ANTIBODY-MEDIATED ENCEPHALITIDES CONSTITUTE A GROUP OF INFLAMMATORY BRAIN DISEASES THAT ARE CHARACTERIZED BY PROMINENT NEUROPSYCHIATRIC SYMPTOMS AND ARE ASSOCIATED WITH ANTIBODIES AGAINST NEURONAL CELL-SURFACE PROTEINS, ION CHANNELS, OR RECEPTORS (TABLE 1). COMMON CLINICAL FEATURES INCLUDE A CHANGE IN BEHAVIOR, PSYCHOSIS, SEIZURES, MEMORY AND COGNITIVE DEFICITS, ABNORMAL MOVEMENTS, DYSAUTONOMIA, AND A DECREASED LEVEL OF CONSCIOUSNESS. THERE ARE, HOWEVER, NO SYSTEMIC MANIFESTATIONS OTHER THAN AUTONOMIC DYSFUNCTION, AND THIS GROUP OF DISEASES IS SEPARABLE FROM TRADITIONAL AUTOIMMUNE DISORDERS SUCH AS SYSTEMIC LUPUS ERYTHEMATOSUS, WHICH MAY AFFECT THE NERVOUS SYSTEM. ALSO SEPARATE FROM THIS GROUP OF ANTIBODY-MEDIATED ENCEPHALITIDES ARE SEVERAL DISORDERS, SOME OF WHICH ARE PARANEOPlastic, SUCH AS CEREBELLAR DEGENERATION, NEUROMYELITIS OPTICA, AND STIFF-PERSON SPECTRUM DISEASES, THAT ARE ASSOCIATED WITH ANTIBODIES AGAINST NEURONAL OR GLIAL CELL-SURFACE ANTIGENS BUT THAT ARE RARELY ASSOCIATED WITH THE AFOREMENTIONED SYMPTOMS.

The antibody-mediated encephalitides occur in persons of all ages, with some types affecting predominantly children and young adults. Certain syndromes are recognizable on clinical grounds, and their autoimmune cause can be established with laboratory tests. Despite the severity of symptoms, prompt diagnosis and treatment lead to improvement or full recovery in most cases. This review focuses on the encephalitides associated with autoantibodies against neuronal cell-surface antigens, for which there is compelling evidence that the antibodies have direct pathogenic effects.

FREQUENCY, IMMUNOLOGIC FEATURES, AND ASSOCIATED DISORDERS

The estimated annual incidence of all types of encephalitis is approximately 5 to 8 cases per 100,000 persons, and in 40 to 50% of the cases, the cause cannot be established. A prospective, multicenter, population-based study suggests that autoimmune disorders are the third most common cause of encephalitis, after infections, usually viral, and acute disseminated encephalomyelitis, which is typically a postinfectious disorder. A study from a center that is specifically concerned with the epidemiology of encephalitis showed that the frequency of the most common form of autoimmune encephalitis, the type with antibodies against the N-methyl-D-aspartate receptor (NMDAR), surpassed the frequency of any individual viral cause of encephalitis in young persons, and in one retrospective study, anti-NMDAR encephalitis accounted for 1% of all admissions of young adults to an intensive care unit. A retrospective Dutch study showed that encephalitis characterized by antibodies against leucine-rich, glioma-inactivated 1 (LGI1) was the second most frequent autoimmune encephalitis, with an incidence of 0.83 cases per 1 million persons.
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* Data are from a review of studies.† ADAM denotes a disintegrin and metalloproteinase; AMPAR α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2 contactin-associated protein–like 2; D2R dopamine 2 receptor; DPPX dipeptidyl-peptidase–like protein 6; GABA γ-aminobutyric acid; GABA<sub>B</sub>R GABA type B receptor; LGI1 leucine-rich, glioma-inactivated 1; mGluR5 metabotropic glutamate receptor 5; NMDAR N-methyl-D-aspartate receptor; and SCLC small-cell lung cancer.

†† The number of patients is the approximate number reported.

‡‡ Data on brain abnormalities are based on T<sub>2</sub>-weighted MRI of the head with fluid-attenuated inversion recovery (FLAIR). Unless otherwise indicated, MRI showed normal features or nonspecific changes.

