgkin lymphoma. As with patients with anti-GABA_B and anti-AMPA receptor antibodies, these patients also had coexisting autoimmunities.⁵⁰ Anti-IgLON5 AE,²² which has several unique features, is discussed below.

Making the Diagnosis: Antibody Testing in Autoimmune Encephalitis

The definitive diagnosis of AE is made by the identification of the associated antibodies. To avoid missing the diagnosis, it is important to perform a comprehensive analysis by testing CSF and serum. A recent analysis of paired serum and CSF samples from 250 patients with anti-NMDA receptor encephalitis showed that whereas 100% of the CSF samples tested positive for IgG GluN1 (NMDA subunit) antibodies via two independent methods, 6% to 13% of the corresponding serum samples tested negative, depending on the testing method used.⁵¹ Moreover, with some testing methods, there is an increased possibility of false-positive results for serum samples,⁵² likely because total serum protein content is magnitudes higher than that of CSF, and thus may result in nonspecific immunostaining. It is therefore difficult to interpret positive results when only the serum is tested or when the serum is positive, but the CSF is negative.⁴ This is particularly important to consider in cases in which the symptoms are atypical for the corresponding syndrome, as such results may represent false-positives.

Commercial laboratories currently test for antibodies against the GluN1 subunit of the NMDA receptor, AMPA receptor, LGI1, CAPSR2, and GABA_B receptor, but not for those against the Glyc_α receptor, GABA_A receptor, mGluR5, and IgLON5. Because there is substantial overlap in the symptoms of many AE, particularly at symptom onset, it can be difficult to determine which antibodies to test for, so the use of panels is reasonable. However, although there are panels grouped according to clinical syndromes, they are often incomplete. Surprisingly, there are no panels grouped by patient's age (e.g., children/teenagers vs. adults), which would potentially be helpful and could reduce costs. For example, in addition to the list of antibodies indicated above, some panels include all antibodies to classic intracellular paraneoplastic antigens, which are unnecessary for many patients, in particular children. One should be aware which antibodies are in the panel and request any others that are suspected. Also, it should be clarified whether the laboratory will test for antibodies in serum and CSF. If the commercial tests are negative and the patient has a syndrome suggestive of autoimmune encephalitis, consider retesting the samples, especially if only serum was examined. Depending on the clinical scenario, consider

commencing treatment as soon as autoimmune encephalitis is suspected, even if antibody results are pending.

Malignancy Screening in Autoimmune Encephalitis

Unlike PNDs, which are cancer related, autoimmune encephalitis can occur with or without a cancer association. Some syndromes (e.g., those associated with mGluR5,²⁰ AMPA receptor,⁵ and GABA_B receptor¹⁷ antibodies) are more often associated with malignancy. For example, more than half of patients with anti-GABA_B receptor antibodies have cancer, most often small cell lung cancer. If a tumor is not found in the initial screening, as the AE are not invariably cancer related, the clinical scenario should guide the need for further evaluation, taking into consideration the neurologic syndrome, the patient's age and sex, the associated antibody, and the patient's personal risk factors for malignancy.

Treatment

Immunotherapeutic Strategies in Autoimmune Encephalitis

Presently, there are no specific autoimmune encephalitis-targeted therapies and no published guidelines for the treatment of these syndromes. The overriding principle of treatment is immunosuppression. The most comprehensive data comes from a retrospective analysis of 501 patients with anti-NMDA receptor encephalitis for which treatment and long-term outcome data were available.²⁶ These patients were treated according to physician's preference and most commonly received corticosteroids, intravenous immunoglobulins (IVIg), or plasmapheresis, either alone or in combination as first-line therapy, and rituximab and/or cyclophosphamide as second-line agents. In this analysis, 94% of patients received first-line therapies and tumor removal when indicated, and 53% of them improved within 4 weeks. Of the patients that did not respond to first-line therapy, 57% received second-line therapy and 43% either continued on first-line treatment or discontinued therapy. Comparing these latter two groups, those who received second-line therapies did functionally better and had fewer relapses than those who did not.

One interpretation of this data is that patients who do not improve within 4 weeks with first-line therapy should be given second-line therapy. Another interpretation would be that because many patients (47%) did not improve with first-line therapies, second-line therapies should be used initially. There is rationale for the latter approach based on the mechanisms of action of the different treatments. In AE, as the antibodies are likely pathogenic, therapies should aim to remove them and/or the antibody-producing plasma cells. Although IVIg and plasmapheresis neutralize or eliminate systemic antibodies,⁵³ they do not target plasma cells and do not address the intrathecal synthesis of antibodies. This may in part explain why some patients do not respond to or experience relapses after these treatments. Rituximab targets the cell surface antigen CD-20, expressed by B-cells and plasmablasts, the precursors to terminally differentiated plasma cells, which do not express CD-20.⁵⁴ The lifetime of a short-lived antibody-producing plasma cell is typically days to weeks,⁵⁵ likely accounting for the delay prior to the response to rituximab, as it targets the next cycle of the immune response (B cells and plasmablasts), while waiting for the current one (plasma cells) to die out.⁵⁶ Cyclophosphamide, a DNA alkylating agent, indiscriminately targets hematopoietic

