



# The Diagnosis and Treatment of Autoimmune Encephalitis

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Autoimmune encephalitis causes subacute deficits of memory and cognition, often followed by suppressed level of consciousness or coma. A careful history and examination may show early clues to particular autoimmune causes, such as neuromyotonia, hyperekplexia, psychosis, dystonia, or the presence of particular tumors. Ancillary testing with MRI and EEG may be helpful for excluding other causes, managing seizures, and, rarely, for identifying characteristic findings. Appropriate autoantibody testing can confirm specific diagnoses, although this is often done in parallel with exclusion of infectious and other causes. Autoimmune encephalitis may be divided into several groups of diseases: those with pathogenic antibodies to cell surface proteins, those with antibodies to intracellular synaptic proteins, T-cell diseases associated with antibodies to intracellular antigens, and those associated with other autoimmune disorders. Many forms of autoimmune encephalitis are paraneoplastic, and each of these conveys a distinct risk profile for various tumors. Tumor screening and, if necessary, treatment is essential to proper management. Most forms of autoimmune encephalitis respond to immune therapies, although powerful immune suppression for weeks or months may be needed in difficult cases. Autoimmune encephalitis may relapse, so follow-up care is important.

**Key Words** autoimmune, antibody, paraneoplastic, encephalitis, anti-NMDAR encephalitis.

## INTRODUCTION

Autoimmune encephalitis is a difficult clinical diagnosis due to the similarities in the clinical, imaging and laboratory findings of many forms of autoimmune and infectious encephalitis. Patients generally have impaired memory and cognition over a period of days or weeks. There may be clues to specific causes on history of physical examination, but often these specific signs are absent. A broad approach to testing for infectious diseases and various neuronal autoantibodies can lead to the correct diagnosis. If a clear autoimmune cause for the symptoms is established, treatment usually involves escalating immune therapies. The process of caring for these patients requires patience and repeated evaluations to determine the proper degree of immune therapy needed at any given time.

## SUBTYPES AND PATHOPHYSIOLOGY OF AUTOIMMUNE ENCEPHALITIS

Autoimmune encephalitis involves several types of diseases with different pathophysiology. Understanding the pathophysiology of these diseases is helpful in using diagnostic testing and choosing appropriate therapies. The first group includes the classic paraneoplastic disorders associated with antibodies to intracellular antigens, such as anti-Hu. These disorders are strongly cancer associated and involve T-cell responses targeting neu-

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rons. The prognosis tends to be poor due to irreversible neuronal killing by these mechanisms, the severity of associated cancers, and the difficulty in controlling these sorts of immune responses. The antibodies in these disorders are useful tumor markers, and in the appropriate context and titer also useful markers of the paraneoplastic neurological disorders. The antibodies themselves are not directly pathogenic. The second group involves autoantibodies to extracellular epitopes of ion channels, receptors and other associated proteins, such as the NMDA receptor. The cancer associations are variable, and the prognosis tends to be much better. The antibodies in these disorders are thought to be directly pathogenic, causing reversible effects on synaptic function in neurons with relatively little neuronal death. There are also important tumor associations in this group of diseases. For instance, patients with anti-NMDAR encephalitis commonly can recover from a totally unresponsive state to eventually resume a good quality of life. Occupying an intermediate position are diseases with autoantibodies to intracellular synaptic proteins such as GAD65. It is unclear whether this group involves T-cell responses and/or functional effects of antibodies. A final group includes other forms of autoimmune encephalitis in which precise antigens are less clearly established, such as lupus cerebritis or ADEM. Some diseases in this group have systemic manifestations outside the nervous system. This review will focus on the disorders with well-defined brain antibodies.

## RECOGNIZING THE SYNDROMES OF AUTOIMMUNE ENCEPHALITIS

Autoimmune encephalitis can manifest with several distinct

syndromes, complicating its recognition. The classical presentation of encephalitis consists of a subacute (days to a few weeks) progressive decrease in the level of consciousness, often with fluctuations, and altered cognition. Memory, especially retention of new information, may be impaired early in the clinical course. Patients may progress to coma. While many cases of autoimmune encephalitis are indistinguishable from each other or viral encephalitis, there may be clues to specific autoimmune etiologies (Table 1).

Psychiatric manifestations are common early in the course of autoimmune encephalitis. These may include psychosis, aggression, inappropriate sexual behaviors, panic attacks, compulsive behaviors, euphoria or fear. Symptoms may fluctuate rapidly. Although this presentation is well known for anti-NMDAR encephalitis,<sup>1</sup> anti-AMPA and anti-GABA-B-R both may have prominent early psychiatric manifestations<sup>2</sup> (Overall, anti-NMDAR encephalitis is more common and should be suspected first, especially in young adults and children, but they could each cause this presentation across a wide range of ages).

Abnormal movements may be the presenting symptom in several types of autoimmune encephalitis. These include anti-NMDAR encephalitis, where movement symptoms may occur early in the disease course, especially in children, who generally have more motor symptoms and fewer psychiatric symptoms than adults.<sup>3</sup> These may resemble dystonia or chorea, with writhing and fixed abnormal postures of the limbs. In adults with anti-NMDAR encephalitis, writhing movements of the face and limbs may be most prominent in the comatose phases of the illness. GAD65 and GlyR autoimmunity may present with stiff person syndrome (SPS) or progressive encephalomyelitis with rigidity and myoclonus

**Table 1.** Clinical clues in the recognition of particular types of autoimmune encephalitis

Clinical finding	Associated autoantibody disorders
Psychosis	NMDAR, AMPAR, GABA-B-R
Dystonia, chorea	NMDAR, Sydenham chorea, D2R
Hyperkplexia	GlyR
Status epilepticus	Most characteristic of GABA-B-R and GABA-A-R but NMDAR is much more common; may occur in other types as well
New onset type 1 diabetes	GAD65
Fasciobrachial dystonic seizures	LGI1
Neuromyotonia, muscle spasms, fasciculations	Caspr2
Stiff-person syndrome and/or exaggerated startle	GAD65, GlyR, Amphiphysin (with GAD65 being most common in stiff person/stiff limb and GlyR in PERM, and Amphiphysin in women with breast cancer)
CNS (myoclonus, startle, delirium) and gastrointestinal hyper-excitability	DPPX
Cranial neuropathies	Ma2, Hu, Miller-Fisher, Bickerstaff (but also infections like Sarcoidosis, Lyme, TB)
Cerebellitis	GAD65, PCA-1 (Yo), ANNA-1 (Hu), DNER (Tr), mGluR1, VGCC

CNS: central nervous system, TB: tuberculosis.

