Autoimmune Epilepsy

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Abstract

Seizures are recognized as a common manifestation of autoimmune limbic encephalitis and multifocal paraneoplastic disorders, but accumulating evidence supports an autoimmune basis for seizures in the absence of syndromic manifestations of encephalitis. Autoimmune encephalitis and epilepsy have been linked to neural-specific autoantibodies targeting both intracellular and plasma membrane antigens. The detection of these antibodies can serve as a diagnostic marker directing physicians toward specific cancers and can assist in therapeutic decision-making, but are not necessary to establish the diagnosis. Response to an immunotherapy trial can support the diagnosis and help establish prognosis. Early recognition is important because expedited diagnosis can facilitate recovery. In this review, the authors summarize the clinical presentation, pathophysiology, and management of autoimmune epilepsies for which neural antigen-specific autoantibodies serve as diagnostic aids.

Keywords
- epilepsy
- autoimmune
- antibodies
- inflammation

Autoimmune Neurology

The study of autoimmune neurologic diseases is an emerging and rapidly evolving subspecialty that encompasses the diagnosis and treatment of neurologic disorders with an autoimmune basis. The last decade has seen a dramatic increase in the discovery of neural and glial-specific antibodies and their target antigens.[1–3] The molecular identification of these antigenic targets provides insights into the pathogenic mechanisms underlying many autoimmune neurologic disorders, including epilepsy.

Historically, the first autoantibodies were detected by binding to brain tissue sections and targeted intracellular antigens (nuclear and cytoplasmic enzymes, transcription factors, and RNA binding proteins).[4,5] These antibodies were frequently associated with underlying neoplasms and were termed paraneoplastic. The identification of paraneoplastic or onconeural autoantibodies can help direct the search for cancer and provides prognostic information. However, paraneoplastic disorders tend to be poorly responsive to immunosuppression. Antigenic proteins inside intact cells are inaccessible to circulating antibodies; thus, these antibodies are not generally considered pathogenic. Rather, it is thought that CD8+ T cell-mediated inflammatory responses are the primary mechanism of neuronal destruction in these disorders (►**Fig. 1**).[6,7]

Not all autoantibodies targeting intracellular antigens have a strong association with malignancy; however some like glutamic acid decarboxylase (GAD65) antibodies, can respond to immunotherapy.[8,9] We explore the reasons for this further in later sections.

Autoantibodies can also target plasma membrane proteins (neurotransmitter receptors, ion channels, water channels, and channel-complex proteins). By contrast, these antibodies are probably pathogenic, as they can access their target proteins in vivo and potentially alter their number or function (►**Fig. 1**). Neurologic diseases associated with plasma membrane autoantibodies tend to be immunoresponsive and are less frequently associated with malignancies.[1,3]

Autoimmunity and Epilepsy

Patients presenting with new-onset epilepsy pose a diagnostic and therapeutic challenge. Despite exhaustive

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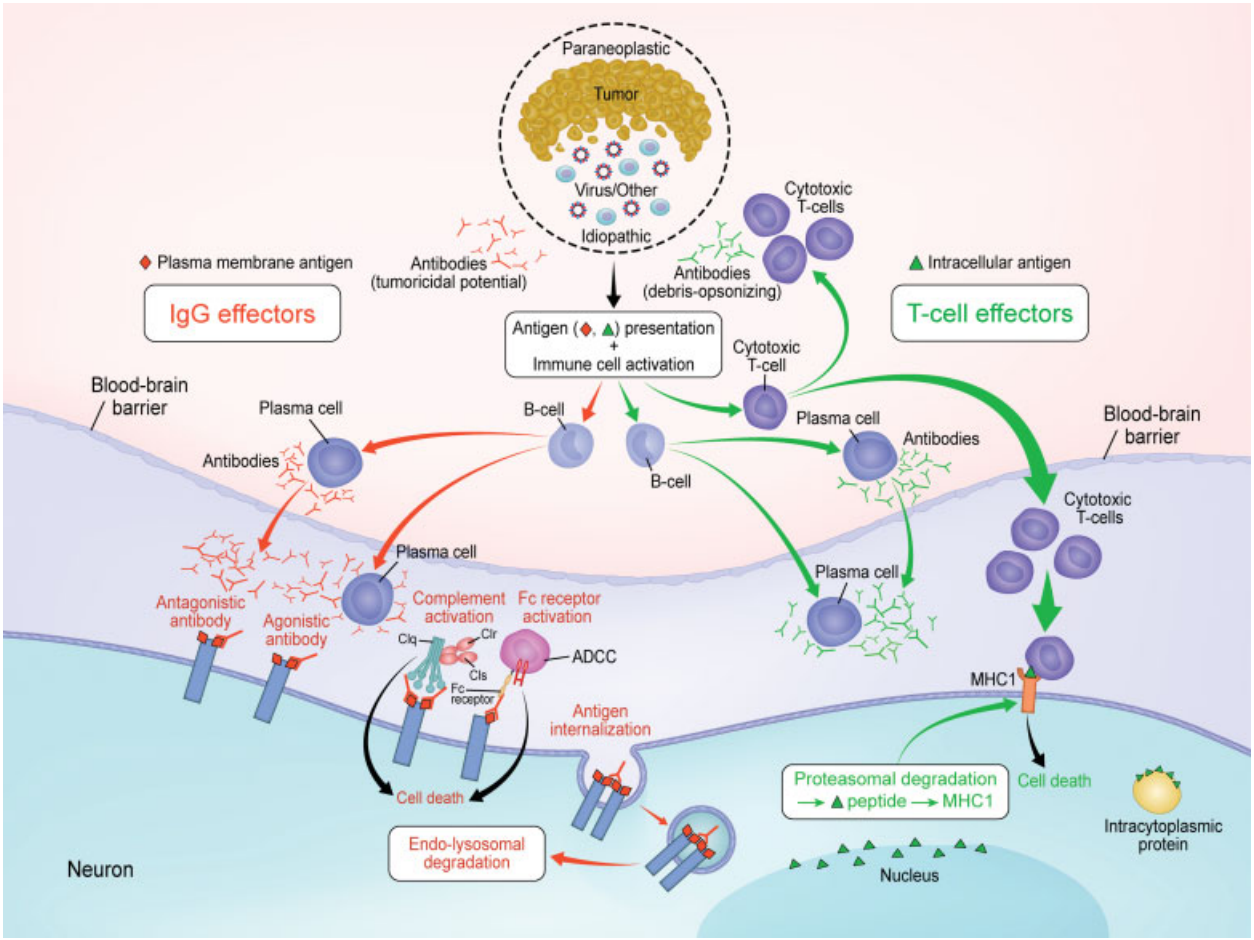

