

Autoimmune encephalitis update

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Cancer-associated immune-mediated disorders of the central nervous system are a heterogeneous group. These disorders include the classic paraneoplastic neurologic disorders and the more recently described autoimmune encephalitis associated with antibodies to neuronal cell-surface or synaptic receptors that occur with and without a cancer association. Autoimmune encephalitis is increasingly recognized as the cause of a variety of neuropsychiatric syndromes that can be severe and prolonged. In contrast to the classic paraneoplastic disorders that are poorly responsive to tumor treatment and immunotherapy, autoimmune encephalitis often responds to these treatments, and patients can have full or marked recoveries. As early treatment speeds recovery, reduces disability, and decreases relapses that can occur in about 20% of cases, it is important that the immune pathogenesis of these disorders is recognized.

Keywords: antibodies, autoimmune, encephalitis, paraneoplastic, synaptic antigens.

Antibody-associated disorders of the central nervous system (CNS) are a diverse group of syndromes that currently can be broadly divided into 2 categories: classic paraneoplastic disorders (PNDs) and autoimmune disorders associated with antibodies to neuronal cell-surface or synaptic receptors (termed here “autoimmune encephalitis”) (Fig. 1).¹ The PNDs are relatively rare, almost always associated with a systemic cancer, and mostly affect older adults (Table 1).² Moreover, the associated antibodies target intracellular neuronal antigens, and the pathology is likely mediated by cytotoxic T-cell responses.^{3,4} The PNDs usually have a monophasic clinical course and limited response to treatment, although stabilization may occur in some patients. In contrast, autoimmune encephalitis is more common than classic PND and occurs with and without a cancer association (Table 2).⁵ These disorders affect a wider age range of patients than classic PND, and some occur predominantly in young adults, adolescents, and children. The associated antibodies mediate neuronal dysfunction by direct interaction with the target antigens, similar to what occurs in Lambert–Eaton myasthenic syndrome and myasthenia gravis.⁶ Symptoms are responsive to treatment, with 70%–80% of patients (depending on the immune response) having substantial or full recovery after immunotherapy and tumor treatment when present. In about 20% of cases the clinical course can be relapsing, and for many the recovery process is often protracted and can require months of hospitalization followed by long stays in rehabilitation care. There is a third group of disorders in which the target antigens are intracellular synaptic

proteins and are paraneoplastic (eg, amphiphysin antibodies and stiff-man syndrome) or not cancer related (antibodies to the 65-kD isoform of glutamic acid decarboxylase [GAD65] and stiff-man syndrome or cerebellar ataxia).^{7,8} It has been postulated that although some of these antigens are intracellular, they can be exposed on the cell surface during synaptic vesicle recycling, and there is evidence that both B- and T-cell mechanisms underlie the neuronal pathology.^{9,10}

The diagnosis of classic PND and autoimmune encephalitis is based on the recognition of the neurologic syndrome, the detection of the specific antibodies in serum or cerebrospinal fluid (CSF), and the identification of the underlying cancer, if paraneoplastic. There are many reviews focused on the diagnosis and approach to treatment for classic PND, and these will not be further discussed.^{11–13} This review focuses on autoimmune encephalitis, including some disorders that have recently been identified; provides an update on the clinical features and underlying disease mechanisms; and discusses newly uncovered clinical associations.

Anti-N-methyl-D-aspartate Receptor Encephalitis

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a highly characteristic and recognizable neuropsychiatric syndrome. It is most common in young women and children,