(PERM).<sup>4</sup> A striking feature of PERM with GlyR antibodies is a pathologically exaggerated startle response, resembling hereditary hyperekplexia, a genetic disease caused by GlyR mutations.<sup>5</sup> Although there is some degree of overlap, GAD65 is more associated with classical SPS while GlyR antibodies may be seen more with symptoms of hyperekplexia and myoclonus, which are prominent in PERM. Stiffness or exaggerated startle combined with other symptoms of encephalitis should raise concern for GlyR antibodies. Basal ganglia encephalitis has also been reported with D2R antibodies, although this may be very rare.<sup>6</sup> Sydenham chorea is a well-recognized autoimmune movement disorder thought to be triggered by streptococcal infections and should be considered in children with this presentation.<sup>7</sup>

Seizures are common in autoimmune encephalitis and may be a presenting symptom. In anti-NMDAR encephalitis seizures may occur at any stage of the illness. Autoantibodies to two important inhibitory receptors in the brain, GABA-B and GABA-A receptors (at high titer) convey a high risk of severe seizures and intractable status epilepticus.<sup>8,9</sup> GAD65 antibodies may present with epilepsy, perhaps also with memory impairment, but with few other symptoms to suggest an autoimmune etiology. GAD65 autoimmunity may therefore resemble other forms of treatment-resistant epilepsy. Fasciobrachial dystonic seizures (FBDS) are brief seizures consisting of rapid jerks of the face and/or ipsilateral arm and shoulder.<sup>10</sup> Seizures may be partial or associated with temporary disruptions in consciousness and may be multifocal and variable on EEG. FBDS are characteristic of LGI1 autoimmunity and may precede other symptoms of the disease by weeks or months. Patients may have hundreds of these seizures per day. These seizures may have only limited response to seizure medications but respond well to immune therapies.

Cerebellitis is a distinct syndrome of ataxia of gait, limb movements, eye movements, voice, and/or swallowing. The precise mixture of symptoms varies from patient to patient. Vertigo and nystagmus are common. Cerebellitis may occur with infectious causes, but the presentation of a subacute cerebellar syndrome portends a good probability a specific autoimmune etiology and also a significant risk of tumors. Paraneoplastic cerebellar degeneration is associated with conventional onconeural autoantibodies such as Yo, but also with cell surface autoantibodies targeting mGluR1, DNER, and other antibodies. GAD65 antibodies are perhaps the most common finding in this phenotype in my experience. Autoimmune cerebellitis may result in the irreversible loss of Purkinje neurons, and the prognosis is recovery may be poorer than with other types of autoimmune encephalitis.

Certain types of autoimmune encephalitis may precede or follow neuromuscular manifestations, particularly acquired neuromyotonia (Isaacs syndrome). Isaacs syndrome presents with muscle spasms, cramps and fasciculations due to peripheral nerve hyper-excitability.<sup>11,12</sup> Morvan syndrome (Morvan's fibrillary chorea) consists of peripheral nerve hyper-excitability with encephalitis and severe insomnia. Some cases of Isaacs syndrome are associated with autoantibodies to Caspr2 or other, often undefined, members of the voltage-gated potassium channel (VGKC) complex.<sup>13,14</sup> Caspr2 antibodies are even more likely in patients with Morvan syndrome, especially patients with thymoma, who may have multiple autoimmune disorders during their disease course. Encephalitis with these neuromuscular manifestations (myasthenia gravis, neuromyotonia) therefore suggests a specific autoimmune etiology.

As discussed below, most of the autoimmune causes of encephalitis are paraneoplastic, each conveying a risk profile for various tumors. Detecting particular tumors may therefore also suggest particular autoimmune causes. For instance, the likelihood of anti-NMDAR encephalitis is increased in a young woman with ovarian teratoma, and the likelihood of anti-DNER is higher in patients with cerebellar degeneration and Hodgkin lymphoma.

## EXCLUSION OF OTHER AUTOIMMUNE DISORDERS

In addition to the antibody-mediated and paraneoplastic forms of encephalitis, there are other autoimmune diseases that may present with encephalitis. In the case of ADEM, encephalitis is a common presentation. The characteristic brain lesions, and sometimes involvement of the optic nerves or spinal cord, are an important clue to diagnosis.

Multiple sclerosis (MS) is generally easier to distinguish from autoimmune encephalitis due to more focal symptoms and characteristic brain imaging findings.

Lupus may affect diverse areas of the nervous system, causing neuropathy, vasculitis, myelitis, venous sinus thrombosis, stroke, and other manifestations.<sup>15</sup> Neuropsychiatric lupus may manifest with seizures, psychosis, or neurovascular disease. These manifestations are most common with severe disease affected other organ systems such as the gastrointestinal, renal and hematological systems. In one large series, one forth of deaths from lupus were related to CNS involvement and 16% were due to CNS infection, suggesting vigilance for both autoimmune and infectious encephalitis is warranted for these patients.<sup>16</sup>

Vasculitis affecting the CNS may rarely present with symptoms resembling encephalitis. When this is suspected, im-

aging of the cerebral vessels, search for other evidence of vasculitis (such as serologies for lupus and other rheumatologic diseases) may be useful.