cells.⁵⁷ Thus, both rituximab and cyclophosphamide target the antibody source, and this may account for why there are fewer relapses when patients are treated with these medications.²⁶ Indeed, rituximab is increasingly used as a first-line therapy (J. Dalmau, personal observation). Whereas the total duration of therapy has not been established, most patients only require one cycle of rituximab (either 375 mg/m² weekly for 4 weeks, or two 500 mg/m² doses 2 weeks apart), and/or monthly doses of cyclophosphamide (750 mg/m² for 4 to 6 months).⁵⁸ It is unknown whether chronic maintenance immunosuppression will be needed for some AE patients, as it is for other autoimmune disorders. Although none of these medications specifically target intrathecal antibody synthesis, beneficial effects are observed with rituximab and cyclophosphamide, despite their limited blood–brain barrier penetration. Overall, more targeted therapeutics against AE are needed.

Additional Therapeutic Considerations in Autoimmune Encephalitis

If a tumor is found, it should be removed as part of the initial therapy. In anti-NMDA receptor encephalitis, patients whose tumors were not removed had worse outcomes and an increased risk of relapses compared with those patients whose tumors were resected.²⁶ Although the other AE patient series are too small to know if it applies generally, these data support early tumor treatment in cancer-associated AE.

Because AE present with a variety of symptoms, including significant behavioral and psychiatric manifestations, a multi-disciplinary approach is needed. Some physicians may not be accustomed to using chemotherapeutic agents as immunotherapies, or have concerns regarding toxicity. Accumulating evidence has shown that rituximab and cyclophosphamide are well tolerated by AE patients, including children,^{58,59} and the benefits of fewer relapses and better outcomes should be balanced against the risks in each clinical situation. Seizures are common in AE, but most patients do not develop long-term seizure disorders after recovery⁶⁰ and antiepileptic drugs can typically be tapered and discontinued.

There has been discussion as to the utility of following antibody titers over time. A recent analysis of anti-NMDA receptor encephalitis patients showed that CSF titers correlated better with the clinical course than serum titers.⁵¹ However, methodologically, titers are dependent upon technical expertise⁶¹ and can even be different for the same sample run at a different time. Moreover, antibody titers can remain detectable even after successful treatment, or when a patient is asymptomatic, as is seen in many other autoimmune disorders. This may be related to the prolonged survival of long-lived plasma cells.⁶² Thus, there may be little utility to following titers. However, a baseline CSF titer after the patient improves may be useful in the future if a relapse is suspected—a rise in titer along with recurrent or new neurologic symptoms would support the diagnosis. In general, it is recommended that treatment be guided by a patient's clinical status.

Evolving Concepts in Autoimmune Encephalitis

Novel Syndromes Associated with Neuronal Cell Surface Autoimmunity: Expanding beyond Autoimmune Encephalitis?

Thus far, the discussion has centered on neuronal surface or synaptic-targeted antibodies associated with subacute autoimmune encephalitis syndromes. However, disorders have emerged that may be expanding the scope of these syndromes beyond autoimmune encephalitis. Recently, an antibody against the neuronal adhesion molecule IgLON5 was described in eight patients with a progressive neurodegenerative sleep breathing disorder that was chronic over months to years in six of them.²² The mean age of the patients was 59 (range 52–76) and five were women. None of the patients had CSF abnormalities, MRI FLAIR hyperintensities, abnormal EEGs, or cancer. There was no response to immunotherapy; the disorder was fatal in most. Autopsy studies of two patients revealed a novel tauopathy involving the brainstem and hypothalamus. This discovery suggests that autoimmune mechanisms may underlie some chronic neurodegenerative disorders, although it remains to be determined whether the anti-IgLON5 antibody is pathogenic, or rather a marker of this neurodegenerative process.

Other antibodies to synaptic receptors have been identified in nonencephalitic syndromes. For example, though antibodies to metabotropic glutamate receptor 1 (mGluR1) have been associated with paraneoplastic ataxia,⁶³ they have more recently been described in noncancer-associated cerebellar degeneration.⁶⁴ Dopamine 2 receptor antibodies have been identified in a small subset of children with basal ganglia encephalitis, Sydenham chorea, and in some cases of Tourette syndrome.⁶⁵ The relationship of the antibodies to these syndromes is still being clarified. Tests for IgLON5, mGluR1, and dopamine 2 receptor antibodies are not yet commercially available.