Received 22 January 2014; accepted 12 February 2014

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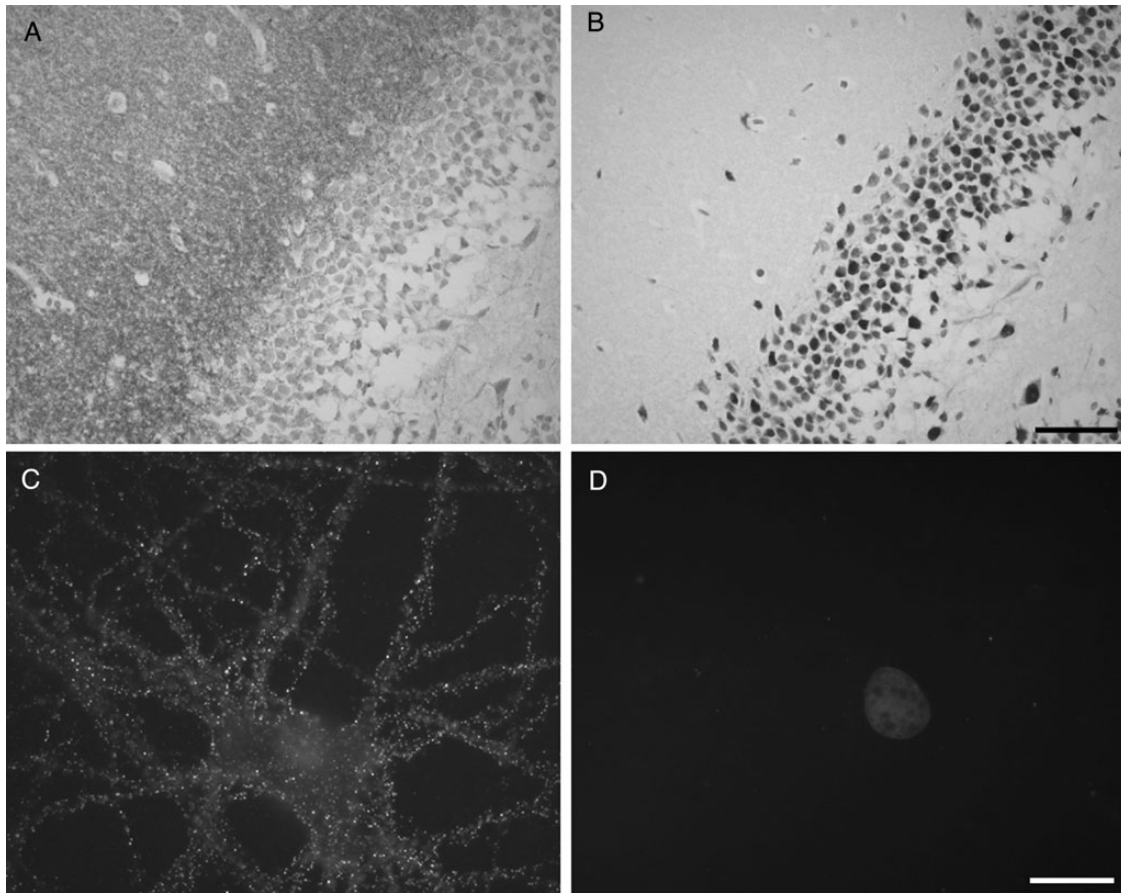


Fig. 1. Comparative immunolabeling of antibodies to cell-surface and intracellular antigens. Panels A and B show the dentate gyrus of hippocampus immunostained with CSF from a patient with NMDA receptor antibodies (A), and the CSF of a patient with Ri antibodies (B). Note that the NMDA receptor antibodies bind the neuropil (areas that contain neuronal processes and synapses), while the Ri antibodies bind to the nuclei of neurons. Scale bar in (B) = 50 μm . Panels C and D show cultures of dissociated rat hippocampal neurons incubated with the CSF of the patient with NMDA receptor antibodies (C) and the CSF of the patient with Ri antibodies (D). The NMDA receptor antibodies bind to cell-surface (extracellular) epitopes of the NMDA receptor, while the Ri antibodies show no binding because they do not penetrate live neurons. Scale bar in (D) = 20 μm .

Table 1. Classic antibody-associated paraneoplastic syndromes

Syndrome	Antibody	Common Cancer Association
PEM including cortical, limbic, brainstem encephalitis, PCD myelitis; PSN, autonomic dysfunction	Anti-Hu	SCLC
PCD	Anti-Yo	Gynecological, breast
PCD, brainstem encephalitis, opsoclonus-myoclonus	Anti-Ri	Breast, gynecological, SCLC
PEM, PCD, chorea, peripheral neuropathy	Anti-CV2/CRMP5	SCLC, thymoma
Limbic, hypothalamic, brainstem encephalitis (infrequently PCD)	Anti-Ma proteins	Germ-cell tumors of testis
Cancer-associated retinopathy	Anti-recoverin	SCLC
PCD	Anti-Tr	Hodgkin lymphoma