Bickerstaff encephalitis and Miller Fisher syndrome enter into the differential diagnosis of autoimmune encephalitis due to the presence of altered mental status and/or cranial neuropathies. These diseases may at first resemble the brain-stem syndrome associated with anti-Ri, but the loss of reflexes is an important clue suggesting Miller Fisher syndrome. Detection of the GQ1b antibody may be helpful in securing these diagnoses.<sup>17</sup>

## EXCLUSION OF INFECTIOUS CAUSES

It is typical for patients with autoimmune encephalitis to have testing for various infectious etiologies and they are frequently covered with antibiotic and/or antiviral therapies (such as acyclovir) empirically as infectious causes are excluded. Some of the relevant risk factors for various causes of encephalitis are listed in Table 2 and the major infections are listed in Table 3.

Most cases of infectious encephalitis are viral. In the USA, leading viral infections include are HSV, VZV, enterovirus, and West Nile virus (WNV).<sup>18</sup> Japanese encephalitis (JE) was once the leading cause of viral encephalitis in East Asia, but has declined dramatically in Korea and other nations due to successful vaccination programs.<sup>19</sup> Bacterial causes include listeria, atypical presentations of streptococcus, syphilis, Lyme disease, and tuberculosis. Fungal causes such as Cryptococcus or aspergillus are particularly likely in immunocompromised patients.

A detailed travel and exposure history is essential. For instance, West Nile encephalitis has been reported only once in Korea, in a patient who had recently traveled to Guinea.<sup>20</sup> Travel to areas endemic for malaria or Lyme disease may be similarly relevant. Exposure to persons with tuberculosis or other infectious agents may be a clue to diagnosis.

Since the risk of various infections depends on the status of the immune system, it is important to know patients' HIV status and consider whether other medical conditions (transplantation, cancer) may have weakened immunity.

**Table 2.** Risk factors for autoimmune and infectious encephalitis

Risk factor	Implications
Travel	Consider infectious causes of encephalitis in visited region
HIV	Opportunistic infections, risk depending on CD4 count
Transplantation	Opportunistic infections (CMV, VZV, HSV1, 6, 7); if recently transplanted, consider infection from donor
Systemic autoimmunity	Consider lupus cerebritis, vasculitis
Cancer	Consider specific paraneoplastic syndromes based on tumor, but also lymphomatous/carcinomatous tumor involvement
Prior encephalitis	Consider relapse of initial encephalitis, secondary autoimmune causes, and (if immunosuppressed) opportunistic infections

Certain types of tumors, such as lymphomas, may weaken the immune system and also increase the risk of paraneoplastic/autoimmune diseases. A detailed review of encephalitis in immunocompromised patients highlighted HSV and VZV as leading causes, along with a host of rarer entities.<sup>21</sup> Infections have been transferred by the organ donor to an organ transplant recipient, including rabies, LCMV, West Nile, CMV, and EBV;<sup>22</sup> these infections are a consideration in encephalitis in the weeks after transplantation.

Human herpesvirus 6 (HHV-6), and less often HHV-7, may cause encephalitis and their reactivation may be an important cause of encephalitis in transplant patients.<sup>23-25</sup> HHV-6 and HHV-7 are diagnosed by PCR, although this may not be positive initially.<sup>26</sup> There are no approved treatments, but ganciclovir, foscarnet, and cidofovir have been used.<sup>27</sup> HHV-6 may be more likely in cases whether the donor and/or recipient of a stem cell transplant carry a particular HLA type (HLA-B\*40:06).<sup>28</sup>

Due to the diversity of potential infections, using a separate test for each pathogen may not be practical. To address this issue, advanced genetic techniques (e.g., metagenomic deep sequencing of cerebrospinal fluid) have been proposed to screen for thousands of pathogens rapidly and efficiently. Early successes with this approach have included diagnosing cases of encephalitis due to leptospirosis, neurotropic astrovirus infection, Balamuthia mandrillaris, and squirrel bornavirus.<sup>29-32</sup> This approach should assume a wider role in diagnosing unusual CNS infections in the coming years.

Cerebellitis may occur as an infectious or post-infectious phenomenon. Leading viral causes include VZV, JC virus, influenza, EBV, and enterovirus. Numerous other bacterial, fungal, malignant, and other causes have also been reported.<sup>33</sup>

## EXCLUSION OF OTHER MEDICAL CAUSES

Wernicke encephalitis, due to thiamine deficiency, is most recognized in alcoholics but may also affect patients with gastric bypass or other causes of insufficient nutrition.<sup>34</sup> A history of weeks to months of rapid weight loss is common

in the later group, who do not have alcohol as a supplemental source of calories (The complex nutritional deficiencies after gastric surgery may present with several distinct syndromes. Of greatest relevance to this review, Wernicke encephalitis may occur along with or following an acute painful lower-extremity-predominant neuropathy.).<sup>35</sup> Prompt and thorough repletion with thiamine, often along with other nutrients, may be life saving and should not wait on laboratory confirmation of the diagnosis.

Intoxications such a neuroleptic malignant syndrome and serotonin syndrome may often present with similarities to

autoimmune encephalitis. Conversely, patients with anti-NMDAR encephalitis may develop psychosis as an initial symptom and be treated with neuroleptics, then later show catatonia, rigidity, autonomic instability and altered level of consciousness; this pattern of findings may be mistaken for neuroleptic malignant syndrome. Autoimmune encephalitis therefore should enter into the differential diagnosis of any case of suspected neuroleptic malignant syndrome (Patients with anti-NMDAR encephalitis may be particularly sensitive to strong dopamine antagonists, and our group attempts to avoid using these medications).