Clues to the Pathophysiology of Autoimmune Encephalitis

Approximately 4 to 6 weeks postherpes simplex encephalitis (HSE), patients may develop relapses of neurologic symptoms, but the virus is not found in the CSF, implying that the patient has been successfully treated. Thus, the source of the relapsing encephalitis has been unclear.⁶⁶ Symptoms are usually different from the viral HSE, often including agitation, insomnia, behavioral changes, autonomic dysfunction, dyskinesias, or abnormal movements, leading to the definition of this complication as choreoathetosis post-HSE.⁶⁷ This constellation of symptoms and a study indicating that some patients with HSE develop NMDA receptor antibodies suggested a link between these disorders, which has now been confirmed by several investigators.^{32,68–72} In one series of patients, serum and CSF were studied at the time of initial HSV encephalitis and then during nonviral relapses.⁷² It was demonstrated that within 1 to 4 weeks after HSV encephalitis and preceding the neurologic relapse, some patients developed anti-NMDA receptor antibodies, with or without other antibodies against yet unknown targets; one of the other antigens was the dopamine receptor.⁷⁰ Many of these patients improved with immunotherapy. Thus, it appears that HSV encephalitis is a robust trigger of antineuronal autoimmunity. This may provide a clue to the pathophysiology of autoimmune encephalitis in some patients, particularly as anti-NMDA receptor encephalitis is often associated with a viral prodrome.

Overlapping Syndromes: Making Diagnosis More Challenging

An overlap has been described between patients with demyelinating disease and anti-NMDA receptor encephalitis.⁷³ In half of the cases, the demyelination occurred either before or after the anti-NMDA receptor encephalitis and in the other half, the disorders were concurrent. Most of these patients were positive for antimyelin oligodendrocyte glycoprotein (MOG) or aquaporin-4 (AQP4) antibodies. The concurrent cases presented a diagnostic quandary, and the diagnoses of the disorders were often delayed, or considered atypical presentations or “expansions” of the clinical syndromes of anti-NMDA receptor encephalitis, acute disseminated encephalomyelitis (ADEM), neuromyelitis optica (NMO), or multiple sclerosis (MS; e.g., anti-NMDA receptor encephalitis with optic neuritis, or NMO spectrum disorder with severe psychiatric symptoms). It is important to recognize that these disorders can co-occur, as the treatments and outcomes are different.

Multiple Concurrent Autoantibodies: A Common Theme of Autoimmunity?

Patients with systemic autoimmune disease commonly have antibodies to multiple autoantigens in their sera, often corresponding with concurrent autoimmune diseases.⁷⁴ Similarities are being noted in AE. For instance, in the series of patients with overlapping demyelination and anti-NMDA receptor encephalitis,⁷² one patient developed anti-NMDA receptor encephalitis, demyelinating disease, and myasthenia gravis. This propensity for autoimmunity has been seen in other AE, such as AMPA,⁵ GABA_A,⁹ GABA_B,¹⁷ CASPR2,⁷⁵ and Glyc receptor encephalitis.¹⁶ In these cases, it is important to differentiate between antibodies that are pathogenically driving the immune response and those that are markers of an autoimmune process and may not necessarily have clinical relevance or disease specificity.

What about Anti-TPO Antibodies?

Antibodies against thyroid peroxidase (TPO) have had an interesting trajectory in the history of autoimmune encephalitides. This antibody, with or without anti-thyroglobulin antibodies, was initially thought to signify an AE known as Hashimoto encephalitis (HE),⁷⁶ although the range of clinical presentations was highly variable, making it difficult to describe a specific HE syndrome. Hashimoto encephalitis was eventually renamed steroid responsive encephalitis with associated autoimmune thyroiditis (SREAT),⁷⁷ as HE patients were generally found to be responsive to steroids. However, this did not clarify the syndrome, as not all syndromes considered to be HE are responsive to steroids. With the identification of novel antibodies recognizing neuronal cell surface epitopes, as opposed to TPO antibodies that do not react with neurons, some patients with HE have been reclassified with specific syndromes, such as anti-NMDA receptor or limbic encephalitis.⁷⁸ The anti-TPO antibodies may be better interpreted as markers of autoimmunity. However, the boundaries of HE are unclear,⁷⁹ and it should be considered only after excluding specific antibody-associated AE.