Fig. 1 Immunopathogenic mechanisms of paraneoplastic and nonparaneoplastic (idiopathic) neural autoantibodies. In cases of paraneoplastic autoimmunity, tumor-targeted immune responses are initiated by onconeural proteins expressed in the plasma membrane (*red diamond*) or in the cytoplasm, nucleus or nucleolus (*green triangle*) of certain tumors. These antigens are also expressed in neural cells and thus are coincidental targets. Although there is evidence to support an analogous infectious-induced mimicry in nonparaneoplastic autoimmunity (e.g., NMDAR encephalitis after HSV encephalitis),[108] the source of the antigen remains elusive in most cases. Antibodies targeting plasma membrane antigens are effectors of injury (*red*): antibodies (*red*) directed at neural cell plasma membrane antigens (e.g., voltage-gated potassium channels complex, NMDA, AMPA, GABA-B receptor) are effectors of cellular dysfunction or injury through multiple effector mechanisms. These mechanisms include receptor agonist or antagonist effects, activation of the complement cascades, activation of Fc receptors leading to antibody-dependent cell-mediated cytotoxicity (ADCC), and antigen internalization (antigenic modulation), thereby altering antigen density on the cell surface. Antibodies targeting nuclear or cytoplasmic antigens are serum markers of a T-cell effector mediated injury (*green*): Intracellular antigens (*green triangles*) are not accessible to immune attack in situ, but peptides derived from intracellular proteins are displayed on upregulated MHC class-I molecules in a proinflammatory cytokine milieu after proteasomal degradation, and are then accessible to peptide-specific cytotoxic T cells. Antibodies (*green*, e.g., ANNA-1, CRMP-5) targeting these intracellular antigens (*green*) are detected in both serum and cerebrospinal fluid, but are not pathogenic. In clinical practice, these antibodies serve as diagnostic markers of a T cell predominant effector process. Modified with permission (Nature Publishing Group) from ►**Fig. 1** (antibodies can have a range of effector functions) from Diamond et al. Losing your nerves? Maybe it's the antibodies. Nature Reviews Immunology 2009;9:449–456.

investigations, no underlying cause is found in ~40% of adult-onset epilepsies, and one-third of cases are intractable to antiepileptic drug therapy.[10] A link between immunity and inflammatory processes in epilepsy has long been recognized. Evidence for this link was first suggested by the anticonvulsant activity of adrenocorticotropic hormone (ACTH) and corticosteroids in some of the childhood epilepsies,[11–13] as well as the presence of chronic inflammation and partial response to immunotherapy in patients with Rasmussen encephalitis.[14,15] The demonstration of proinflammatory molecules (such as interleukin- (IL-) 1β) in the serum of patients with febrile seizures,[16] and the increased frequency of seizures in patients with systemic autoimmune disorders such a systemic lupus erythematosus has provided further evidence for this link.[17] Inflammation also appears to be a central mechanism of seizure generation in some experimental models of epilepsy, although the extent to which this applies in human epilepsies remains to be elucidated.[18,19]

Perhaps one of the most promising developments in this field has come from the discovery of multiple neural-specific autoantibodies occurring in patients with seizures and status epilepticus intractable to antiepileptic drug therapy. As with other autoimmune disorders affecting the nervous system, the first such antibodies discovered targeted intracellular

proteins (►**Table 1**).[20] In recent years, antibodies targeting plasma membrane proteins have been identified that have broadened the phenotypic spectrum of autoimmune epilepsies (►**Table 2**).[21–26] Unlike patients with antibodies to intracellular targets, these patients respond remarkably well to immunotherapy. Many neurologists still suspect a paraneoplastic or autoimmune etiology for seizures only in the presence of syndromic features of limbic or extralimbic encephalitis. This is unfortunate, as a growing body of evidence supports an autoimmune basis for seizures in the absence these syndromic manifestations for a subset of patients with drug-resistant epilepsy.[21,22,27–31]

Clinical clues that help identify these patients include subacute onset (evolving over days to weeks), an unusually high seizure frequency, intraindividual seizure variability or multifocality, antiepileptic drug resistance, personal or family history of autoimmunity, or history of recent or past neoplasia.[28,30,32,33] Rapidly evolving cognitive impairment, neuropsychiatric symptoms, evidence of multilevel involvement of the central nervous system (CNS), or new-onset movement disorder, suggest, but are not necessary, for the diagnosis. The detection of neural-specific autoantibodies in serum or cerebrospinal fluid (CSF) can help to establish the diagnosis and guide management. Other helpful paraclinical aids include the presence of inflammation on magnetic resonance imaging (MRI) or fluorodeoxyglucose positron-emission tomography (FDG-PET), as well as evidence of neuroinflammation in the CSF.

In this article, we summarize the clinical presentation, pathophysiology, and management of autoimmune epilepsies for which neural antigen-specific autoantibodies serve as diagnostic aids. Epilepsies where inflammation occurs, but the full pathogenic cascade or role of antibodies is either not clear (e.g., Rasmussen encephalitis) or only hypothesized fever-induced refractory epilepsy in school-age children (FIRES), are not discussed.

Clinical Characteristics and Pathophysiological Mechanisms of Neural-Specific Autoimmune Epilepsy

Autoantibodies Specific for Intracellular Antigens

ANNA-1 (Anti-Hu)

Antineuronal nuclear antibody type 1 (ANNA-1, also known as anti-Hu) binds to the Hu family of RNA binding proteins, which participate in posttranscriptional regulation of RNA in postmitotic neurons.[34–36] ANNA-1 is highly associated with small-cell carcinoma, but can also occur with thymoma and neuroblastoma.[33] Neurologic manifestations include, in decreasing order of frequency: peripheral neuropathy, limbic encephalitis, encephalomyelitis, and gastrointestinal dysmotility.[33,34] Seizures, epilepsia partialis continua, and status epilepticus may occur in the absence of other syndromic manifestations of limbic encephalitis.[37,38]

Seizures are probably caused by cytotoxic T-cell-mediated damage to both mesial temporal and extralimbic structures. Autopsy studies of ANNA-1 seropositive patients with paraneoplastic encephalomyelitis showed inflammatory infiltrates, gliosis, microglial nodules, and neuronophagia.[39,40] Although perivascular infiltrates contained both B and T cells, it was T cells that predominated in parenchymal infiltrates[39]: CD4+ T cells predominated in the perivascular regions, whereas CD8+ T cells were pervasive in the interstitial spaces. Consistent with these observations of a cytotoxic T-cell-