Abbreviations: PEM, paraneoplastic encephalomyelitis; PCD, paraneoplastic cerebellar degeneration; PSN, paraneoplastic sensory neuronopathy; CRMP5, collapsin response mediator protein 5.

although men and older patients of both sexes can be affected.¹⁴ Many patients experience a viral-like prodrome, followed by the development of severe psychiatric symptoms, memory loss, seizures, decreased consciousness, and dyskinesias, often of the

mouth and face but sometimes involving the limbs and trunk. Some patients may initially appear to have a primary psychiatric disorder.¹⁵ In younger patients (≤ 18 y) the initial symptoms tend to be more neurologic (eg, dyskinesias, seizures), although 40%

Table 2. Autoimmune encephalitis associated with antibodies against neuronal cell-surface or synaptic proteins

Antigen Target	Syndrome	Cancer Association if Present	Observations
NMDA receptor	Characteristic neuropsychiatric syndrome with movement disorders, seizures, autonomic dysfunction	Age-related association with ovarian teratoma	Predominantly affects young adults, adolescents, and children
AMPA receptor	Limbic encephalitis, psychosis	Lung, breast, thymus in ~70% of cases	Frequent coexisting autoimmunities
GABA _B receptor	Limbic encephalitis with early, prominent, and severe seizures	SCLC or other neuroendocrine tumor of lung in ~50% of cases	Frequent coexisting autoimmunities
LG11	Limbic encephalitis, seizures, hyponatremia, myoclonus	Thymoma in <10% of cases	Frequent tonic seizures that may be misdiagnosed as myoclonus or startle
Caspr2	Encephalitis and/or peripheral nerve hyperexcitability	Rarely thymoma	Symptoms of overlapping immune disorders such as myasthenia have led to misdiagnosis of motor neuron disease
GABA _A receptor	Status epilepticus or refractory seizures and encephalitis	None	Frequent coexisting autoimmunities; extensive and often multifocal MRI abnormalities
DPPX	Encephalopathy, agitation, tremor, startle with muscle rigidity, seizures, and gastrointestinal dysfunction	None	Severe gastrointestinal symptoms can mislead diagnoses
Glycine receptor	Stiff-person, hyperekplexia, PERM, and encephalitis	Rare associations with cancer but usually not paraneoplastic	
mGluR1	Cerebellar ataxia	Hodgkin lymphoma	
mGluR5	Limbic encephalitis	Hodgkin lymphoma	Known as Ophelia syndrome
Dopamine-2 receptor	Basal ganglia encephalitis, Sydenham chorea	None	
Amphiphysin	Stiff-man syndrome	Breast, SCLC	
GAD	Stiff-man syndrome at times with cerebellar ataxia, refractory seizures	Rarely thymoma or other tumors	Have been reported in other syndromes, such as limbic encephalitis and epilepsy; frequent coexisting autoimmunities

Abbreviation: PERM, progressive encephalomyelitis with rigidity and myoclonus.

will develop psychiatric manifestations.¹⁶ Older patients (≥ 45 y) tend to present with memory difficulties, leading to a wide differential diagnosis.¹⁷ For all patients, within days to a few weeks of presentation, the syndrome progresses to include autonomic and breathing instability requiring intensive care support. Over half of the patients have an associated tumor, most commonly an ovarian teratoma. The presence of a tumor is age dependent. Approximately 45% of female patients older than 18 will have uni- or bilateral ovarian teratomas, while <9% of girls younger than 14 years have a teratoma. Identification and removal of the tumor is important, as patients without tumor removal have less frequent recoveries and an increased risk of relapses.¹⁴ The CSF usually shows a lymphocytic pleocytosis and, less commonly, increased proteins and/or oligoclonal bands. About 35% of patients have increased signal on MRI fluid-attenuated inversion recovery (FLAIR) or T2 sequences and, less often, faint or transient contrast enhancement of the cerebral cortex, overlying meninges, basal ganglia, or brainstem.