Keeping a Critical Eye on the Literature

There are many reports in the literature associating antibodies against neuronal surface antigens with several disorders, including neuropsychiatric lupus,⁸⁰ bipolar disorder,⁸¹ and neurodegenerative conditions.⁸² These antibodies must be distinguished from those that have

been shown to be syndrome specific. Thus, critical reading of the emerging literature is important. For instance, in anti-NMDA receptor encephalitis, the associated antibodies are IgGs that target the GluN1 subunit of the NMDA receptor.⁷ These are highly specific and pathogenic antibodies that, when well characterized in serum and particularly CSF, are not found in other disorders. Other NMDA receptor subunit-targeted antibodies or IgA or IgM antibody subtypes are unrelated to anti-NMDA receptor encephalitis; they have been reported in the sera of patients with a myriad of neurologic and psychiatric diseases⁸³ at the same frequency as in healthy subjects (rv10%),⁸⁴ without clear pathogenic effects. Indeed, an emerging problem in the literature is the oversimplified use of the term “NMDA receptor antibodies” for all types of antibodies (IgA, IgM, IgG) and antibodies targeting different subunits. Additional problems include antibodies detected using high concentrations of serum and/or without validation with independent tests or appropriate controls, altogether resulting in misleading conclusions.⁸⁴ Similar problems have started to occur with other antibodies, even those directed against the classic paraneoplastic intracellular antigens.

Additionally, it is difficult to know the significance of antibody test results if the antigens have not been fully characterized, or if they have only been identified from the serum, particularly for CNS disorders. For example, it is now known that VGKC antibodies target many proteins, known collectively as the VGKC complex.⁸⁵ These include LGI1 and CASPR2 antibodies that have each been identified in the serum or CSF of patients with syndromes consisting of specific constellations of symptoms.^{18,19} The identity and location of other antigens in the VGKC complex is unknown. That is, it is unknown if non-LGI1 or non-CASPR2 antibodies against the VGKC complex react with the cell surface of neurons. The repertoire of symptoms and syndromes linked to VGKC complex antibodies other than LGI1 and CASPR2 is increasing and includes nonimmune-mediated CNS disorders, such as hepatic encephalopathy.⁸⁶ Thus, these antibodies, especially when identified solely from the serum, should be interpreted with caution, as they may be unrelated to the patients' symptoms.

Conclusion

The scope of syndromes associated with neuronal surface antibodies is expanding, as new antibodies are identified and the associated clinical features are delineated. Some antibodies have only been reported in small numbers of patients, and the characterizations of the syndromes may evolve over time. It is important to be familiar with the syndromes, as well as current principles and emerging problems in the field, to make prompt and correct diagnoses and to institute appropriate treatments.

Acknowledgments

Supported in part by grant R25NS065743 from the National Institute of Neurologic Disorders and Stroke at the National Institutes of Health, USA (JL); grant R01NS077851 from the National Institutes of Health, USA (JD); grant 11/ 01780 from the Fondo Investigaciones Sanitarias, Spain (JD); and grant TV3 from Fundació la Marató, Spain (JD).

References

1. Vora NM, Holman RC, Mehal JM, Steiner CA, Blanton J, Sejvar J. Burden of encephalitis-associated hospitalizations in the United States, 1998-2010. *Neurology*. 2014; 82(5):443–451. [PubMed: 24384647]
2. Prüss H, Dalmau J, Harms L, et al. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. *Neurology*. 2010; 75(19):1735–1739. [PubMed: 21060097]
3. Wingfield T, McHugh C, Vas A, et al. Autoimmune encephalitis: a case series and comprehensive review of the literature. *QJM*. 2011; 104(11):921–931. [PubMed: 21784780]
4. Lancaster E, Dalmau J. Neuronal autoantigens—pathogenesis, associated disorders and antibody testing. *Nat Rev Neurol*. 2012; 8(7):380–390. [PubMed: 22710628]
5. Lai M, Hughes EG, Peng X, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. *Ann Neurol*. 2009; 65(4):424–434. [PubMed: 19338055]
6. Hughes EG, Peng X, Gleichman AJ, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *J Neurosci*. 2010; 30(17):5866–5875. [PubMed: 20427647]
7. 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(32):11082–11094. [PubMed: 22875940]
8. Mikasova L, De Rossi P, Bouchet D, et al. Disrupted surface cross-talk between NMDA and Ephrin-B2 receptors in anti-NMDA encephalitis. *Brain*. 2012; 135:1606–1621. Pt 5. [PubMed: 22544902]
9. Petit-Pedrol M, Armangue T, Peng X, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABA_A receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. *Lancet Neurol*. 2014; 13(3):276–286. [PubMed: 24462240]
10. Moscato EH, Peng X, Jain A, Parsons TD, Dalmau J, Balice-Gordon RJ. Acute mechanisms underlying antibody effects in anti-N-methyl-D-aspartate receptor encephalitis. *Ann Neurol*. 2014; 76(1):108–119. [PubMed: 24916964]
11. Rosenfeld MR, Dalmau JO. Paraneoplastic disorders of the CNS and autoimmune synaptic encephalitis. *Continuum (Minneapolis)*. 2012; 18(2):366–383. [PubMed: 22810133]
12. Bien CG, Vincent A, Barnett MH, et al. Immunopathology of autoantibody-associated encephalitis: clues for pathogenesis. *Brain*. 2012; 135:1622–1638. Pt 5. [PubMed: 22539258]
13. Leypoldt F. [Autoimmune encephalitis]. *Fortschr Neurol Psychiatr*. 2013; 81(9):523–537. quiz 538. [PubMed: 23986460]
14. Dalmau J, Rosenfeld MR. Autoimmune encephalitis update. *Neuro-oncol*. 2014; 16(6):771–778. [PubMed: 24637228]
15. Dalmau J, Tüzün E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol*. 2007; 61(1):25–36. [PubMed: 17262855]
16. Hutchinson M, Waters P, McHugh J, et al. Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. *Neurology*. 2008; 71(16):1291–1292. [PubMed: 18852446]
17. Lancaster E, Lai M, Peng X, et al. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. *Lancet Neurol*. 2010; 9(1):67–76. [PubMed: 19962348]
18. Irani SR, Alexander S, Waters P, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. *Brain*. 2010; 133(9):2734–2748. [PubMed: 20663977]
19. Lai M, Huijbers MGM, Lancaster E, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. *Lancet Neurol*. 2010; 9(8):776–785. [PubMed: 20580615]
20. Lancaster E, Martinez-Hernandez E, Titulaer MJ, et al. Antibodies to metabotropic glutamate receptor 5 in the Ophelia syndrome. *Neurology*. 2011; 77(18):1698–1701. [PubMed: 22013185]
21. Boronat A, Gelfand JM, Gresa-Arribas N, et al. Encephalitis and antibodies to dipeptidyl-peptidase-like protein-6, a subunit of Kv4.2 potassium channels. *Ann Neurol*. 2013; 73(1):120–128. [PubMed: 23225603]