**Table 3.** Infectious causes of encephalitis

Pathogen	Test	Notes
HSV	PCR	A common cause in both healthy and immune-compromised patients, with particular predilection for the temporal lobes <sup>86</sup> Specific anti-viral therapy may be life-saving Rare cases of secondary anti-NMDAR encephalitis afterwards <sup>85</sup>
CMV	PCR	
VZV	PCR	
JE	PCR	Once a leading cause in East Asia, but declining due to vaccination programs
Enterovirus	PCR	Other, non-polio, strains may also be neurotropic and it is a relatively common cause of encephalitis
HHV6	PCR	Important cause in transplant patients 1% of persons have HHV-6 in their genome, so PCR test can be misleading
HHV7	PCR	Rare cause in immune compromised patients
Neuroborreliosis (Lyme disease)	Serology	10-15% of untreated patients have neurological symptoms Manifestations include meningitis, encephalitis, radiculitis, cranial neuritis, and peripheral neuropathy <sup>87</sup>
WNV (West Nile)	PCR, Serology	Widely distributed mosquito-born flavivirus Most infections asymptomatic or minimally symptomatic Encephalitis is the most common presentation, followed by meningitis and flaccid paralysis <sup>88</sup>
Syphilis	Serologies	Most cases are sexually transmitter. Neurological symptoms may occur years or decades after exposure. Manifestations are protean
Cryptococcus	Latex agglutination antigen test, culture	More often presents with meningitis in patients with AIDS and other immune-compromised states CSF opening pressure may be marked elevated
Aspergillus fumigatus	Culture, biopsy, antigen ELISA and other methods	Disseminated CNS aspergillosis is mostly in immune compromised (transplant patients), and pathology usually involves basal ganglia and/or thalami <sup>89</sup>
Mucor	Culture, biopsy (ideally for nasal involvement)	May affect both immunocompromised and immune intact persons Prognosis is grim
Tuberculosis	Chest X-ray, PPD, Serology	In one study the second most common cause of infectious temporal lobe encephalitis behind HSV <sup>86</sup> May also present with Rhombencephalitis
Listeria	Culture	Rhombencephalitis and meningitis are the two main manifestations
Streptococcus	Culture	
Toxoplasmosis	Serology	Classically, a common cause of brain lesions in patients with AIDS

CNS: central nervous system.

Lymphoma or carcinomatous meningitis may present similarly to autoimmune encephalitis.<sup>36</sup> Particularly, symptoms may have a subacute onset and involve multiple cranial neuropathies. Both may occur in patients with or without known tumors. Repeating CSF cytology, awareness of known tumors, and screening for malignancy may all help lead to recognition of these causes.

## DIAGNOSTIC APPROACHES

### Antibody testing

Autoantibody testing is extremely important for the proper diagnosis of autoimmune encephalitis. However, the tests have complexities that require consideration, and taking certain test results as conclusive evidence of autoimmune encephalitis can be a mistake.

Commercial tests for autoantibodies to NMDAR, LGI1, Caspr2, AMPAR (GluR1, GluR2 subunits), and GABA-B-R are widely available. Newer cell surface antigens like GABA-A-R and DPPX are more difficult to test clinically. The synaptic intracellular antigens GAD65 and Amphiphysin, as well as the conventional intracellular “onconeural” antibodies are widely available. In the correct clinical context, these antibodies can be diagnostic. But there are complexities to interpreting some of these tests.

NMDAR and other cell surface antibody tests are most sensitive and specific with CSF. Serum may offer a low false positive rate and a higher false negative rate. Pathogenic cell surface or synaptic autoantibodies are IgG responses. NMDAR IgM and IgA responses have been reported in patients with schizophrenia and other psychiatric disease but also in up to 10% of normal controls; these IgM and IgA responses have no established role in diagnosing autoimmune encephalitis.<sup>37</sup> Conversely, the types of IgG responses associated with anti-NMDAR encephalitis are not found in patients with schizophrenia.<sup>38</sup>

The availability of titers for NMDAR antibodies has led some practitioners to attempt to use these titers to guide treatment. However, titers have limited clinical utility for several reasons: 1) absolute titers provide little information on disease severity, 2) titers in serum do not correlate reliably with disease status, and 3) CSF titers correlate only roughly to disease status within a given patient using side-by-side comparisons of multiple samples.<sup>39</sup> Therefore, it is better to focus on the clinical status of the patient and not changes in antibody titer during the early phases of the illness. NMDAR CSF titers may be compared to earlier samples side-by-side in assessing whether clinical worsening represents a true relapse, but this is only rarely helpful.

Caspr2 and LGI1 each associate with VGKCs. The VGKC

antibody test is based on immunoprecipitation of a complex of protein containing VGKCs, LGI1, Caspr2 and other proteins. The VGKC RIA was created 15 years before the recognition of LGI1 or Caspr2 antibodies,<sup>40</sup> and patients with these antibodies were thought, incorrectly, to actually have antibodies to potassium channel subunits themselves.<sup>13,14,41</sup> The VGKC test may still detect patients with LGI1 or Caspr2 immunity, but low titer serum positive results have uncertain clinical significance. For instance, Paterson et al.<sup>42</sup> reported that only 4 of 32 patients with low titer VGKC results (100–400 pM) actually had an autoimmune disorder. Thus a low titer serum VGKC result without corresponding evidence of LGI1 or Caspr2 antibodies, ideally in the CSF, should not be taken as definitive evidence of autoimmune encephalitis.

GAD65 antibodies have diverse clinical correlates, including SPS, cerebellar degeneration, epilepsy, and type 1 diabetes.<sup>43</sup> In the context of encephalitis, especially with epilepsy, a CSF GAD65 response is evidence of an autoimmune etiology. However, GAD65 may co-exist with other autoantibodies, such as GABA-B-R, so may or may not represent the most relevant pathophysiological mechanism in some patients with multiple antibodies. In addition, low titer GAD65 serum responses may not be specific for a neurological disorder, and GAD65 serum antibodies provide little additional information in a patient with known type 1 diabetes. Conversely, I have observed patients who develop type 1 diabetes after the onset of their neurological syndrome in the context of GAD65 antibodies. Testing CSF of these patients for GAD65 and a panel of other autoantibodies may be informative in these cases.