All patients have IgG antibodies against the GluN1 subunit of the NMDA receptor.¹⁸ A recent study has shown that at the time of diagnosis, these antibodies are always present in CSF but are

absent in the serum of 13% of patients, demonstrating the importance of including CSF for diagnosis.¹⁹

Anti-Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid Receptor Encephalitis

Patients with alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor encephalitis most commonly present with classic symptoms of limbic encephalitis, including subacute onset of confusion, disorientation, and memory loss.²⁰ These are often associated with psychiatric symptoms and seizures. The disorder predominantly affects middle-aged women and is paraneoplastic in about 70%.²¹ The more commonly associated tumors involve thymus, lung, or breast.²² Patients frequently have additional autoantibodies, such as thyroid peroxidase and antinuclear antibodies, suggesting a susceptibility to autoimmunity. CSF findings are similar to those of anti-NMDA receptor encephalitis with predominant lymphocytic pleocytosis. Brain MRI usually shows abnormal FLAIR signal involving the medial temporal lobes, rarely with transient signal changes in other areas.

Anti-Gamma-aminobutyric Acid_B Receptor Encephalitis

The most distinctive features of this disorder are early and prominent seizures in association with limbic encephalitis, including memory loss, confusion, hallucinations, and personality change.²³ Rarely, patients' develop ataxia or opsoclonus-myoclonus along with seizures. Gamma-aminobutyric acid_B (GABA_B) receptor encephalitis has been described in both men and women, and about half have an associated tumor, either a small-cell lung cancer (SCLC) or a neuroendocrine tumor of the lung. Patients with tumors are older (median age 67.5 y) compared with those without tumor (median 39 y). When the disorder is paraneoplastic, the encephalitis usually precedes the cancer diagnosis. Imaging and CSF findings are similar to other types of limbic encephalitis. As in many of these disorders, these patients frequently have additional autoantibodies (eg, thyroid peroxidase, antinuclear antibodies, GAD65), suggesting a tendency to autoimmunity or reflecting the presence of an underlying cancer, such as antibodies to *sry*-related box genes (*Sox*) (suggesting the presence of an SCLC).^{24–26}

Anti-Leucine-rich Glioma Inactivated 1 Limbic Encephalitis

Patients with antibodies to leucine-rich glioma inactivated 1 (LGI1) are older individuals who usually develop a classic picture of limbic encephalitis.²⁷ About 60% also develop hyponatremia and, less often, rapid eye movement (REM) sleep behavior disorders (including dream enacting behavior and abnormal REM sleep patterns).²⁸ A few patients experience myoclonus-like movements that have been described as tonic or dystonic movements in the face, arm, or leg that may precede memory and cognitive changes. These movements may be misdiagnosed as myoclonus or as a startle disorder but in fact are brief tonic seizures that are often refractory to antiepileptic treatments.²⁹ Less than 10% of patients with LGI1 antibodies have an underlying neoplasm, usually a thymoma. The CSF is often normal, although mild inflammatory changes or oligoclonal bands may be present. Antibodies are almost always detectable in CSF, although for unclear reasons this disorder does not usually associate with intrathecal synthesis of antibodies. MRI findings are similar to the other forms of limbic encephalitis. LGI1 is a secreted neuronal protein that interacts with pre- and postsynaptic epilepsy-related proteins,^{30,31} and mutations of LGI1 result in a syndrome named autosomal dominant lateral temporal lobe epilepsy.^{32,33} Anti-LGI1 antibodies as well as anti-contactin-associated protein-like 2 (*Caspr2*) antibodies were previously described as voltage-gated potassium channel (VGKC) antibodies. The identification of the correct and disease-specific antigens calls into question the clinical value of so-called anti-VGKC complex antibodies.

Anti-Caspr2 Associated Encephalitis

Patients with *Caspr2* antibodies usually develop Morvan syndrome, a disorder that includes symptoms of peripheral nerve hyperexcitability (neuromyotonia) and limbic encephalitis.^{28,34} Although some patients with neuromyotonia have *Caspr2* antibodies, the large majority of patients are antibody negative.