22. Sabater L, Gaig C, Gelpi E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. *Lancet Neurol.* 2014; 13(6):575–586. [PubMed: 24703753]
23. Gultekin SH, Rosenfeld MR, Voltz R, Eichen J, Posner JB, Dalmau J. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. *Brain.* 2000; 123:1481–1494. Pt 7. [PubMed: 10869059]
24. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry.* 2004; 75(8):1135–1140. [PubMed: 15258215]
25. Graus F, Ariño H, Dalmau J. Paraneoplastic neurological syndromes in Hodgkin and non-Hodgkin lymphomas. *Blood.* 2014; 123(21):3230–3238. [PubMed: 24705493]
26. Titulaer MJ, McCracken L, Gabilondo I, 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(2):157–165. [PubMed: 23290630]
27. Poloni M, Rocchelli B, Scelsi R, Pinelli P. Intrathecal IgG synthesis in multiple sclerosis and other neurological diseases: a comparative evaluation by IgG-index and isoelectric focusing. *J Neurol.* 1979; 221(4):245–255. [PubMed: 92550]
28. Lansberg MG, O'Brien MW, Norbash AM, Moseley ME, Morrell M, Albers GW. MRI abnormalities associated with partial status epilepticus. *Neurology.* 1999; 52(5):1021–1027. [PubMed: 10102423]
29. Baumgartner A, Rauer S, Mader I, Meyer PT. Cerebral FDG-PET and MRI findings in autoimmune limbic encephalitis: correlation with autoantibody types. *J Neurol.* 2013; 260(11):2744–2753. [PubMed: 23900756]
30. Kaplan PW, Sutter R. Electroencephalography of autoimmune limbic encephalopathy. *J Clin Neurophysiol.* 2013; 30(5):490–504. [PubMed: 24084182]
31. Armangue T, Petit-Pedrol M, Dalmau J. Autoimmune encephalitis in children. *J Child Neurol.* 2012; 27(11):1460–1469. [PubMed: 22935553]
32. Armangue T, Titulaer MJ, Málaga I, et al. Spanish Anti-N-methyl-D-Aspartate Receptor (NMDAR) Encephalitis Work Group. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. *J Pediatr.* 2013; 162(4):850–856. e2. [PubMed: 23164315]
33. 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(11):1094–1100. [PubMed: 22933737]
34. Graus F, Boronat A, Xifró X, et al. The expanding clinical profile of anti-AMPA receptor encephalitis. *Neurology.* 2010; 74(10):857–859. [PubMed: 20211911]
35. Bataller L, Galiano R, García-Escrig M, et al. Reversible paraneoplastic limbic encephalitis associated with antibodies to the AMPA receptor. *Neurology.* 2010; 74(3):265–267. [PubMed: 20083804]
36. Jeffery OJ, Lennon VA, Pittock SJ, Gregory JK, Britton JW, McKeon A. GABA_B receptor autoantibody frequency in service serologic evaluation. *Neurology.* 2013; 81(10):882–887. [PubMed: 23925760]
37. Vincent A, Buckley C, Schott JM, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain.* 2004; 127:701–712. Pt 3. [PubMed: 14960497]
38. Iranzo A, Graus F, Clover L, et al. Rapid eye movement sleep behavior disorder and potassium channel antibody-associated limbic encephalitis. *Ann Neurol.* 2006; 59(1):178–181. [PubMed: 16278841]
39. Andrade DM, Tai P, Dalmau J, Wennberg R. Tonic seizures: a diagnostic clue of anti-LGI1 encephalitis? *Neurology.* 2011; 76(15):1355–1357. [PubMed: 21482953]
40. Irani SR, Stagg CJ, Schott JM, et al. Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. *Brain.* 2013; 136:3151–3162. Pt 10. [PubMed: 24014519]