Table 1 Neuronal nuclear cytoplasmic antibodies

Antibody	Oncological association	Frequency of tumor	Response to immunotherapy	Clinical relevance	Neurologic manifestations
ANNA-1 (anti-Hu)	Small-cell carcinoma	> 90%	Poor	High	Limbic/cortical encephalitis autonomic neuropathies, sensory neuronopathy, other peripheral neuropathies
Ma1, Ma2	Testicular (Ma2); breast, colon, testicular (Ma1)	> 90%	Moderate	High	Limbic encephalitis, encephalomyelitis brainstem encephalitis, peripheral neuropathy
CRMP-5	Small-cell carcinoma, thymoma	> 90%	Poor		Encephalitis, optic neuritis and retinitis, myelopathy, neuropathy, Lambert–Eaton myasthenic syndrome
Amphiphysin	Small-cell carcinoma, breast adenocarcinoma	> 90%	Poor	High	Limbic encephalitis myelopathy, stiff-person syndrome, cerebellar degeneration
GAD65	Thymoma; renal cell, breast or colon adenocarcinoma	< 5%	Moderate	High	Limbic/cortical encephalitis, stiff-person syndrome, stiff-person phenomena, brainstem encephalitis, cerebellar degeneration

Abbreviations: ANNA-1, Antineuronal nuclear antibody type 1; CRMP-5, collapsin response mediator protein-5; GAD65, glutamic acid decarboxylase 65.

Table 2 Antibodies target neural plasma membrane ion channels, receptors, and synaptic proteins

Antibody	Oncological association	Frequency of tumor	Response to immunotherapy	Clinical relevance	Neurologic manifestations
VGKC complex **LGI1+** **Caspr2+** LGI1-;Caspr2-	Small-cell lung carcinoma, thymoma or adenocarcinoma of breast or prostate	< 20%	 Good Good Moderate	 High High Uncertain	Limbic encephalitis, dementia, hyponatremia, faciobrachial dystonic seizures, peripheral nerve hyperexcitability, or both (Morvan syndrome)
NMDAR	Ovarian Teratomas, Testicular germinoma, neuroblastoma	Varies with age, gender, and ethnicity	Good	High	Psychiatric disturbances, dyskinesias, catatonia, central hypoventilation and autonomic instability, opsoclonus–myoclonus
AMPAR	Thymic tumors, lung carcinoma, breast adenocarcinoma	70%	Good	High	Limbic encephalitis, nystagmus
GABA-B receptor	Small-cell lung carcinoma, other neuroendocrine neoplasia	70%	Good	High	Limbic encephalitis, orolingual dyskinesias
mGluR5 receptor	Hodgkin lymphoma	> 90%	Good	High	Cerebellar ataxia and limbic encephalitis (Ophelia syndrome)
DPPX	None described to date		Moderate	Uncertain	Encephalitis, sleep disturbances, myoclonus, hyperekplexia, dysautonomia, gastrointestinal dysmotility
P/Q- and N-type VGCC	Small-cell carcinoma, breast	~ 50%	Moderate	Uncertain	Encephalopathy, myelopathy, neuropathy, Lambert–Eaton myasthenic syndrome
gAChR	Adenocarcinoma, thymoma, small-cell carcinoma		Moderate	Uncertain	Dysautonomia, peripheral neuropathy

Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Caspr2, contactin-associated protein-like 2; DPPX, dipeptidyl-peptidase-like protein-6; GABA-B, γ-aminobutyric acid-B; gAChR, neuronal ganglionic nicotinic acetylcholine receptor; LGI1, leucine rich glioma inactivated protein I; mGluR5, metabotropic glutamate receptor 5; NMDAR, N-methyl-D-aspartate receptor; VGCC, voltage gated calcium channel; VGKC, voltage gated potassium channel.

mediated process, T cells expressing TIA-1 (a component of cytotoxic granules) were observed in clusters around neurons, whereas C9neo, a marker of antibody-mediated complement activation, was absent.[41]

Ma-1 and Ma-2 (Ta)

Ma-1 and Ma-2 (Ta) are neuronal nuclear proteins thought to play a role in RNA transcription and regulation of apoptosis.[42,43] Dual Ma-1/Ma-2 positivity (also known as anti-Ma) is more common in females and is associated with breast, ovarian, and colon cancer. Ma-2 positivity (also known as anti-Ta) is associated with testicular germ-line cancers in males. Autoantibodies binding to these antigens are associated with limbic or brainstem encephalitides. Neurologic manifestations are likely cytotoxic T-cell mediated.[42]

CRMP-5/CV2-IgG

Collapsin response mediator protein-5 antibodies bind to a protein of the same name involved in axonal development in the early nervous system.[44,45] The most common associated malignancies are small-cell-lung carcinoma and thymoma.[46] Common manifestations include cerebellar degeneration, chorea as a "basal ganglionitis," optic neuropathy, retinopathy, myelopathy, radiculoneuropathy, and autonomic dysfunction. It can also present with limbic encephalitis and seizures. Autopsy findings have been reported in one CRMP-5 IgG seropositive patient with optic neuritis, retinitis, and encephalomyelopathy, and this demonstrated CD8+ T cell predominance.[47]

Amphiphysin

Amphiphysin antibodies target a synaptic vesicle-bound protein that works with dynamin to retrieve membrane constituents after neurotransmitter exocytosis.[48] The most commonly associated malignancies are breast and small-cell-lung carcinoma.[49] Initially described in paraneoplastic stiff-person-like syndrome, its spectrum is now appreciated to be much wider, including limbic and diffuse encephalitis.[50]

Neuropathological autopsy specimens of patients with amphiphysin-seropositive patients demonstrate CD8+ T cell predominance.[50,51] Contrary to this hypothesis, one group reported electrophysiology in an animal model of amphiphysin autoimmunity, as well as in vitro findings in mouse neuronal cell culture that they interpreted as evidence of a direct functional effect of amphiphysin antibody.[52] The authors reported that purified amphiphysin IgG induced a stiff-person-like disorder in rats when injected intrathecally. They also reported internalization of fluorescent nanocrystal-tagged amphiphysin antibody into mouse hippocampal neurons.[52] The mechanism by which IgG is purported to be endocytosed and then become pathogenic has not been demonstrated.