§§ The association with teratoma is sex- and age-dependent. Young women frequently have an ovarian teratoma, but the presence of a tumor is uncommon in children and young men.

¶¶ Most patients have progressive symptoms over a period of more than 3 months.

‖‖ CASPR2 antibodies are frequently associated with Morvan’s syndrome, a chronic disorder characterized by neuromyotonia, cognitive deterioration, sleep dysfunction (agrypnia excitata), and autonomic features.

** The frequency of an underlying tumor in patients with CASPR2 antibodies varies according to the syndrome; although patients with limbic encephalitis rarely have an underlying tumor (but if they do, the type of tumor may vary from patient to patient), 40% of patients with Morvan’s syndrome have an underlying thymoma.
Beginning in the 1980s, studies of paraneoplastic neurologic syndromes associated with antibodies against intracellular neuronal antigens informed subsequent clinical and laboratory research on the autoimmune encephalitides. The distinction between these two groups of disorders is important because some of the triggers and syndromes are similar but their pathogenic mechanisms and outcomes are different. A comparison of the antibodies associated with these two categories is shown in Figure 1A through 1F. In the autoimmune encephalitides, the antibodies bind to extracellular epitopes of cell-surface proteins and cause reversible neuronal dysfunction. These features may explain the better outcomes for patients with autoimmune encephalitides, as compared with the outcomes for patients with neurologic syndromes related to antibodies against intracellular proteins, in which neuronal loss is frequent and cytotoxic T-cell mechanisms predominate (Fig. 1G through 1I).

Most autoimmune encephalitides occur in patients with no apparent immunologic triggers, leading some investigators to postulate a genetic predisposition to these disorders. Two studies showed an association of anti-LGI1 encephalitis with HLA class II genes, including HLA-DRB1*07 (DR7) and HLA-DRB4 in a Dutch population and DRB1*07:01–DQB1*02:02 in a Korean population. In the same two studies, no specific HLA association was found with anti-NMDAR encephalitis, but another study suggested a genetic predisposition in Maori and Pacific Island populations.

Two potential triggers of autoimmune encephalitides are tumors (Table 1) and viral encephalitis. Some of the implicated tumors contain nerve tissue or the tumor cells express the neuronal proteins targeted by the autoantibodies, suggesting that the ectopic expression of these proteins may play a role in initiating the autoimmune response. Herpes simplex encephalitis, and possibly other viral encephalitides, can trigger antibodies against the NMDAR and other neuronal cell-surface proteins; such antibodies might explain relapsing neurologic symptoms that arise weeks after the onset of herpes simplex encephalitis. This delayed complication affects approximately 20% of patients with herpes simplex encephalitis and is manifested predominantly as choreoathetosis in children and as psychiatric and behavioral alterations in adults. Immunotherapy with glucocorticoids, plasma exchange, intravenous immune globulin, or rituximab is partially effective during relapse and does not appear to confer a predisposition to reactivation of the herpes simplex virus.

**Figure 1 (facing page). Antibody Reactivity and Pathological Features of Encephalitis Associated with Antibodies against Neuronal Cell-Surface Antigens as Compared with Encephalitis Associated with Antibodies against Intracellular Antigens.**