Hashimoto's encephalopathy is generally defined as encephalopathy associated with thyroid autoantibodies that responds to steroids or other immune therapies.<sup>44</sup> It has not been shown that thyroid antibodies can directly affect the brain, and the abnormalities in thyroid hormone levels are generally too mild to explain the brain disease. Some of these cases are due to other autoantibodies, such as to the NMDAR or GABA-B-R, but the true cause of most cases is unknown. Thyroid antibodies are therefore sometime tested in patients with autoimmune encephalitis. Finding thyroid antibodies should prompt a careful search for responsive other autoantibodies to brain that would provide a more convincing explanation of the symptoms. But if these antibodies are not found immune therapy should be considered.

### Imaging

Brain MRI in patients with NMDAR, AMPAR, LGI1, Caspr2, and GABA-B antibodies may be normal or show increased T2 signal, especially in the medial temporal lobes.<sup>1,8,13,41</sup>

This pattern is similar to the findings seen in HSV encephalitis, where 95% of patients have abnormalities on MRI,<sup>45</sup> or other viral causes of encephalitis. Tuberculosis, Syphilis, or other infections may present similarly. Autoantibodies to DPPX or GABA-A may have less characteristic findings.<sup>9,46</sup> Brain MRI therefore does not distinguish between infectious and autoimmune causes, and a normal brain MRI does not exclude these causes.

Advanced brain imaging with PET or SPECT has shown diverse areas of regional hyper- or hypo-metabolism in patients with NMDAR, LGI1, Caspr2 or other autoantibodies.<sup>47</sup> These studies have not reached the point where any particular form of encephalitis can be distinguished from another, so I do not generally rely on these studies to rule in or rule out autoimmune causes in my practice.

### EEG

EEG is useful in patients with autoimmune or infectious encephalitis for excluding subclinical seizures, for prognosis, and sometimes for suggesting particular diagnoses. In patients with HSV encephalitis, EEG may predict prognosis in addition to helping exclude non-convulsive seizures; normal EEG correlates with good outcomes independent of other prognostic factors.<sup>48</sup>

Seizures may occur at any point during the disease course of anti-NMDAR encephalitis, including at presentation.<sup>49</sup> The extreme delta brush pattern may be observed in patients with anti-NMDAR encephalitis, most often in patients who are comatose.<sup>50</sup> This distinctive EEG pattern should prompt testing for NMDAR antibodies. Patients with anti-NMDAR encephalitis and other forms of autoimmune encephalitis may also have prolonged periods of unresponsiveness and abnormal behaviors that are not due to seizures, so in these cases prolonged EEG monitoring may be very helpful.

Status epilepticus may occur in several forms of autoimmune encephalitis. The highest risk appears to be in patients with autoantibodies to the major brain inhibitory receptors GABA-A and GABA-B. High-titer antibodies to either of these antigens conveys a risk of status, which may be refractory to the unusual treatments. Since these antibodies are both much rarer than other autoantibodies to the NMDA receptor, the status epilepticus in the setting of autoimmune encephalitis probably occurs more frequently with NMDAR antibodies overall.

LGI1 antibodies are associated with FBDS, which may present weeks or months prior to other symptoms. The clinical characteristics of these seizures are distinctive, involving rapid jerking of one side of the face and/or upper extremity. Each seizure tends to be unilateral but they may occur on both sides. Some events are simple partial and very rap-

id, but complex partial seizures may occur as they become more frequent. EEG may show multifocal onset seizures and other abnormalities.

In my experience, seizures in autoimmune encephalitis are associated with active disease (e.g., are unlikely to persist after remission of other symptoms of autoimmune encephalitis). These seizures may be very difficult to control with anti-seizure medications until the autoimmune disease is treated.

### Biopsy

Brain biopsy generally is not used in the diagnosis of encephalitis for several reasons. Infections may be detected by PCR, culture or other less invasive methods. The well-defined autoantibody causes typically have antibody tests that are much less invasive and much more definitive. In addition, the results of biopsy are generally not definitive for a particular autoimmune etiology. Overall, the clinical impact of biopsy done for suspected encephalitis is low, with only about 8% of cases having clear benefit.<sup>51</sup>

### Cancer screening

Paraneoplastic disorders are, in general, autoimmune disorders that are triggered by tumors. In many cases the target antigen is expressed by tumor tissue, such as HuD proteins in small cell lung cancer and NMDARs in ovarian teratoma.<sup>52,53</sup> In these patients it is likely that presentation of the antigen in the context of the tumor triggers the autoimmune response. However, other patients without tumors may have an identical clinical syndrome and immunological response (antibody specificity, neuropathology, etc.).

It is important to detect tumors promptly for several reasons. 1) Treating the relevant tumor is thought to be helpful for treating the autoimmune disorder. 2) Tumor therapy and immune therapy may need to be given simultaneously and in a coordinated fashion. 3) Treatment with steroids, rituximab, or cyclophosphamide could complicate tumor diagnosis in the case of tumors like lymphoma.

In the case of “onconeural” antibodies to intracellular antigens such as Hu, the antibodies may occur more commonly in cancer patients than in patients with the autoimmune disease. For instance low titer serum Hu responses are common in small cell lung cancer patients without the anti-Hu neurological syndromes. For this reason, finding such an antibody should prompt a careful evaluation for tumor even if there is not a corresponding autoimmune disease. For instance, an elderly diabetic smoker may be tested (inappropriately) for anti-Hu to evaluate a mild slowly progressive small fiber neuropathy. In this case, a low titer serum Hu antibody would be far less likely to explain the neuropathy than the diabetes, but should nonetheless prompt

screening for lung cancer. Similarly, a patient with known lung cancer may develop neuropathy after chemotherapy; finding Hu antibodies in such a patient should not be taken as definitive evidence of a paraneoplastic disorder.