GAD65

GAD65 is the synaptic vesicle-associated antigen that catalyzes synthesis of γ-aminobutyric acid (GABA) from L-glutamate. The 65 kDa isoform of GAD has been identified as an autoreactive T-cell target in autoimmune diabetes mellitus type 1.[53] GAD65 is also often detected in patients with autoimmune neurologic disease, but usually on an order of magnitude higher than in those with type 1 diabetes mellitus.[54,55] When occurring on its own it is rarely paraneoplastic; however, it can frequently present in association with other onconeural antibodies, which should raise suspicion for an underlying malignancy. Neurologically, it is associated with stiff-person syndrome,[54,56] cerebellar ataxia, encephalomyelitis, and extrapyramidal disorders,[57] but can also present with epilepsy.[27]

Because GAD65 is an intraneuronal antigen, GAD65 autoantibodies are unlikely to be directly pathogenic, but may be associated with T-cell-mediated autoimmunity. Findings in neuropathological studies of three patients with GAD65 antibody seropositive encephalitis demonstrated multiple apposition of GrB+ cytotoxic T cells to neurons and a higher CD8/CD3 ratio than patients with antibodies to plasma membrane antigens.[58] There was no evidence of IgG or complement deposition.[58] Contrary to this, 30 to 50% of patients with GAD65-associated autoimmunity respond favorably to immunosuppression, including intravenous immunoglobulins,[30,59,60] suggesting similarities with disease associated with plasma membrane targets. A likely explanation for this could be the coexistence of pathogenic autoantibodies targeting as of yet unrecognized plasma membrane antigens, such as the glycine receptor autoantibody recently demonstrated to coexist with GAD65 antibody in some patients with stiff-person syndrome,[9] or the detection of GABA-B receptor antibodies in patients with GAD65-associated encephalitis.[61]

Autoantibodies Specific for Plasma Membrane Antigens

Voltage-Gated Potassium Channel Complex Antibodies

The voltage-gated potassium channels (VGKCs) modulate neuronal excitability, axonal conduction, and neurotransmitter release in the central, peripheral, and autonomic system.[62] Only the Shaker Kv1 VGKCs sensitive to α-dendrotoxin (Kv 1.1, Kv 1.2, and Kv 1.6) appear pertinent to neurologic autoimmunity.[63] Voltage-gated potassium channels form macromolecular complexes interacting with cell-adhesion molecules and scaffolding proteins, including metalloproteinase-22 (ADAM22), and a soluble binding partner of ADAM22-leucine-rich glioma-inactivated (LGI1) protein, contactin-associated protein-2 (Caspr2), membrane-associated guanylate kinases, and disintegrin.[64,65] Recent evidence suggests that some of the serum autoantibodies that bind macromolecular complexes containing VGKCs, measured by radioimmunoprecipitation from solubilized mammalian brain membranes, are actually directed at the extracellular domains of these associated proteins.[66,67]

LGI1 and Caspr2 are the two antigenic targets in the potassium channel complex that have been well characterized, but up to 54% of patients positive for potassium channel complex antibodies have no positivity for either of these, suggesting that there is at least one further target yet to be identified.[68] Although LGI1 antibodies are more frequently associated with limbic encephalitis, and Caspr2 antibodies

with peripheral nervous system manifestations, both antibodies can affect all levels of the nervous system.[68]

Neurologic manifestations of VGKC autoimmunity include limbic encephalitis, as well as peripheral nervous system hyperexcitability disorders.[69–71] More recently, a wider spectrum has been appreciated including reversible dementia-like syndromes,[72–74] autonomic and peripheral neuropathy, pain syndromes,[75] and autoimmune epilepsy.[28,70,76] Seizures tend to be focal at onset, with mesial temporal or hippocampal onset more common than extratemporal.[28,30,66] A new seizure type termed "faciobrachial dystonic seizure" has been described in VGKC-complex antibody encephalitis, and, if present, it is virtually pathognomonic.[77] The incidence of cancer detection in patients with VGKC complex antibodies is relatively low ($< 20\%$), and the types of cancer diverse (small cell carcinoma, thyroid carcinoma, thymoma, neuroblastoma, and adenocarcinoma).[70]

The pathophysiological mechanisms by which VGKC antibodies cause seizures remain ill-defined. Presumably, these are partly due to alterations in the function of the VGKC caused by antibody-mediated disruption of specific associated proteins such as LGI1. Linkage analysis studies revealed that mutations of LGI1 are associated with autosomal dominant lateral temporal epilepsy (ADLTE), an inherited epileptic syndrome characterized by focal seizures with predominant auditory symptoms originating from the temporal lobe cortex.[78,79] Knockout models of LGI1, ADAM22, or Kv1 result in severe epileptic phenotypes suggesting a functional association between these proteins.[80–82] Similarly, mutations of CNTNAP2, the gene that codes for Caspr2, have been linked to psychosis, autism, mental retardation, and intractable focal seizures.[83,84] In a recent study, investigators incubated rat hippocampi with IgG from a patient with LGI1 positive limbic encephalitis and showed increased afterdischarges upon extracellular stimulation in the stratum lucidum of the CA3 subregion compared with control IgG.[85] At the single cell level, IgG from the test subject was associated with CA3 pyramidal cell excitability and dyssynchronization of excitatory stimulus coming from mossy fibers unto these cells.[85] These effects could be reproduced when utilizing the VGKC antagonist α-dendrotoxin, leading the authors to hypothesize that the effects observed were secondary to reduction in VGKC function.[85]

Another possible mechanism of seizure generation may relate to tissue injury secondary to inflammation. Neuropathologic evaluation of brain specimens of patients with VGKC autoantibodies reveals perivascular and parenchymal lymphocytes, astrogliosis, and diffuse microglial activation in biopsied or resected mesial temporal regions.[71,86,87] One detailed report of a postmortem specimen showed focal inflammation of both hippocampi and amygdalae with loss of pyramidal neurons in the CA4 region.[88] Consistent with an antibody- and complement-mediated process, a more recent study of both postmortem and biopsy specimens noted C9neo deposition in the cytoplasm and surface of hippocampal CA4 neurons, as well as in dentate gyrus and cortical neurons.[58] These areas of complement deposition co-localized with regions of acute neuronal death.[58] The above findings correlate well with changes observed in imaging. Up to 50% of patients with VGKC-associated encephalitis have MRI evidence of inflammation and apoptosis manifested as enlargement, T2 hyperintensity, enhancement, and restricted diffusion of the mesial temporal lobe structures in the acute phase.[89] Serial MR imaging frequently shows mesial temporal sclerosis, even in successfully treated patients (►**Fig. 2**).[89] Neuronal cell loss in mesial temporal structures may account in part for the seizures in this patient population and may explain why some patients need to remain on antiepileptic drug therapy in spite of response to immunotherapy.