In encephalitis associated with antibodies against cell-surface antigens, the antibodies have access to the epitopes and can potentially alter the structure and function of the cognate antigen (Panel A), whereas in encephalitis associated with antibodies against intracellular antigens, the antibodies cannot reach the intracellular epitopes, and cytotoxic T-cell mechanisms are predominantly involved (Panel B). N-methyl-D-aspartate receptor (NMDAR) antibodies (Panels C and E) are examples of the group of antibodies against cell-surface antigens, and Hu antibodies (Panels D and F) are examples of the group of antibodies against intracellular antigens. In immunofluorescence studies of rodent brain with tissue permeabilized to allow entry of antibodies, NMDAR antibodies are characterized by a pattern of neuropil-like immunolabeling (Panel C, green staining), whereas Hu antibodies have a discrete pattern of cellular immunolabeling (Panel D, green staining). In contrast, with live cultured neurons, NMDAR antibodies have access to the target antigen (Panel E, intensive immunolabeling), whereas Hu antibodies cannot reach the intracellular antigen (Panel F, no immunolabeling). Autopsy studies have shown that patients with anti-NMDAR encephalitis have moderate brain inflammatory infiltrates along with plasma cells (Panel G, cells stained brown with a CD138 antibody), deposits of IgG (Panel H, diffuse brown staining with an antihuman IgG antibody), and microglial proliferation (Panel H inset, microglial cells stained red with a CD68 antibody), without evidence of T-cell–mediated neuronal loss (not shown). In contrast, patients with anti-Hu paraneoplastic encephalitis have extensive neuronal loss and inflammatory infiltrates (not shown); the T cells are in direct contact with neurons (Panel I, arrows; hematoxylin and eosin), probably contributing to neuronal degeneration through perforin and granzyme mechanisms (Panel J, arrow; granzyme B staining). All human tissue sections (Panels G through J) were obtained from the hippocampus.
resonance imaging (MRI) of the head and cerebrospinal fluid (CSF) assessment resemble those in cases due to viral infection. Symptoms progress over a period of days or weeks, with the exception of some patients who have autoimmune encephalitis with antibodies against contactin-associated protein–like 2 (CASPR2), dipeptidyl-peptidase–like protein 6 (DPPX), or LGI1, which may have a more indolent course. Approximately 60% of patients with autoimmune encephalitis have prodromal low-grade fever, malaise, or headache. Some prodromal symp-
toms are characteristic of particular types of autoimmune encephalitides — for example, faciobrachial dystonic seizures and paroxysmal dizzy spells occur with anti-LGI1 encephalitis,22,23 and severe diarrhea and weight loss occur in the prodromal phase of anti-DPPX encephalitis24 (Table 1).

The disorders most frequently recognized on clinical grounds are anti-NMDAR encephalitis and limbic encephalitis. Anti-NMDAR encephalitis affects predominantly children and young adults (median age, 21 years), with a predominance of cases in females (4:1) that becomes less evident after the age of 45 years.25 Up to 58% of affected young female patients have an ovarian teratoma (extragonadal teratomas are a rare cause); in men and children, the association with tumors is less frequent.25 Young children typically present with insomnia, seizures, abnormal movements, or a change in behavior such as irritability, temper tantrums, agitation, and reduction of verbal output. Teenagers and adults more often present with psychiatric symptoms, including agitation, hallucinations, delusions, and catatonia, which may lead to hospital admission for psychosis. The disease progresses in a period of days or weeks to include reduction of speech, memory deficit, orofacial and limb dyskinesias, seizures, decreased level of consciousness, and autonomic instability manifested as excess salivation, hyperthermia, fluctuations of blood pressure, tachycardia, or central hypventilation.26 Bradycardia and cardiac pauses are infrequent but require a temporary pacemaker in some patients. One month after disease onset, regardless of the symptoms at presentation, most children and adults have a syndrome that combines several of the above-mentioned symptoms; in approximately 5% of patients, the disease may remain monosymptomatic (e.g., psychiatric symptoms).25

MRI of the head is abnormal in 30% of affected patients, mainly showing increased fluid-attenuated inversion recovery (FLAIR) signal involving the cortical, subcortical, or cerebellar regions (Fig. 2A).25 The diagnosis of anti-NMDAR encephalitis is confirmed by the detection of CSF antibodies against the GluN1 subunit of the NMDAR; serum testing is less reliable, with false negative results in up to 14% of cases.27 In children who have symptoms suggestive of anti-NMDAR encephalitis but with discordant MRI changes involving the basal ganglia and brain stem, the possibility of encephalitis due to antibodies against the dopamine 2 receptor should be considered (Fig. 2B).28

In contrast to anti-NMDAR encephalitis, limbic encephalitis can result from immune responses against several different neuronal cell-surface proteins (Table 1).19 Patients with limbic encephalitis are usually older than 45 years, with a sex predominance that varies with the type of antibody (Table 1). Symptoms include confusion, behavioral changes, seizures, and inability to form new memories, with relative preservation of the old ones. The MRI scan shows increased FLAIR signal in the medial aspect of the temporal lobes, which in rare cases is enhanced with gadolinium infusion. In some cases, the MRI scan is normal or shows unilateral changes (Fig. 2C). If only one temporal lobe is involved, the differential diagnosis includes cortical edema from ongoing seizures, glioma, and herpes simplex encephalitis.