Other patients with *Caspr2* antibodies develop symptoms of classic limbic encephalitis, but they are a minority. Some patients have other, coexisting immune-mediated disorders such as myasthenia gravis with anti-acetylcholine or muscle-specific kinase antibodies. The combination of symptoms related to neuromyotonia, such as cramps, fasciculations, motor weakness, and symptoms related to overlapping autoimmunities (eg, bulbar symptoms, atrophy), has resulted in some patients being diagnosed with atypical motor neuron syndrome.³⁴ As anti-*Caspr2* associated encephalitis responds to immunotherapy, formulating the correct diagnoses is important. Anti-*Caspr2* associated symptoms are more likely to be cancer related (most commonly thymoma) in patients with Morvan syndrome compared with those with other symptoms. *Caspr2* is expressed in brain and at the juxtaparanodal region of myelinated axons, and mutations are associated with psychosis, schizophrenia, autism, refractory seizures, mental retardation, and in some cases neuromyotonia.^{35,36}

Anti-Gamma-aminobutyric Acid_A Receptor Encephalitis

This syndrome was recently described in children and adults (3–63 y) who developed a rapidly progressive encephalopathy with refractory seizures, status epilepticus, and/or *epilepsia partialis continua*.³⁷ The seizures were preceded by or associated with change of behavior or cognition. The CSF usually shows lymphocytic pleocytosis, increased protein concentration, and, less often, oligoclonal bands. In contrast to other autoimmune encephalitis in which MRI is either normal or shows predominant involvement of the limbic system, patients with GABA_A receptor encephalitis have multifocal and extensive FLAIR/T2 abnormalities. Patients with this disorder rarely have an underlying tumor, but when present it is usually thymoma. Many of the patients have other, less relevant autoantibodies (thyroid peroxidase, GAD65), although in some cases there is overlap with antibodies against other synaptic receptors, such as GABA_B or NMDA receptors. The disorder appears to be responsive to immunotherapy, although the seizures often require pharmacologically induced coma until improvement.

Anti-Dipeptidyl-peptidase-like Protein-6 Encephalitis

Antibodies to dipeptidyl-peptidase-like protein-6 (DPPX) were initially described in 4 adults (45–76 y) who developed a rapidly progressive encephalopathy and symptoms of CNS hyperexcitability such as agitation, hallucinations, myoclonus, and seizures.³⁸ Three of the 4 patients had diarrhea, which was severe in 2 and accompanied by substantial weight loss. Some patients had cerebellar signs such as ataxia and nystagmus, and 1 developed prominent startle responses. The disorder can be severe and result in long hospitalizations. DPPX plays a critical role in the regulation of Kv4.2 VGKC and is expressed by neurons in the myenteric plexus, although how this may result in the associated diarrhea has not yet been clarified.³⁹ The disorder does not associate with cancer, but the severe diarrhea and weight loss often leads to the suspicion of a paraneoplastic etiology of the disorder.

Other Disorders

Antibodies to amphiphysin associate with paraneoplastic stiff-person syndrome.^{8,40} Antibodies to GAD commonly associate with nonparaneoplastic stiff-person syndrome but rarely occur in cancer-associated cases.⁴¹ Additionally, there are an increasing number of reports showing that GAD antibodies associate with late-onset cerebellar degeneration, limbic encephalitis, and refractory epilepsy.^{7,42} Antibodies to the alpha subunit of the glycine receptor have been found in patients with brainstem/spinal cord hyperexcitability disorders; some of these cases have been cancer related, although the frequency of this association remains to be determined.^{43,44} Antibodies against metabotropic glutamate receptor 1 (mGluR1) have been identified in a few patients with idiopathic or paraneoplastic cerebellar ataxia associated with Hodgkin' lymphoma,^{45,46} while antibodies to mGluR5 have been identified in patients with Hodgkin' lymphoma and limbic encephalopathy (known as Ophelia syndrome).^{45,47} Dopamine-2 receptor antibodies have been reported in children with basal ganglia encephalitis and Sydenham chorea and in a subgroup of patients with Tourette' syndrome, none associated with cancer.⁴⁸