Ionotropic Glutamate Receptor Antibodies

N-Methyl-D-aspartate receptors (NMDARs) are glutamate-gated cation channels involved in hippocampal synaptic transmission, neuronal plasticity, and long-term potentiation.[90,91] The receptors are heterotetrameric complexes formed by subunits derived from three related families: NR1, NR2, and NR3. NMDAR-specific antibodies target the NR1/NR2 subunits.[92]

NMDAR encephalitis was first described in young women with ovarian teratomas,[93] but the disease is now known to affect men, infants, and patients without tumors as well.[23,94] About one-third of women over 18 years with this disorder have a teratoma, but the likelihood of finding a tumor varies according to age, sex, and ethnicity.[23] Approximately 5% of men have testicular germ-cell tumors, and ovarian teratomas are more frequent in African Americans.[23] The classic presentation is characterized by a viral-like prodrome followed by psychiatric disturbances with associated oro-lingual-facial dyskinesias and seizures. If untreated, central hypoventilation, autonomic dysfunction, and even coma can follow, requiring intensive care in most cases.[23] Seizures can occur early and then disappear later in the course of the disease either due to rapid response to immunotherapy or due to progression to a more severe stage. Unlike in patients with VGKC-associated epilepsy, there is no predilection for mesial temporal structures, and seizures can arise temporally, extratemporally, or multifocally.[95] In a recent case series of continuous electroencephalogram (EEG) recording of 23 patients with NMDAR encephalitis, 60% had electrographic seizures without clinical correlate, and 30% had a unique electrographic pattern that the investigators named "extreme delta brush" because of similarities to waveforms seen in premature infants.[96] The specificity of this pattern is not yet determined, but its presence should raise suspicion for NMDAR encephalitis.

Data from in vitro experiments are consistent with the hypothesis that NMDAR encephalitis is antibody-mediated. Rat hippocampal neurons treated with patient CSF or NMDAR IgG cause cross-linking and internalization of the target receptors, accompanied by reduced synaptic NMDAR-mediated currents.[97] Antibody-depleting therapies and tumor removal optimize recovery, which can be complete in up to 75% of patients. Cases in whom there is no underlying tumor identified have a worse prognosis and a higher rate of relapse.

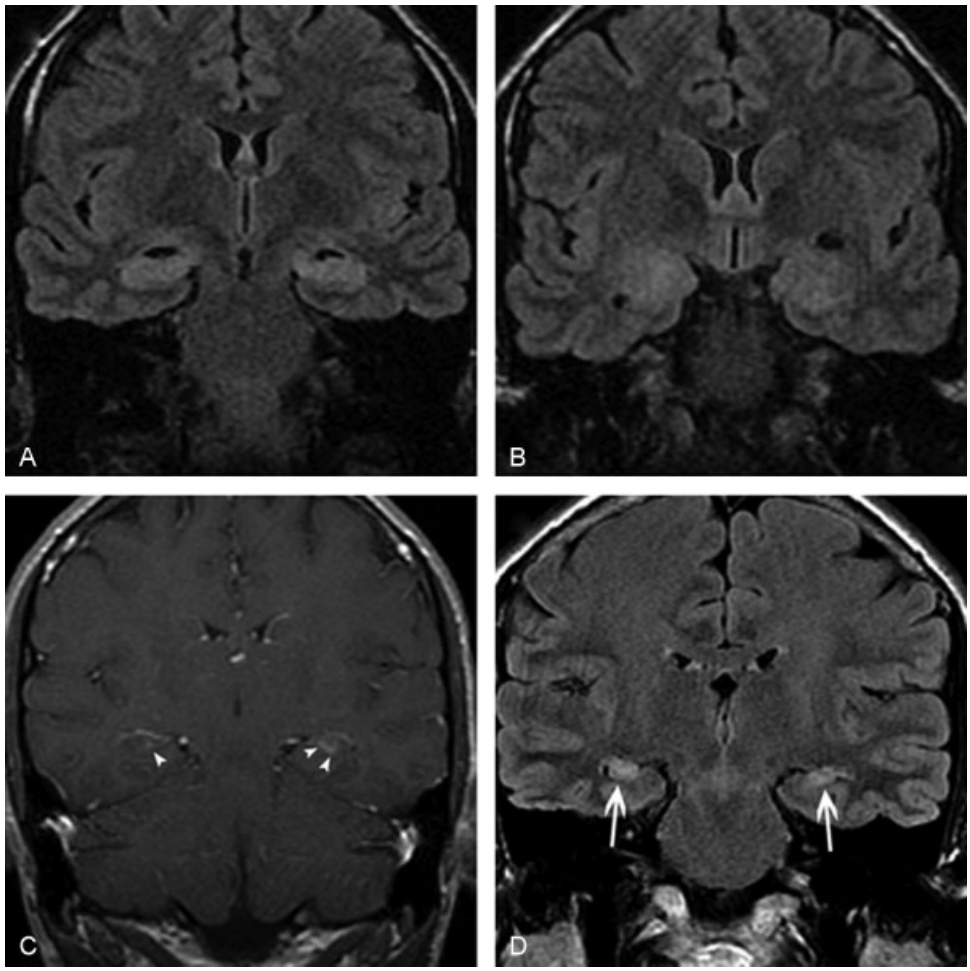

Fig. 2 A 25-year-old man with autoimmune voltage-gated potassium channels epilepsy. Imaging at presentation shows enlargement and increased signal intensity in the bilateral hippocampi (**A**) and bilateral amygdalae (**B**) on coronal fluid-attenuated inversion-recovery (FLAIR), with faint ill-defined enhancement (*arrowheads*) of the hippocampi (**C**) on coronal contrast-enhanced T1. Follow-up coronal FLAIR imaging (**D**) at 4 years shows progression to bilateral mesial temporal sclerosis (*arrows*). From Kotsenas AL, Watson RE, Pittock SJ, et al. MRI findings in autoimmune voltage-gated potassium channel complex encephalitis with seizures: one potential etiology for mesial temporal sclerosis. AJNR Am J Neuroradiol 2014;35(1):84–89.[89] Copyrighted and used with permission from the American Society of Neuroradiology.

AMPA Receptors Antibodies

The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors mediate most fast excitatory neurotransmission in the brain. Antibodies directed at one or both of the GluR1 and GluR2 subunits of the AMPA receptors have been associated with limbic encephalitis.[24] In the initial case report only 4 of 10 patients had seizures, and 8 had MRI findings of temporal lobe inflammation. Seven out of 10 patients had cancers subsequently identified (small-cell and non-small-cell lung cancer, thymoma, and breast cancer).[24]

Similarly to NMDR antibodies, AMPA receptors are internalized following AMPA receptor antibody binding. Patients tend to respond to immunotherapy and tumor removal when applicable, but relapses appear to be common and patients may require long-term immunosuppression.[24]