The likelihood and type of underlying tumor and the response to treatment differ according to the type of limbic encephalitis. LGI1 antibodies account for the majority of cases of limbic encephalitis, and hyponatremia is a feature of 65% of these cases; an underlying tumor is rare.21 Limbic encephalitis associated with antibodies against γ-aminobutyric acid (GABA) type B receptor (GABA_B2) and that associated with antibodies against α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) are the next most frequent types of limbic encephalitis; 50 to 60% of patients with limbic encephalitis due to one of these antibodies have cancer (Table 1).29,30 Limbic encephalitis can also be a manifestation of the aforementioned conventional paraneoplastic syndromes with antibodies against intracellular antigens (e.g., Hu and Ma2)9 or the 65-kDa isoform of glutamic acid decarboxylase (GAD65). These syndromes usually respond less well to immunotherapy than do the autoimmune encephalitides.19

Other autoimmune encephalitides (Table 1) have less distinctive symptoms and MRI findings. Certain clinical features nevertheless suggest a specific type of autoimmune encephalitis, such as refractory status epilepticus with...
Antibody-Mediated Encephalitis

GABA type A receptor (GABA<sub>A</sub>R) antibodies; encephalopathy, insomnia, dysautonomia, ataxia, peripheral-nerve hyperexcitability, and neuropathic pain with CASPR2 antibodies; and myoclonus, tremors, and exaggerated startle responses (hyperekplexia) with DPPX antibodies. In most autoimmune encephalitides, the MRI is normal or shows nonspecific inflammatory changes; two exceptions are limbic encephalitis and encephalitis with antibodies against γ-aminobutyric acid (GABA) type A receptor (GABA<sub>A</sub>R) is usually associated with multiple cortical and subcortical FLAIR signal changes (Panel D). Patients with various acute inflammatory demyelinating diseases may have clinical and MRI findings that are indistinguishable from the findings in patients with autoimmune encephalitis. For example, an MRI scan showing extensive, bilateral FLAIR signal abnormalities was obtained from a patient in whom sudden-onset confusion and encephalopathy developed that were caused by acute disseminated encephalomyelitis associated with antibodies against myelin oligodendrocyte glycoprotein (Panel E). The clinical and radiologic features of autoimmune encephalitides can occasionally be misleading. For example, a young man was admitted for severe encephalitis and refractory seizures that required pharmacologically induced coma. Studies showed a large thymoma, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) antibodies, and MRI findings (Panel F) that suggested widespread cortical damage and a poor prognosis. However, removal of the tumor and immunotherapy resulted in complete clinical recovery.

Figure 2. MRI Findings in Antibody-Mediated Encephalitis.

Shown are representative MRI scans from patients with several types of autoimmune encephalitides. Anti-NMDAR encephalitis is often present despite normal MRI findings or mild signal abnormalities on fluid-attenuated inversion recovery (FLAIR) images (Panel A). Basal ganglia encephalitis associated with dopamine 2 receptor antibodies typically affects the striatum (Panel B). Limbic encephalitis may result from several different immune responses and is typically indicated by FLAIR signal increases in the medial temporal lobes (Panel C). In contrast, encephalitis with antibodies against γ-aminobutyric acid (GABA) type A receptor (GABA<sub>A</sub>R) is usually associated with multiple cortical and subcortical FLAIR signal changes (Panel D). Patients with various acute inflammatory demyelinating diseases may have clinical and MRI findings that are indistinguishable from the findings in patients with autoimmune encephalitis. For example, an MRI scan showing extensive, bilateral FLAIR signal abnormalities was obtained from a patient in whom sudden-onset confusion and encephalopathy developed that were caused by acute disseminated encephalomyelitis associated with antibodies against myelin oligodendrocyte glycoprotein (Panel E). The clinical and radiologic features of autoimmune encephalitides can occasionally be misleading. For example, a young man was admitted for severe encephalitis and refractory seizures that required pharmacologically induced coma. Studies showed a large thymoma, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) antibodies, and MRI findings (Panel F) that suggested widespread cortical damage and a poor prognosis. However, removal of the tumor and immunotherapy resulted in complete clinical recovery.