Mechanisms of Disease

The target antigens in these disorders are neuronal cell-surface proteins or synaptic receptors that play varying roles in neuronal function, including synaptic transmission or plasticity (AMPA, GABA, mGluR5, mGluR1, NMDA, dopamine, glycine receptors, LGI1), clustering of ion channels (Caspr2), and modulation of potassium channels and somatodendritic signal integration (DPPX). The accessibility of the target antigens to the circulating antibodies, the correlation of patients' symptoms with antibody titers (often better with CSF titers), and the reversibility of the syndromes have suggested a primary pathogenic role of the antibodies that has now been demonstrated for several of these syndromes. For example, patients' antibodies to NMDA receptor cause a titer-dependent, reversible decrease of synaptic and extrasynaptic NMDA receptor through a mechanism of capping, crosslinking, and internalization.^{6,18} Anti-AMPA receptor antibodies affect receptor function through similar mechanisms, causing a reversible decrease in synaptic AMPA receptor and associated synaptic currents.²⁰ In contrast GABA_A receptor antibodies disrupt receptor signaling by significantly reducing receptor density in synapses but not at extrasynaptic sites, suggesting that the antibodies cause relocation of receptors from synaptic to extrasynaptic sites rather than a total removal of receptors.³⁷

Treatment Approaches

Treatments are focused on eliminating the antibodies based on their pathogenicity. Many patients are initially treated with first-line immunotherapy, including corticosteroids, intravenous immunoglobulin, plasma exchange, or a combination of these with no data supporting one treatment over another. However, these antibody-depleting strategies are not very effective at decreasing intrathecal antibody titers, and additional immunotherapies are often required. The largest experience evaluating outcomes and treatment is in anti-NMDA receptor encephalitis. A review of 577 patients showed that just over half who received first-line immunotherapy and tumor treatment (when

appropriate), showed improvement within the first 4 weeks of treatment, and almost all of these patients had a good outcome at 24-month follow-up (modified Rankin Scale score of 0–2).¹⁴ Patients who did not respond to first-line therapies and then received second-line immunotherapy (rituximab, cyclophosphamide, or both) had better outcomes than those who continued with first-line immunotherapy or who received no further immunotherapy. Thus, identification and treatment of an associated tumor, and prompt initiation of second-line immunosuppression if there is no clear response to first-line treatment, is a reasonable treatment approach.

Antibody Determination and Titers

For some syndromes, such as anti-NMDA receptor encephalitis, the presentation of a patient with the highly characteristic clinical picture is sufficient, after excluding an infectious process, to make an initial diagnosis and initiate treatment. The diagnosis is confirmed by the presence of the antibodies in serum and/or CSF, but until recently there was no formal evaluation of the sensitivity and specificity of serum versus CSF testing or of the use of different antibody measurement techniques (eg, immunohistochemistry in brain tissue, cell-based assay). A recent study comparing testing of matched serum and CSF samples from patients with anti-NMDA receptor encephalitis has addressed these issues and demonstrated several important findings.¹⁹ At initial evaluation, the CSF of 100% of the patients were positive with all testing methods. However, when the matched serum samples were studied, 13% were negative when tested using a cell-based assay and 6% were negative when tested using immunohistochemistry. While practitioners likely have no control over which laboratory or methodology is used for antibody testing, these results demonstrate the importance of including CSF at initial evaluation. The study also showed that the change of titers in CSF associated better with clinical relapses than the titers of serum, also supporting the evaluation of CSF when trying to characterize new-onset symptoms as possible relapses. Additionally, over the course of the disease, levels of antibodies decline, but even after recovery most patients still had antibodies in both serum and CSF. Whether these findings apply to other autoimmune encephalitis is not known. However, it would be prudent for clinicians to be aware of the limitations of testing only serum and to be suspicious when atypical clinical situations arise, such as a patient with a characteristic syndrome but antibodies reported as negative (only serum tested) or serum that is positive but CSF that is negative, in which case retesting with an additional method should be considered, as this likely represents a false positive result.