GABA-B Receptor Antibodies

The metabotropic gamma-amino butyric Acid (GABA-B) receptors are G-protein coupled receptors that are functionally linked to potassium channels and elicit both presynaptic and slow postsynaptic inhibition. They are heterodimers of a GABA-B1 subunit (ligand binding) and a GABA-B2 subunit (responsible for signaling and membrane targeting). GABA-B receptors antibodies have been recently recognized as a cause of epilepsy associated with limbic encephalitis. In the initial case series, all 15 patients had seizures with 13 of them complaining of seizures as their presenting symptom.[25] Furthermore, three patients developed status epilepticus. The vast majority of seizures in these patients were determined to be of temporal lobe onset, and most had MRI evidence of inflammation in the temporal lobes.[25]

GABA-B antibodies have been associated with small-cell lung and breast cancer. They also frequently coexist with GAD-65 antibodies and voltage-gated calcium channel antibodies.[3] GABA-B antibodies are thought to impair receptor function, but unlike NMDAR antibodies they do not cause receptor internalization. Patients respond to immunosuppression and tumor removal, if applicable; relapses are rare.

mGluR5 Antibodies

Metabotropic glutamate receptors (mGluR) are G-protein receptors that modulate neuronal activity by activating intracellular signaling pathways. Eight different receptor types are divided into three groups on the basis of structure and function: I (mGluR1 and mGluR5), II (mGluR2 and mGluR3), and III (mGluR4, mGluR6, mGluR7, and mGluR8). Only mGluR1 and mGluR5 have been documented to be pertinent autoantigens. mGluR5 is particularly prevalent in the hippocampus; autoantibodies to this receptor have been identified in two patients with Hodgkin lymphoma and limbic encephalitis (Ophelia syndrome).[26]

Other Antibodies

Both neuronal ganglionic nicotinic acetylcholine receptor (gAChR) and voltage-gated calcium channel N-type and P/Q-type (VGCC N/VGCC P/Q) antibodies have been described in patients suspected of having autoimmune epilepsy in a nonparaneoplastic context.[30] Up to 30% of patients with gAChR have cancer, usually adenocarcinoma, although some have small-cell lung cancer and thymoma.[98] Clinical presentations most commonly include dysautonomia and peripheral neuropathy, although occasionally encephalopathy.[98] P/Q-type VGCCs are detected in 85% of cases of Lambert–Eaton myasthenic syndrome, and 50% of these cases are associated with small-cell lung cancer.[99] Both paraneoplastic and nonparaneoplastic encephalomyelopathy and cerebellar ataxia have been described with coexisting N-and PQ-type VGCCs.[99] The pathogenic role of these antibodies in autoimmune epilepsy remains uncertain, and may be secondary to coexisting autoantibodies such a GABA-B, which is known to co-occur with VGCC antibodies.[25]

Recently, seizures have been described in patients harboring antibodies targeting dipeptidyl-peptidase-like protein-6 (DPPX).[100,101] DPPX is a regulatory subunit of the voltage-gated A-type (rapidly inactivating) Kv4.2, and is the principal channel responsible for transient, inhibitory currents in the central and peripheral nervous systems. These currents regulate repetitive firing rates and back-propagation of action potentials into neuronal dendrites.[102,103] There is a broad clinical presentation including encephalopathy, symptoms of central hyperexcitability, myelopathy, dysautonomia, and seizures.[100,101]

Algorithmic Approach to Diagnosis and Treatment

Diagnosis

Early recognition of autoimmune epilepsy is paramount as prompt initiation of treatment is associated with better outcomes,[28,30,104] but establishing the diagnosis can be challenging. Although suggestive, syndromic manifestations of limbic or extralimbic encephalitis are not always present, and new-onset epilepsy may be the sole presenting manifestation. Moreover, the presence of a neural autoantibody does not always suffice to establish the diagnosis or determine prognosis. Several studies have confirmed the presence of VGKC-complex antibodies (usually low titers and without LGI1 or CASPR2 reactivity), and GAD65 antibodies in around 10% of adults with longstanding epilepsies.[21,27,105] The pathogenic role of the antibodies in these cases remains unclear. Also, the presence of GAD65 antibodies, even in cases of classic limbic encephalitis, does not always predict response to immunotherapy.[30] Conversely, failure to detect an autoantibody in patients presenting with a clinical picture suggestive of autoimmune epilepsy does not rule out the diagnosis, and some of these patients can respond to immunosuppression.[30] The reasons for this are unclear, although it is possible that they harbor as yet to be discovered pathogenic autoantibodies. Response to an immunotherapy trial can support the diagnosis in these cases, and can help to identify those most likely to respond to maintenance immunosuppressive therapy.[30] Such positive responses need to be interpreted with caution, however, as immunotherapy is sometimes used to treat intractable epilepsies not proven to be autoimmune.[12,13]

Acknowledging the above difficulties, here we propose a diagnostic and therapeutic approach based on available data and our own clinical experience (►**Fig. 3**).

When to Suspect Autoimmune Epilepsy

Clinicians should suspect autoimmune epilepsy in patients presenting with

- Recent-onset cryptogenic epilepsy arising in the presence of a well-defined clinical syndrome such as limbic encephalitis, faciobrachial dystonic seizures, or NMDAR encephalitis *or*
- Cryptogenic status epilepticus (including nonconvulsive status epilepticus) *or*
- Subacute onset (maximal seizure frequency $<$ 3 months) of cryptogenic epilepsy

Supportive clinical features include

- Viral prodrome
- Antecedent psychiatric symptoms
- Antiepileptic drug resistance
- History of systemic autoimmunity
- History of recent or past neoplasia, particularly with a tumor known to be associated with autoimmune epilepsy

These patients should undergo a thorough evaluation looking for paraclinical biomarkers supportive of the diagnosis of autoimmune epilepsy, including neural-specific autoantibodies. Care should be taken to rule out infective, metabolic, neoplastic, or structural causes of epilepsy. Selective antibody testing is not advised because no single neural antibody is definitively associated with seizures, and markers of occult cancer may be missed.[1,106]

Supportive paraclinical biomarkers include

- Evidence of CNS inflammation on:
  - CSF (elevated protein, pleocytosis, oligoclonal bands, elevated IgG index or synthesis rate)
  - MRI brain scan (mesial temporal or parenchymal fluid-attenuated inversion-recovery (FLAIR)/T2-weighted hyperintensity)
  - Functional imaging (FDG-PET) (hypermetabolism)