Cell surface/synaptic antibodies are generally found in the spinal fluid only in patients with the relevant neurological disorder and are not found incidentally. Each of these antibodies has a cancer risk profile that should inform the search for tumors.

The testing strategy depends on the specific autoantibody and/or clinical syndrome. Where there is risk for lung cancer or other solid tumors, CT scans and PET/CT may be appropriate. In syndromes associated with ovarian teratoma, evaluation with ultrasound or pelvic MRI. In young men where Ma2 is diagnosed or suspected testicular ultrasound is important. Breast imaging with mammogram or MRI, pap smear, and pelvic imaging may be most helpful in women with anti-Yo. Screening should be broad in patients with high-risk syndromes such as cerebellar degeneration even when a particular antibody is not identified. Tumors may be very small when the neurological symptoms begin, so screening is typically done on initial presentation and repeated at increasing intervals. For instance, a young woman with anti-NMDAR encephalitis may have pelvic MRI at diagnosis, and repeated studies at 6 months, 1 year, and 2 years. A patient with DNER antibodies (conveying a 90% risk of Hodgkin lymphoma) might have PET-CT at diagnosis then close follow-up with an oncologist and repeat studies starting 3–4 months later.

## SPECIFIC TYPES OF AUTOIMMUNE ENCEPHALITIS

### Autoantibodies to cell surface antigens

Anti-NMDAR (N-methyl-D-aspartate receptor) encephalitis has a characteristic clinical syndrome in most patients. Symptoms of psychosis and memory impairment are commonly the initial findings with abnormal movements, seizures, and depressed level of consciousness emerging later.<sup>1</sup> Patients may experience the psychotic symptoms again as they wake from coma, a phenomenon analogous to the psychotic symptoms seen after recovery from phencyclidine anesthesia (Phencyclidine, also known as PCP or “angel dust”, is an NMDAR antagonist developed as an anesthetic but is not used due to the high risk of psychosis). Ovarian teratoma affects many female patients of reproductive age, but other tumors (and tumors outside women of reproductive age) are rare. The response to immune therapy is generally good, particularly if the more effective treatments are used promptly. However, treatment may take many months

to reach its full effects, and some patients have persistent deficits, especially in the domains of memory and cognition. The mechanisms of NMDAR antibodies have been extensively studied: these antibodies cross-link and internalize the target receptors, depleting NMDARs from synapses.<sup>54</sup> The antibodies are clearly directly pathogenic; passive transfer into the brains of rodents produced neurological symptoms that correlate with reduction in surface NMDARs on neurons.<sup>55</sup>

Anti-LGI1 (Leucine-rich, glioma-inactivated 1) encephalitis accounts for most cases of encephalitis previously attributed to VGKC antibodies<sup>14,41</sup> (The VGKC test, as described above, detects most LGI1 cases and also most Caspr2 cases). Myoclonus, hyponatremia, and fascio-brachial dystonic seizures are common. In some cases fascio-brachial dystonic seizures precede other symptoms of the disease by months. These seizures have characteristic appearance and respond well to immune therapy.<sup>10,56</sup> Respiratory failure and critical illness are less common with LGI1 than NMDAR antibodies, but the course may be slower. The median age is about 60 years, significantly older than anti-NMDAR encephalitis. LGI1 is a secreted synaptic protein that organizes AMPA receptors and VGKCs at CNS synapses. LGI1 antibodies have been shown to affect AMPA receptor localization on cultured neurons,<sup>57</sup> but additional mechanisms involving the localization of potassium channels are also possible. Cancers are relatively rare in this disorder, and some of these may be chance events in this older age group.

Anti-Caspr2 (contactin-associated protein-like 2) associate with encephalitis, Morvan syndrome and acquired neuromyotonia (Isaacs syndrome).<sup>13,14</sup> The most common phenotype is Morvan syndrome, but peripheral nerve symptoms may precede or follow encephalitis by months or years. Encephalitis tends to be slower in onset than anti-NMDAR encephalitis, and responds to immune therapy but is prone to relapse with taper of immune therapy. Some patients may have thymoma and this subgroup is particularly prone to comorbid myasthenia gravis and other autoimmunities found in thymoma patients. The median age is about 60 years, significantly older than anti-NMDAR encephalitis. Caspr2 is a cell adhesion molecule that organizes VGKCs at the juxtaparanodes of myelinated axons in the central and peripheral nervous system. It is unknown why some patients have CNS versus peripheral nerve symptoms since the antigen is the same on both types of axons.

Anti-AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor encephalitis may have psychiatric symptoms on presentation like anti-NMDAR encephalitis.<sup>58</sup> AMPA receptors are a widely expressed type of glutamate ionotropic receptors used for much of the rapid excitatory transmission in the brain. There is significant risk



of tumors of the lung, breast, and thymus in these patients. Most patients are female and they are mostly middle-aged and older.

Anti-GABA-B ( $\gamma$ -Aminobutyric acid B) receptor encephalitis is characterized by encephalitis with severe seizures or status epilepticus.<sup>8</sup> This is logical due to the inhibitory role of the GABA-B receptor system in the brain (GABA-B receptors are important for limiting excessive neuronal activity). About half of patients have small cell lung cancer and the patients are mostly older adults. Antibodies to the GABA-B receptor may be the most common type of immune cause found in patients with lung cancer.

Anti-GABA-A ( $\gamma$ -Aminobutyric acid A) receptor encephalitis has been reported in children and adults. At high titer these antibodies, which target the primary inhibitory ionotropic receptor in the brain, associate with severe encephalitis with status epilepticus or *epilepsia partialis continua*.<sup>9</sup> So far only 1 of 6 patients had a tumor, Hodgkin lymphoma, but the full cancer associations will become clearer as more cases are found.