41. Lancaster E, Huijbers MG, Bar V, et al. Investigations of caspr2, an autoantigen of encephalitis and neuromyotonia. *Ann Neurol*. 2011; 69(2):303–311. [PubMed: 21387375]
42. Irani SR, Pettingill P, Kleopa KA, et al. Morvan syndrome: clinical and serological observations in 29 cases. *Ann Neurol*. 2012; 72(2):241–255. [PubMed: 22473710]
43. Mat A, Adler H, Merwick A, et al. Ophelia syndrome with metabotropic glutamate receptor 5 antibodies in CSF. *Neurology*. 2013; 80(14):1349–1350. [PubMed: 23486886]
44. McKeon A, Martinez-Hernandez E, Lancaster E, et al. Glycine receptor autoimmune spectrum with stiff-man syndrome phenotype. *JAMA Neurol*. 2013; 70(1):44–50. [PubMed: 23090334]
45. Woodhall M, Çoban A, Waters P, et al. Glycine receptor and myelin oligodendrocyte glycoprotein antibodies in Turkish patients with neuromyelitis optica. *J Neurol Sci*. 2013; 335(1-2):221–223. [PubMed: 24045088]
46. Wuerfel E, Bien CG, Vincent A, Woodhall M, Brockmann K. Glycine receptor antibodies in a boy with focal epilepsy and episodic behavioral disorder. *J Neurol Sci*. 2014; 343(1-2):180–182. [PubMed: 24880541]
47. Mas N, Saiz A, Leite MI, et al. Antiglycine-receptor encephalomy-elitis with rigidity. *J Neurol Neurosurg Psychiatry*. 2011; 82(12):1399–1401. [PubMed: 21148607]
48. Martinez-Hernandez E, Sepulveda M, Rostasy K, et al. Antibodies to AQP4, MOG and glycine receptor in patients with uni or bilateral, severe, or recurrent isolated optic neuritis. *JAMA Neurol*. in press.
49. Balint B, Jarius S, Nagel S, et al. Progressive encephalomyelitis with rigidity and myoclonus: a new variant with DPPX antibodies. *Neurology*. 2014; 82(17):1521–1528. [PubMed: 24696508]
50. Ohkawa T, Satake S, Yokoi N, et al. Identification and characterization of GABA(A) receptor autoantibodies in autoimmune encephalitis. *J Neurosci*. 2014; 34(24):8151–8163. [PubMed: 24920620]
51. Gresa-Arribas N, Titulaer MJ, Torrents A, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol*. 2014; 13(2):167–177. [PubMed: 24360484]
52. Vacciocoz A, Desestret V, Ducray F, et al. Clinical specificities of adult male patients with NMDA receptor antibodies encephalitis. *Neurology*. 2014; 82(7):556–563. [PubMed: 24443452]
53. Saydain G, George L, Raoof S. New therapies: plasmapheresis, intravenous immunoglobulin, and monoclonal antibodies. *Crit Care Clin*. 2002; 18(4):957–975. [PubMed: 12418449]
54. Reff ME, Carner K, Chambers KS, et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. *Blood*. 1994; 83(2):435–445. [PubMed: 7506951]
55. Shapiro-Shelef M, Calame K. Regulation of plasma-cell development. *Nat Rev Immunol*. 2005; 5(3):230–242. [PubMed: 15738953]
56. Kosmidis ML, Dalakas MC. Practical considerations on the use of rituximab in autoimmune neurological disorders. *Ther Adv Neurol Disord*. 2010; 3(2):93–105. [PubMed: 21179602]
57. Brummaier T, Pohanka E, Studnicka-Benke A, Pieringer H. Using cyclophosphamide in inflammatory rheumatic diseases. *Eur J Intern Med*. 2013; 24(7):590–596. [PubMed: 23528932]
58. Rosenfeld MR, Dalmau J. Anti-NMDA-receptor encephalitis and other synaptic autoimmune disorders. *Curr Treat Options Neurol*. 2011; 13(3):324–332. [PubMed: 21298406]
59. Dale RC, Brilot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. *Neurology*. 2014; 83(2):142–150. [PubMed: 24920861]
60. Pandit AK, Ihtisham K, Garg A, Gulati S, Padma MV, Tripathi M. Autoimmune encephalitis: a potentially reversible cause of status epilepticus, epilepsy, and cognitive decline. *Ann Indian Acad Neurol*. 2013; 16(4):577–584. [PubMed: 24339583]
61. Littman AJ, Jackson LA, White E, Thornquist MD, Gaydos CA, Vaughan TL. Interlaboratory reliability of microimmunofluorescence test for measurement of Chlamydia pneumoniae-specific immunoglobulin A and G antibody titers. *Clin Diagn Lab Immunol*. 2004; 11(3):615–617. [PubMed: 15138190]
62. Winter O, Dame C, Jundt F, Hiepe F. Pathogenic long-lived plasma cells and their survival niches in autoimmunity, malignancy, and allergy. *J Immunol*. 2012; 189(11):5105–5111. [PubMed: 23169863]