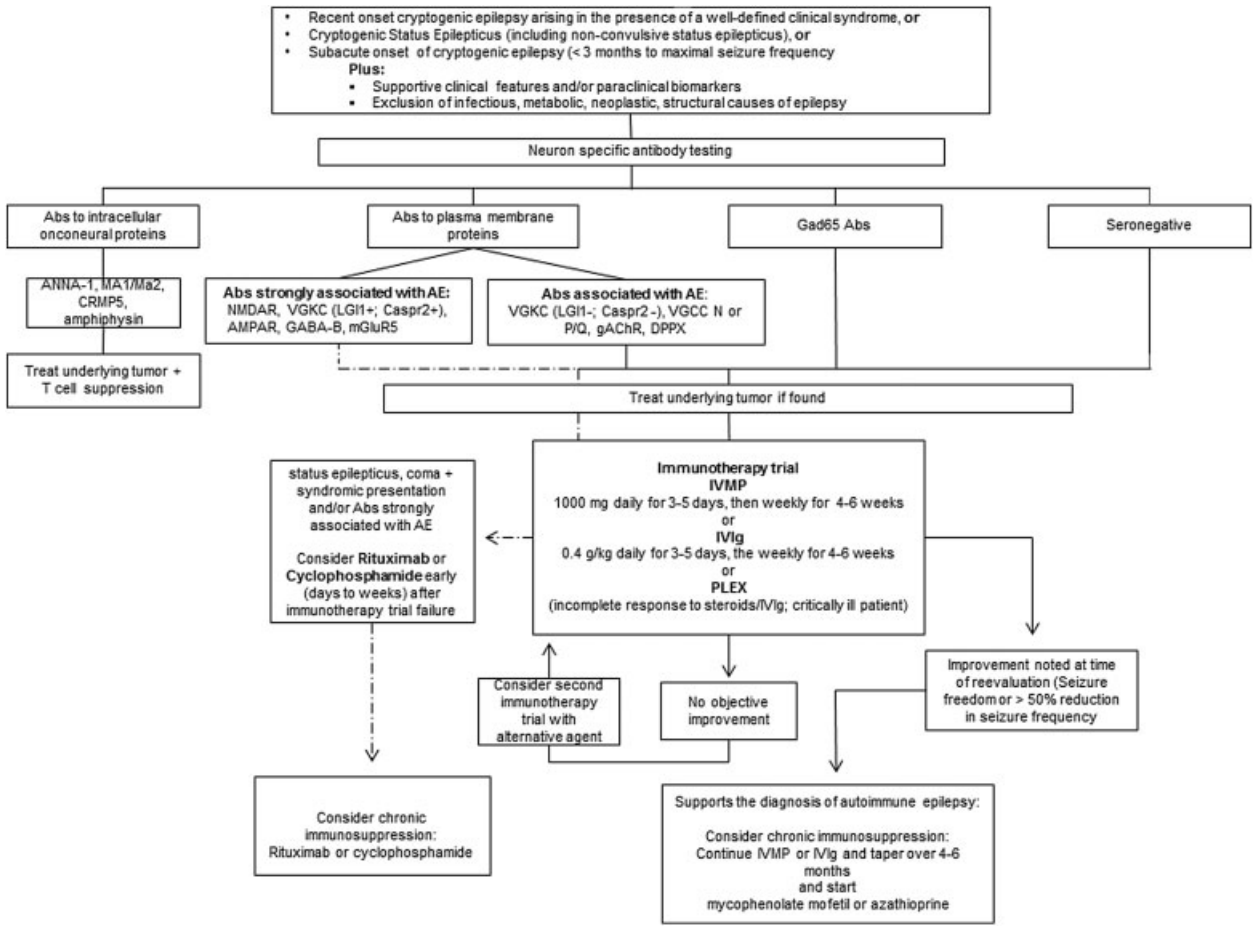

Fig. 3 Diagnostic and therapeutic approach to autoimmune epilepsy. AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ANNA-1, Antineuronal nuclear antibody type 1; Caspr2, contactin-associated protein-like 2; CRMP-5, Collapsin response mediator protein-5; DPPX, dipeptidyl-peptidase-like protein-6; GABA-B, γ-aminobutyric acid-B; gAChR, neuronal ganglionic nicotinic acetylcholine receptor; GAD65, glutamic acid decarboxylase 65; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; LGI1, leucine rich glioma inactivated protein I; mGluR5, metabotropic glutamate receptor 5; NMDAR, N-methyl-D-aspartate receptor; PLEX, plasma exchange; VGCC, voltage gated calcium channel; VGKC, voltage gated potassium channel.

- EEG showing extreme delta brush
- Serological markers of systemic autoimmunity such as antinuclear antibody (ANA) or thyroid peroxidase (TPO) antibody positivity

Once the diagnosis of autoimmune epilepsy is suspected based on clinical features and presence of paraclinical biomarkers, neural specific autoantibody status dictates management, and, together with response to an immunotherapy trial, helps to determine prognosis.

Tumor Screening Based on the Results of Antibody Testing

Finding an autoantibody to intracellular onconeural proteins should prompt a thorough search for an associated malignancy. If this reveals a neoplasm atypical for the paraneoplastic antibody, then clinicians should consider the possibility of a second more typical occult malignancy.[106] Computed tomography (CT) of the chest and pelvis is recommended as a screening tool, but if this is negative FDG PET-CT is the next investigation.[107] Antibodies against plasma membrane proteins (NMDAR, AMPAR, GABA-B, mGluR5) can also be paraneoplastic, and tumor surveillance may be indicated in these cases even if an initial search for a malignancy is negative. Fluorodeoxyglucose positron-emission tomography is not appropriate in a female with NMDAR encephalitis or in other patients suspected of having a germ-cell tumor. Ultrasound scanning or MRI are preferred modalities in these cases.

Treatment

Despite a paucity of formal evidence, a rational therapeutic approach can be devised based on treatments that have been successfully applied previously in a variety of autoimmune disorders. We typically use a protocol divided into acute and chronic therapeutic phases (►**Fig. 3**). Our standardized approach is guided by what we term the three "M's" of therapy:

- Maximum reversibility (at least >50% reduction in seizure frequency)
- Maintenance of reversibility
- Minimal therapeutic dose

Acute Therapy: Diagnostic Test

Response to immunotherapy in the acute treatment phase can have both diagnostic and therapeutic value. We generally give a trial of high-dose intravenous (IV) methylprednisolone or IV immunoglobulin (►**Fig. 3**, ►**Table 3**). We tend to reserve IV immunoglobulin for children (due to its perceived favorable side-effect profile in children compared with corticosteroids), and for patients who either have, or are at risk for, diabetes mellitus (i.e., patients seropositive for GAD65 or IA-2 autoantibodies). Plasma exchange is also a useful first-line acute treatment generally reserved for critically ill patients or when IV methylprednisolone or IV immunoglobulin is poorly tolerated. After an initial 4- to 6-week trial of therapy, patients should be re-evaluated for subjective and objective clinical improvement. Repeat, imaging, EEG and/or CSF analysis may help if these had been abnormal at first evaluation. If there is a strong suspicion, a trial with a different first-line agent may be warranted even if a patient fails to respond to the first agent tried.[30] Rituximab and cyclophosphamide can be considered as second-line agents when there is either no, or incomplete, response to first-line treatments (►**Fig. 3**, ►**Table 3**). The duration of the trial and timing of starting a second-line agent may vary according to the severity of presentation and the degree of confidence in the diagnosis. Status epilepticus in a patient with NMDAR antibody positivity or in a patient with limbic encephalitis and LGI1 positivity may warrant more rapid escalation of immunotherapy (►**Fig. 3**).