Anti-mGluR1 (metabotropic glutamate receptor 1) have been reported in a small number of patients with paraneoplastic cerebellar degeneration.<sup>59,60</sup> There is a high risk of Hodgkin lymphoma in these patients. Similarly, antibodies to Homer-3, which organizes mGluR1 at synapses, have been reported in a single patient.

Anti-mGluR5 (metabotropic glutamate receptor 5) have been reported in a few patients with Ophelia syndrome, a relatively mild form of encephalitis that occurs in patients with Hodgkin lymphoma.<sup>60</sup> Typically the patients become confused and often seem adrift in time, as described by Carr<sup>61</sup> in his original reports. Patients do not generally have the sorts of psychosis, agitation, seizures, and autonomic instability seen, for example, in patients with NMDAR antibodies. Patients improve dramatically with treatment of the lymphoma. Although mGluR1 and mGluR5 are close homologs, the antibodies do not cross react and the clinical syndromes are distinct.

Anti-DNER (delta/notch-like epidermal growth factor-related receptor) target a transmembrane protein expressed on Purkinje neurons and associate with cerebellar degeneration and a very high risk (90%) of Hodgkin lymphoma.<sup>62,63</sup> Before the precise definition of the antigen, these antibodies were referred to as “anti-Tr” and often classified with the conventional paraneoplastic disorders.<sup>64</sup> Patients should be carefully and repeatedly screened for Hodgkin lymphoma. Even with successful tumor treatment there is often permanent cerebellar injury.

Anti-GlyR (Glycine receptor) target the primary inhibitor ionotropic receptor in the spinal cord.<sup>65</sup> Symptoms accord-

ingly resemble strychnine toxicity: increased muscle tone, spasms, and pathologically exaggerated startle response. These antibodies should be considered in patients with SPS, especially those showing a PERM-like phenotype.<sup>4</sup> There is some risk of cancer, although most patients do not have tumors.

Anti-DPPX (dipeptidyl-peptidase-like protein-6) associate with a syndrome of gastrointestinal and nervous system hyper-excitability.<sup>46</sup> In addition to memory loss, seizures, and confusion, symptoms of exaggerated startle, myoclonus, rigidity and hyper-reflexia have been reported. Patients may have severe diarrhea or alternatively have constipation. A small group of these patients may have tumors such as lymphoma.

### Autoantibodies to intracellular synaptic proteins

Anti-GAD65 (glutamic acid decarboxylase 65kd) target the synaptic isoform of the enzyme necessary to synthesize GABA. GAD65 antibodies have diverse clinical associations, including type 1 diabetes, cerebellar ataxia and SPS.<sup>66</sup> In patients with the neurological symptoms a strong antibody response in the CSF is common. In the paraneoplastic context (that is, when cancer is present), GAD65 antibodies associate with diverse syndromes including encephalitis, SPS and paraneoplastic cerebellar degeneration.<sup>67</sup> When cancer is present GAD65 antibodies more frequently co-existing to autoantibodies to GABA-A or GABA-B.

Anti-Amphiphysin target an intracellular protein important for recycling synaptic vesicles.<sup>68</sup> The antibodies are very strongly associated with SPS in women with breast cancer.<sup>69</sup> The SPS more often affects the cervical region and responds to tumor therapy and/or immune therapy.

### Autoantibodies to intracellular antigens

Anti-Hu (ANNA-1) was the first type of onconeurological antibody described. Patients with anti-Hu most often have sensory-predominant neuropathy but may also or alternatively have cerebellar degeneration, encephalitis or encephalomyelitis.<sup>70</sup> Multifocal involvement is common. The antibodies target a family of intracellular proteins. These antibodies are not directly pathogenic and do not cause disease in active immunization or passive transfer animal models. Pathology studies show CD8 positive T-cell infiltrates in affected tissues. The association with small cell lung cancer is very strong (approximately 86% in one series) and outcomes are often poor.

Anti-Ri (ANNA-2) associate with diverse syndromes including cerebellar degeneration and encephalitis. Most patients have lung or breast cancers.<sup>71</sup>

ANNA-3 have only rarely been described and the clinical

features are multifocal and have a similar range as anti-Hu.<sup>72</sup>

Anti-Yo (PCA-1) are found in women with breast or ovarian cancers in more than 90% of cases.<sup>73</sup> Patients usually have paraneoplastic cerebellar degeneration. Approximately half of patients die of their tumors, and tumors are often only detected after identification of the paraneoplastic disorder.<sup>74</sup> There is some evidence that the antibodies may enter neurons, but other researchers think T-cell mechanisms are more likely.<sup>75</sup>

PCA-2 have only rarely been reported and may associate with encephalitis or cerebellar syndromes.<sup>76</sup>

Anti-CRMP-5 have diverse associations including cognitive impairment, cerebellar syndromes, abnormal movements (chorea), and cranial neuropathies. Optic neuritis has also been reported.<sup>77-79</sup>

Anti-Ma2 (PMNA-2) are found most often in young men with germ cell tumors. Neurological symptoms could include encephalitis, cerebellar degeneration, or neuropathy. Limbic and/or brainstem syndromes may be most common.<sup>80</sup>

## TREATMENT APPROACHES

Treatment for suspected autoimmune encephalitis is often given empirically prior to specific antibody test results. This may include steroids and/or IVIG. If a cell-surface/synaptic antibody disorder is diagnosed, initial treatments may include IVIG, plasmapheresis, and/or steroids. Steroids may be beneficial in a range of autoimmune disorders but could potentially create problems with the diagnosis of certain disorders such as CNS lymphoma. IVIG offers an important advantage of being unlikely to make infectious encephalitis worse. Plasmapheresis is also unlikely to significantly worsen infectious encephalitis.