63. Sillevs Smitt P, Kinoshita A, De Leeuw B, et al. Paraneoplastic cerebellar ataxia due to autoantibodies against a glutamate receptor. *N Engl J Med*. 2000; 342(1):21–27. [PubMed: 10620645]
64. Marignier R, Chenevier F, Rogemond V, et al. Metabotropic glutamate receptor type 1 autoantibody-associated cerebellitis: a primary autoimmune disease? *Arch Neurol*. 2010; 67(5): 627–630. [PubMed: 20457964]
65. Dale RC, Merheb V, Pillai S, et al. Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. *Brain*. 2012; 135:3453–3468. Pt 11. [PubMed: 23065479]
66. De Tiège X, Rozenberg F, Des Portes V, et al. Herpes simplex encephalitis relapses in children: differentiation of two neurologic entities. *Neurology*. 2003; 61(2):241–243. [PubMed: 12874408]
67. Kullnat MW, Morse RP. Choreoathetosis after herpes simplex encephalitis with basal ganglia involvement on MRI. *Pediatrics*. 2008; 121(4):e1003–e1007. [PubMed: 18378549]
68. Prüss H, Finke C, Höltje M, et al. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. *Ann Neurol*. 2012; 72(6):902–911. [PubMed: 23280840]
69. Leypoldt F, Titulaer MJ, Aguilar E, et al. Herpes simplex virus-1 encephalitis can trigger anti-NMDA receptor encephalitis: case report. *Neurology*. 2013; 81(18):1637–1639. [PubMed: 24089390]
70. Mohammad SS, Sinclair K, Pillai S, et al. Herpes simplex encephalitis relapse with chorea is associated with autoantibodies to N-methyl-D-aspartate receptor or dopamine-2 receptor. *Mov Disord*. 2014; 29(1):117–122. [PubMed: 24115338]
71. Hacoen Y, Deiva K, Pettingill P, et al. N-methyl-D-aspartate receptor antibodies in post-herpes simplex virus encephalitis neurological relapse. *Mov Disord*. 2014; 29(1):90–96. [PubMed: 24014096]
72. Armangue T, Leypoldt F, Málaga I, et al. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. *Ann Neurol*. 2014; 75(2):317–323. [PubMed: 24318406]
73. Titulaer MJ, Höftberger R, Iizuka T, et al. Overlapping demyelinating syndromes and anti-N-methyl-D-aspartate receptor encephalitis. *Ann Neurol*. 2014; 75(3):411–428. [PubMed: 24700511]
74. Cojocaru M, Cojocaru IM, Silosi I. Multiple autoimmune syndrome. *Maedica (Buchar)*. 2010; 5(2):132–134. [PubMed: 21977137]
75. Díaz-Manera J, Rojas-García R, Gallardo E, et al. Antibodies to AChR, MuSK and VGKC in a patient with myasthenia gravis and Morvan's syndrome. *Nat Clin Pract Neurol*. 2007; 3(7):405–410. [PubMed: 17611489]
76. Brain L, Jellinek EH, Ball K. Hashimoto's disease and encephalopathy. *Lancet*. 1966; 2(7462): 512–514. [PubMed: 4161638]
77. Castillo P, Woodruff B, Caselli R, et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis. *Arch Neurol*. 2006; 63(2):197–202. [PubMed: 16476807]
78. Tüzün E, Erda E, Durmus H, et al. Autoantibodies to neuronal surface antigens in thyroid antibody-positive and -negative limbic encephalitis. *Neurol India*. 2011; 59(1):47–50. [PubMed: 21339658]
79. Chong JY, Rowland LP, Utiger RD. Hashimoto encephalopathy: syndrome or myth? *Arch Neurol*. 2003; 60(2):164–171. [PubMed: 12580699]
80. Steup-Beekman G, Steens S, van Buchem M, Huizinga T. Anti-NMDA receptor autoantibodies in patients with systemic lupus erythematosus and their first-degree relatives. *Lupus*. 2007; 16(5): 329–334. [PubMed: 17576734]
81. Choe CU, Karamatskos E, Schattling B, et al. A clinical and neurobiological case of IgM NMDA receptor antibody associated encephalitis mimicking bipolar disorder. *Psychiatry Res*. 2013; 208(2):194–196. [PubMed: 23246244]
82. Prüss H, Höltje M, Maier N, et al. IgA NMDA receptor antibodies are markers of synaptic immunity in slow cognitive impairment. *Neurology*. 2012; 78(22):1743–1753. [PubMed: 22539565]
83. Steiner J, Walter M, Glanz W, et al. Increased prevalence of diverse N-methyl-D-aspartate glutamate receptor antibodies in patients with an initial diagnosis of schizophrenia: specific relevance of IgG NR1a antibodies for distinction from N-methyl-D-aspartate glutamate receptor encephalitis. *JAMA Psychiatry*. 2013; 70(3):271–278. [PubMed: 23344076]