A recent retrospective study looked at the use of an immunotherapy trial in evaluating patients with suspected autoimmune epilepsy.[30] Sixty-two percent of patients improved overall, and of those receiving a second agent after not responding to the first, 43% improved. Responders included 93% patients with antibodies to plasma membrane antigens, 33% of patients seropositive for GAD 65 antibodies, and 33% of patients without detectable antibodies. Beyond the detection of plasma membrane autoantibodies, the strongest predictor of response was a shorter interval between symptom onset and starting treatment, highlighting the importance of prompt initiation of immunotherapy when suspecting an autoimmune cause. Other reported predictors of response include subacute onset, multiple seizure types, and CSF findings of inflammation (elevated protein, oligoclonal bands or pleocytosis).[28,31]

Patients with antibodies to intracellular onconeural antigens tend to carry a worse prognosis, but should still have the underlying malignancy treated. Clinicians should consider a trial of immunotherapy as described above; some patients may respond preferentially to agents targeting T-cell cytotoxic mechanisms, such as cyclophosphamide. However, fewer than 10% of these patients make a substantial recovery.[1]

Long-Term Therapy

Objective improvements (> 50% reduction in seizure frequency) should prompt consideration of a long-term plan for immunotherapy because symptoms relapse in most patients on withdrawal of acute therapies (►**Fig. 3**, ►**Table 3**). Medium- to long-term treatment with corticosteroids or IV immunoglobulin is sometimes required in these patients, but the overall the goal is eventually to stop these. This may be achieved by adding an oral long-term immunosuppressant such as azathioprine or mycophenolate mofetil, each of which has been used widely in treating organ-specific autoimmune diseases such as myasthenia gravis. In our practice, we gradually extend the interval between infusions of IV methylprednisolone or IV immunoglobulin over a period of 4 to 6 months from weekly to fortnightly, every 3 weeks, and then monthly. A faster taper of IV therapy can result in a relapse. When using daily oral prednisone, a slow reduction from 60 mg of prednisone over months is preferable. It is important to overlap corticosteroid or IV immunoglobulin treatment with the oral long-term immunosuppressant (~12 weeks for azathioprine and 8 weeks for mycophenolate mofetil). Some patients, however, remain dependent on corticosteroids or IV immunoglobulin, despite of optimization of oral long-term immunosuppression. In general, we prefer IV corticosteroid "pulse therapy" over long-term oral corticosteroids, as the evidence suggests a more benign side-effect profile and safer drug cessation. Rituximab and cyclophosphamide can be considered as long-term therapies in patients who required these agents during the acute phase or patients who relapse and fail to respond to first-line therapies.

There are no data to guide the duration of long-term immunosuppression in autoimmune epilepsy. Some patients experience spontaneous remission, whereas others depend upon lifelong immunosuppression to maintain remission. We generally start a trial of immunosuppressant medication withdrawal after 2 years.

Antiepileptic Drugs in Patients with Autoimmune Epilepsy

Patients with autoimmune epilepsy are typically resistant to antiepileptic drugs; generally, by the time immunotherapy is started, many are on multiple antiepileptic drugs. There are no data comparing immunotherapy alone versus combined treatment in autoimmune epilepsy. We generally keep patients on at least one antiepileptic drug during the acute phase for symptomatic treatment, with a goal of eventually stopping these if feasible. Some patients require maintenance therapy with an antiepileptic drug; this may be related to chronic mesial temporal atrophy secondary to the initial immunomediated process.

Conclusion

The recognition that a subset of antiepileptic drug-resistant epilepsies may have an autoimmune basis has dramatically changed the evaluation and management of new-onset seizures. The last decade has seen a dramatic increase in

Table 3 Therapeutic options in patients with autoimmune epilepsy

Drug	Dose	Route	Frequency	Some common and severe side effects encountered	Therapeutic phase
Methylprednisolone	1000 mg	IV	Daily for 3–5 d, then weekly for 4–8 wk	Insomnia, increased appetite, psychiatric disturbance, Cushing syndrome, diabetes, cataracts, osteoporosis, hip avascular necrosis, skin thinning Addisonian crisis on rapid withdrawal of physiologic doses of corticosteroid	Acute and chronic, then taper
Immunoglobulin	0.4 g/kg	IV	Daily for 3 d, then alternate weeks for 6–8 wk	Aseptic meningitis, deep venous thrombosis, headache, anaphylaxis, renal failure	Acute and chronic, then taper
Azathioprine	1 mg/kg/d to 2 mg/kg/d	PO	Two daily divided doses	Myelotoxicity, liver toxicity, hypersensitivity reaction, rash	Chronic
Mycophenolate mofetil	500 mg/d to 2000 mg/d	PO	Two daily divided doses	Myelotoxicity, CNS lymphoma, diarrhea, hypertension, renal failure	Chronic
Rituximab	1000 mg once, then again 2 wk later	IV	Every 6 mo	Infusion reactions, edema, hypertension, fever, fatigue, chills, headache, insomnia, rash, pruritus, nausea, diarrhea, weight gain, cytopenias, neutropenic fever, liver toxicity, hepatitis B reactivation	Acute (2^{nd} line) and chronic
Cyclophosphamide	500 mg/m^2/mo to 1000 mg/m^2/mo (IV) 1 mg/kg/d to 2 mg/k/d (PO)	IV or PO	Monthly (IV) Daily (PO)	Chronic infertility, alopecia mucositis, hemorrhagic cystitis, myelotoxicity	Acute (2^{nd} line) and chronic

Abbreviations: CNS, central nervous system; IV, intravenous; mo, month; PO, by mouth.

discovery of neural-specific autoantibodies and their target antigens. Laboratory testing, on a service basis, is now available for most of these autoantibodies, and can help establish the diagnosis and determine prognosis. Detection of autoantibodies to intracellular onconeural proteins can guide the search for specific cancers, but generally they carry a worse prognosis. Autoantibodies to plasma membrane proteins can also be paraneoplastic, but are in general immunoresponsive. The absence of neural-specific autoantibodies does not rule out an immunoresponsive epilepsy. Response to an immunotherapy trial can support the diagnosis of autoimmune epilepsy, and can help identify those most likely to respond to maintenance immunosuppressive therapy.

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