Overlap and Associations With Other Disorders

Demyelinating Disorders

As the autoimmune encephalitis syndromes are increasingly recognized, particularly anti-NMDA receptor encephalitis due to its frequency, it is not surprising that novel associations with other disorders are beginning to emerge. A recent review of a large cohort of patients with anti-NMDA receptor encephalitis revealed a group of patients with overlapping clinical and/or MRI findings compatible with optic neuritis, myelitis, or prominent brainstem dysfunction.⁴⁹ These patients often had multifocal,

infratentorial, or extensive abnormalities on T2/FLAIR sequences compatible with a demyelinating disorder and often coexisting immune mechanisms such as aquaporin-4 or myelin oligodendrocyte glycoprotein antibodies. For the majority of patients, the demyelinating episodes were more resistant to treatment than was the anti-NMDA receptor encephalitis and often resulted in more residual deficits. In just over half of the patients, anti-NMDA receptor encephalitis was preceded or followed by the demyelinating syndrome, and in the others the disorders were concurrent. In the latter group the diagnosis was usually challenging; they were often suspected to have acute disseminated encephalomyelitis, neuromyelitis optica, or multiple sclerosis, but eventually the presence of prominent psychiatric symptoms, orofacial dyskinesias, and/or autonomic dysfunction suggested the diagnosis of anti-NMDA receptor encephalitis. The recognition that anti-NMDA receptor encephalitis and a demyelinating disorder may occur in the same patient is important because treatment and outcome vary for each disorder.

Herpes Simplex Encephalitis

Relapses after herpes simplex encephalitis (HSE) occur in up to 25% of cases.⁵⁰ Some cases represent viral reactivation, and patients often respond to reinstitution of antiviral therapy. Other patients develop new symptoms, often including choreoathetosis, but viral studies are negative and there is no response to antiviral therapy.⁵¹ There are case reports of patients developing anti-NMDA receptor encephalitis after HSE, and now a recent study has shown a robust link between NMDA receptor antibodies and relapses.^{16,52,53} Examination of serum and CSF from patients with HSE and during relapsing symptoms demonstrated novel NMDA receptor antibody synthesis during the weeks between the HSE and the development of the new symptoms.⁵⁴ These patients improved with immunotherapy including corticosteroids, rituximab, and cyclophosphamide. In other patients, the relapsing symptoms were accompanied by the development of antibodies to other uncharacterized neuronal cell-surface antigens, suggesting that HSE infection is a general trigger for brain autoimmunity. Recognition of anti-NMDA receptor encephalitis after HSE is important to prompt initiation of immunotherapy.

Summary

There are many unanswered questions regarding autoimmune brain disease. In order to develop preventative strategies and optimal treatment approaches, it will be important to elucidate the mechanisms that initiate and maintain the autoimmune responses in PND and synaptic encephalitis. In cancer-associated disorders, the immune response is likely initiated against neuronal antigens expressed by the tumor, but what is the immunological trigger in non-tumor associated autoimmune encephalitis? The occurrence of a viral-like prodrome in many patients suggests that an infectious process may potentially play a role activating the immunological system. A relationship between the development of autoimmunity and a recent viral infection is supported by the finding of anti-NMDA receptor seroconversion after HSE. What is the role of the blood-brain barrier in these disorders? Do systemic antibodies cross into the CNS and by what mechanism? Is the immune response carried out behind the blood-brain barrier, as

suggested by the intrathecal synthesis of antibodies and presence of plasma cell infiltrates in the brain of some patients?^{55,56}

The identification of autoimmune synaptic encephalitis has uncovered the immune pathogenesis of a variety of disorders; many of these disorders were previously known by descriptive terms such as dyskinetic encephalitis lethargica and choreoathetosis post-HSE, and other disorders were diagnosed as “idiopathic” or “viral” encephalopathy, even with negative viral studies.^{57–59} Some patients are comatose for weeks or longer, and their families are left with little reason to hope for improvement or functional recovery. The identification of similar immune mechanisms and continued research in these disorders will lead to improved outcomes and a clearer understanding of how immune mechanisms affect nervous system function.

Funding

This work was supported by Fondo de Investigación Sanitaria, Spain PI11/01780 (J.D.); National Institutes of Health, USA RO1NS077851 and MH094741 (J.D.); and Fundació la Marató TV3 Catalunya #101530 (J.D.).

Conflict of interest statement. Drs Dalmou and Rosenfeld hold patents for the use of Ma2 and NMDA receptor as autoantibody tests and have filed patents for the use of DPPX, GABA_A receptor, and GABA_B receptor as diagnostic tests.

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