84. Hammer C, Stepniak B, Schneider A, et al. Neuropsychiatric disease relevance of circulating anti-NMDA receptor autoantibodies depends on blood-brain barrier integrity. *Mol Psychiatry*. 2013
85. Montojo MT, Petit-Pedrol M, Graus F, Dalmau J. Clinical spectrum and diagnostic value of antibodies against the potassium channel related protein complex. *Neurologia*. 2014
86. Paterson RW, Zandi MS, Armstrong R, Vincent A, Schott JM. Clinical relevance of positive voltage-gated potassium channel (VGKC)-xcomplex antibodies: experience from a tertiary referral centre. *J Neurol Neurosurg Psychiatry*. 2014; 85(6):625–630. [PubMed: 23757422]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Antineuronal antibody-associated autoimmune encephalitis syndromes

Antigen	Clinical syndrome	Tumor	Additional
NMDAR (GluN1)	Anti-NMDAR encephalitis: Psychiatric manifestations, insomnia, reduction of verbal output, seizures, amnesia, movement disorders, catatonia, autonomic instability, coma	Age-dependent: ~10-45%, rare in children, ovarian teratomas, rarely carcinomas	~50% Viral prodrome; EEG: "delta brush pattern" in ~30% of patients; relapses 12% at 2 years
AMPA	Limbic encephalitis; may occur with pure psychiatric manifestations	70% (Lung, breast, thymoma)	Relapses common
GABA _B R	Limbic encephalitis, prominent seizures	50% (Lung, neuroendocrine)	Status epilepticus
LGI1	Limbic encephalitis, focal faciobrachial seizures, REM sleep behavior disorder, myoclonus	<10% (Lung, thymoma)	~60% Hyponatremia
CASPR2	Encephalitis, Morvan syndrome, neuromyotonia	0–40% (Thymoma)	Encephalitis relapses common
mGluR5	Limbic encephalitis, myoclonus	Hodgkin lymphoma; may occur without tumor	Very few cases
GlyαR	Stiff-person, PERM, limbic encephalitis, cerebellar degeneration, or optic neuritis	Infrequent	Wide clinical spectrum
DPPX	Encephalitis with CNS hyperexcitability: Confusion, psychiatric manifestations, tremor, myoclonus, nystagmus, hyper-ekplexia, PERM-like symptoms, ataxia	None	Diarrhea common
GABA _A R	Refractory seizures, status epilepticus, or epilepsy partialis continua	Infrequent	Low titer antibody; Stiff-person syndrome, opsoclonus
IgLON5	Abnormal sleep movements and behaviors, obstructive sleep apnea, stridor, dysarthria, dysphagia, ataxia, chorea	None	Chronic in most; refractory to immunotherapy

Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2, contactin-associated protein-like 2; CNS, central nervous system; DPPX, dipeptidyl-peptidase-like protein-6; EEG, electroencephalograph; GABA_R, gamma-amino-butyric acid receptor; GlyαR, glycine α receptor; IgLON5, immunoglobulin-like family member 5; LGI1, leucine-rich, glioma-inactivated 1; mGluR5, metabotropic glutamate receptor 5; NMDAR, N-methyl-D-aspartic acid receptor; PERM, progressive encephalomyelitis with rigidity and myoclonus; REM, rapid eye movement.