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The target antigens in autoimmune encephalitides are cell-surface proteins involved in neuronal signaling and synaptic plasticity. The associated syndromes show substantial resemblance to the syndromes observed when the function of the same proteins is altered by genetic modification or pharmacologic antagonists. For example, many clinical features of anti-NMDAR encephalitis resemble those observed with the adminis-
**Antibody-Mediated Encephalitis**

**A. Herpes Simplex Virus**
- Virus
- Damaged neuron
- Antigen

**B. Systemic Tumor**
- Apoptotic tumor cell
- Antigen uptake

**C. Neuronal Dysfunction**
- Transport to regional lymph nodes
- Antigen exposure
- Differentiation
- Maturadon
- Systemic antibodies
- Transport to the brain

**D. GABA_\text{R} Antibodies**
- Functional blocking of target antigen
- GABA
- GABA_\text{R}
- G proteins
- Inactive G proteins
- Effector proteins
- Blocking of receptor signaling

**E. NMDAR Antibodies**
- Glycine
- Glutamate
- NMDAR
- Ca^{2+} and Na^{+}
- Cross-linking and internalization
- Reduced NMDAR density

**F. LGI1 Antibodies**
- Voltage-gated K^+ channel
- ADAM23
- LGI1
- ADAM22
- Disruption of protein–protein interactions
- Decrease in AMPAR

**G. Ventricular infusion of NMDAR antibodies**
- Intensity of human IgG immunostaining
- Density of synaptic NMDAR (no. of synaptic clusters/µm^2 of dendrite)
- Memory (novel-object recognition index)

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tration of noncompetitive NMDAR antagonists (ketamine or phencyclidine). The ways in which the immune response is initiated and the antibodies reach or are produced in the brain are starting to be elucidated. It has been postulated that the autoimmune response is initiated by antigens released by the viral destruction of neurons (e.g., in herpes simplex encephalitis) (Fig. 3A), by tumors (Fig. 3B), or by unknown mechanisms. In the case of anti-NMDAR encephalitis, there is preliminary evidence that memory B cells reach the brain, where they undergo restimulation, antigen-driven affinity maturation, clonal expansion, and differentiation into antibody-producing plasma cells (Fig. 3C). This is supported by brain biopsy and autopsy studies showing plasma cells (Fig. 1G), deposits of IgG (Fig. 1H), and reduced levels of NMDAR and by CSF studies showing an ongoing, antigen-driven, intrathecal immune response characterized by clonally expanded plasma cells producing antibodies against NMDAR. Similar mechanisms may apply to those autoimmune encephalitides that are also characterized by intrathecal synthesis of antibodies, little clinical evidence of blood–brain barrier disruption, and low or undetectable serum antibody levels in patients with severe deficits.

For all autoimmune encephalitides, pathogenic effects of the antibodies have been shown in primary cultures of neurons. These effects include blocking of receptor function (e.g., in the case of GABABR), cross-linking and internalization of receptors (NMDAR), and interference with protein–protein interactions (LGI1) (Table 1 and Fig. 3D, E, and F). Even though some antibodies are of subclass IgG1 or IgG3, there is limited evidence that complement fixation plays a major role in autoimmune encephalitides. In a mouse model involving passive cerebroventricular transfer of the antibody from the CSF of affected patients or of a human recombinant antibody derived from CSF plasma cells, the antibodies disrupted the interaction between NMDAR and the ephrin-B2 receptor, leading to receptor internalization, impairment of long-term synaptic plasticity, memory deficits, anhedonia, and depressive behaviors. These alterations gradually resolved after the antibody infusion was stopped (Fig. 3G). The pathogenicity of NMDAR antibodies from affected patients has been suggested in other experimental models. No animal models are available for other autoimmune encephalitides.