If a synaptic/cell-surface antibody is detected and the patient has any significant symptoms, first-line therapy should be given if it has not already been tried. In general, prompt treatment, and escalation of treatment in patients who remain ill, is associated with better outcomes. Although there are not randomized treatment trials, protocols have been proposed for anti-NMDAR encephalitis,<sup>1</sup> and these approaches have been applied to other diseases in the cell-surface/synaptic autoantibody category. Our group often uses IV solumedrol (1 gram daily for 3–5 days then a taper over several weeks) and IVIg (0.4 g/kg/day for 5 days). Other groups have advocated plasmapheresis instead of IVIg, and so far there is not convincing evidence of superiority for either approach.

If the patient remains significantly impaired after first-line therapy, second-line treatments are typically used. Some groups might wait 2 weeks or longer to allow first-line ther-

apies time to work, but our group often proceeds more quickly to second line therapy sooner in patients who are very ill, for instance comatose patients with anti-NMDAR encephalitis. Second line therapies include rituximab (often 375 mg/m<sup>2</sup> weekly for 4 weeks) or cyclophosphamide (750 mg/m<sup>2</sup> IV monthly until improvement is noted), or both. Rituximab is a monoclonal antibody targeting CD20, so plasmapheresis generally should not be done after it is administered. Rituximab depletes CD19+/CD20+ B-cells, and circulating levels of these cells typically become undetectable for several months after treatment. Due to its relatively favorable safety profile, rituximab is more often used as monotherapy in children. Rituximab is thought to be generally effective against neurological diseases where the autoantibodies are of the IgG4 subtype.<sup>81</sup> Since IgG4 responses predominate in LGI1 and Caspr2 encephalitis this provides an additional theoretical support for using rituximab in those diseases. Cyclophosphamide has several important toxicities, including a risk of infertility, especially in young women who received repeated doses (The risk cumulatively increases, potentially up to 40% after 12 doses). This risk can be reduced with use of a GnRH agonist in women,<sup>82</sup> or addressed with egg/sperm collection.

## AUTOIMMUNE ENCEPHALITIS IN CHILDREN

Anti-NMDAR encephalitis is by far the most common type of antibody-mediated encephalitis in children. The age distribution of other types of synaptic autoimmune disorders either skews much older (the median age for LGI1 or Caspr2 antibodies is about 60 years) or the disorders are much less common (GABA-A antibodies) or both. In a study by the California encephalitis project, anti-NMDAR encephalitis was more common than any single viral etiology.<sup>83</sup>

Anti-NMDAR encephalitis in children may present differently than in adults.<sup>84</sup> Children are more likely to have abnormal movements (chorea, incoordination) early in the disease course and also may have atypical motor symptoms such as ataxia or hemiparesis. Children more often have seizures than adults. The classic symptoms of psychosis seen in adults are less common, but behavioral regression is frequently noted. Patients may have prominent speech difficulties. Treatment strategies are similar in children and adults, but physicians may be more reluctant to use cyclophosphamide, relying more on rituximab as a second line treatment (As with adults, the optimal treatment strategies are not known). Responses to treatment are similar in children and adults, with about half failing first line therapies. Ovarian teratoma is less likely in female children before puberty, so

tumors are uncommon in young children.

## RELAPSING ENCEPHALITIS

Patients with encephalitis may recover, completely or partially, and then experience worsening symptoms. In autoimmune encephalitis, relapse tends to follow a similar clinical course to the initial attack. In anti-NMDAR encephalitis, these relapse tend to be milder than the initial attack and manifest with confusion, worsening memory, personality change, hallucinations or new seizures (In my experience, seizures in my cases of autoimmune encephalitis remit with appropriate treatment, and new seizure should always raise concern for relapse). The risk of relapse in anti-NMDAR encephalitis is approximately 12% over two years (but continues beyond that) and is highest in untreated patients, intermediate in patients who had only first-line therapy, and lowest in patients treated with second-line therapies.<sup>84</sup> Relapsed patients are usually treated with second-line therapies, possibly after first line therapies. These patients may be treated for longer periods of time with second line therapy, especially rituximab, but the optimal duration of treatment has not been established. In other types of autoimmune encephalitis, the risk of relapse is less clearly established. LGI1 antibodies and Caspr2 antibodies may associate with milder encephalitis, compared with NMDAR antibodies, than is chronic or relapsing. Similar treatment strategies may be used with these antibodies.

An important recent advance has been the recognition that patients with HSV encephalitis may rarely develop anti-NMDAR encephalitis several weeks later as a post-infectious complication.<sup>85</sup> In these patients CSF from the initial attack has no NMDAR antibodies with positive PCR for HSV, but CSF from the second attack now has NMDAR antibodies with negative PCR for HSV. This phenomenon may be due to exposure of CNS antigens to the immune system in the presence of a powerful infectious stimulus. Patients who worsen after infectious encephalitis should therefore be carefully evaluated for both infectious and autoimmune etiologies. Similarly, patients who have been treated for autoimmune encephalitis may be immunosuppressed and at risk for diverse infections. However, opportunistic CNS infections after autoimmune encephalitis are probably very rare compared to worsening of the autoimmune disease.

## CONCLUSIONS

The proper diagnosis and management of autoimmune encephalitis requires an organized approach. Evaluation should begin with a detailed history and physical examination to

detect clues to specific causes. A diverse range of infections should be considered, and appropriate testing should be done to exclude relevant pathogens. Ancillary testing with MRI, EEG, and lumbar puncture may further support a diagnosis of encephalitis and potentially suggest particular causes. A broad group of autoantibody tests may be used to diagnose or exclude particular autoimmune causes, but these tests are complex and not every positive result is definite evidence of an autoimmune disorder. The risk of neoplasm should always be considered during initial treatment and follow-up visits, both in terms of diagnosing serious cancers and because specific tumors may suggest particular autoimmune causes. Treatment should depend on the pathophysiology of the disorder (e.g., T-cell-mediated or antibody mediated) and the clinical situation of the patient. Patients may relapse and should receive appropriate follow-up care from a physician familiar with the diseases.

### Conflicts of Interest

The author has no financial conflicts of interest.

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