**TREATMENTS AND OUTCOME**

Treatment recommendations are based largely on retrospective series and expert opinion, since few clinical trials have been conducted. The current approach includes immunotherapy and removal of the immunologic trigger, such as teratoma or another tumor, when applicable. Early tumor treatment is particularly important in achieving a good outcome. In most autoimmune encephalitides, antibody production and inflammatory changes occur behind the blood–brain barrier, which probably explains the limited effectiveness of plasma exchange and of intravenous immune globulin, in contrast to the beneficial effects of these interventions in systemic antibody-mediated diseases such as myasthenia gravis. Nevertheless, in practice, most patients are treated with glucocorticoids, intravenous immune globulin, or plasma exchange, and if there is no clinical response, rituximab and cyclophosphamide are used. Rituximab is usually effective in refractory cases, and it appears to reduce the risk of a clinical relapse, which accounts for its increasing use as an initial treatment. Although hyperthermia, muscle rigidity, mutism, and coma may develop in patients with anti-NMDAR encephalitis independent of the use of neuroleptic agents, studies suggest an increased susceptibility to the adverse effects of these drugs (e.g., the neuroleptic malignant syndrome); the mechanisms underlying this complication are unknown.

The speed of recovery, degree of residual deficit, and frequency of relapse vary according to the type of autoimmune encephalitis. In a series of 577 patients with anti-NMDAR encephalitis, 53% had clinical improvement within 4 weeks, and 81% had substantial recovery (i.e., mild or no residual symptoms) at 24 months. Another study showed that patients with anti-LGI1 encephalitis had a more rapid response but that only 70% had substantial recovery at 24...
months. For autoimmune encephalitides that are frequently associated with cancer, such as anti-AMPA and anti-GABA\(_R\) encephalitides, the rate of response to immunotherapy is lower, particularly when additional paraneoplastic mechanisms such as antibodies and cytotoxic T-cell responses against intracellular antigens are identified. For all types of autoimmune encephalitides, prompt immunotherapy has been associated with a favorable outcome; spontaneous clinical improvement is infrequent. The frequency of clinical relapse in the encephalitides associated with antibodies against NMDAR, AMPAR, LGI1, CASPR2, or DPPX ranges from 12 to 35%. Relapses often occur when immunotherapy is reduced or discontinued. There is anecdotal evidence that cases of anti-LGI1 or anti-NMDAR encephalitis can relapse many years after the first episode. Relapses may herald recurrence of the associated tumor or a tumor that was missed in the initial episode. Immuno-therapy and treatment of the tumor, if it was missed initially, usually result in improvement.

**FUTURE STUDIES**

The discovery of the category of autoimmune encephalitides has changed the diagnostic and treatment approach to many neurologic or psychiatric syndromes that were previously considered to be idiopathic. The rapid increase in the number of syndromes and autoantibodies identified over the past 10 years suggests that other autoimmune encephalitides have yet to be discovered. Antibody titers correlate imperfectly with the course of the disease and may remain detectable (albeit at a low titer) after clinical recovery, indicating the need to identify biomarkers for prognosis and treatment decisions. The usefulness of neuropsychological testing, electroencephalography, advanced neuroimaging, and \(^{18}\)F-fluorodeoxyglucose–positron-emission tomography in the diagnosis of autoimmune encephalitides, assessment of treatment efficacy, and prognosis requires investigation. Preliminary data suggest that the protracted clinical course of anti-NMDAR encephalitis is due to antibody production by long-lived plasma cells in the brain, along with the antibody effects on brain circuitry. Further studies are needed to confirm these hypotheses and determine whether they apply to other autoimmune encephalitides. Studies of how autoantibodies alter the structure and function of synaptic proteins and cause symptoms are critical for an understanding of the underlying pathogenic mechanisms, which in turn could lead to the development of new treatment strategies. For example, the observation that NMDAR antibodies alter the interaction between NMDAR and the ephrin-B2 receptor and that a soluble agonist of the ephrin-B2 receptor antagonizes the antibody effects suggests a potential treatment strategy. Finally, knowing how antibodies cause symptoms, such as the psychosis caused by anti-NMDAR antibodies, may help to understand psychiatric diseases in which the same receptors may be altered by other mechanisms.

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