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Progress in autoimmune epileptic encephalitis

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Abstract

Purpose of review—Autoimmune epileptic encephalopathy is a potentially treatable neurological syndrome characterized by the coexistence of a neuronal antibody in the CSF and serum. Patients present with combinations of seizures, neuropsychiatric features, movement disorder and cognitive decline, but some patients have isolated seizures either at first presentation or during their illness. This review summarises our current understanding of the roles of specific neuronal antibodies in epilepsy-related syndromes and aims to aid the clinician in diagnosis and treatment.

Recent findings—Antigen discovery methods in three neuroimmunology centres independently identified antibodies to different subunits of the GABA_A receptor; high levels of these antibodies were found mainly in patients with severe refractory seizures. These and other antibodies were also found in a proportion (<10%) of children and adults with epilepsy. A clinical study comparing immunotherapy in patients with autoantibodies or without an identified target antigen found neuroinflammatory features were predictive of a therapeutic response. New in-vitro and in-vivo studies, and spontaneous animal models, have confirmed the pathogenicity and epileptogenicity of neuronal antibodies and their relevance to other mammals.

Summary—Neuronal antibodies are an important cause of autoimmune epileptic encephalopathy, early recognition is important as there may be an underlying tumour, and early treatment is associated with a better outcome. In the absence of an antibody, the clinician should adopt a pragmatic approach and consider a trial of immunotherapy when other causes have been excluded.

Keywords

Autoimmune encephalitis; autoimmune epilepsy; neuronal surface antibodies; immunotherapy

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Conflicts of interest

AV, and the Nuffield Department of Clinical Neurosciences in Oxford receive royalties and payments for antibody assays

Introduction

Autoimmune encephalitis is now an established neurological diagnosis in patients presenting with combinations of neuropsychiatric features, seizures, movement disorder and autonomic symptoms. The most commonly described neuronal targets strongly associated with seizures are the N-methyl-D-aspartate (NMDA), alpha amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and gamma amino butyric acid-B (GABA_B) receptors, leucine-rich-glioma protein 1 (LGI1, part of the VGKC-complex), glutamic acid decarboxylase (GAD) and more recently the GABA_A receptor [1–6]. Given the predominance of seizures in some patients with these disorders, an autoimmune aetiology is now often suspected in patients with a “seizure-plus” presentation [7, 8]. This has important implications in terms of therapy as early recognition and treatment with immunotherapy is potentially curable and therapeutic response may be of diagnostic use in selected cases, even in the absence of neuronal antibodies [9, 10].

This review summarises the main presentations of autoimmune epileptic encephalopathies, describes recent findings in epilepsy cohort studies and the limited evidence so far for efficacy of immunotherapies in these patients, and reports new studies into the underlying cellular pathophysiological mechanisms.

Clinical presentation of antibody-mediated autoimmune epileptic encephalopathies

NMDAR-antibody encephalitis

Autoantibodies to the NMDAR were first identified in a case series of 12 young females (14–44 years) who developed severe encephalopathy with specific clinical features, including psychiatric symptoms, seizures, cognitive and autonomic dysfunction, movement disorder and decreased level of consciousness, often requiring ventilatory support [11]. As eleven of the patients had an ovarian teratoma, and one a mature teratoma in the mediastinum, and the patients responded symptomatically to a combination of tumour removal and immunotherapy, this disorder was initially reported as a paraneoplastic encephalitis affecting young women. However, many studies since have reported cases that include males, children and patients with no underlying malignancy [1, 12–16]. Although males are not so common, a recent observational study found 61.5% (8/13) of adult males presented initially with a seizure that was focal in five [1]. By contrast, only 8/58 (14%) female cases presented with seizures initially, and these were mostly generalized. In the single large cohort of 577 patients, seizures as part of the initial presentation were again more common in men than women (27% vs 11%), although in both groups psychiatric disturbance was even more frequent [17].

One of the striking aspects of NMDAR-antibody encephalitis is a specific interictal “extreme delta brush” EEG pattern found in up to 30% of patients during the course of the illness [18]. This distinct waveform, characterized by rhythmic delta activity with superimposed beta frequency “riding” on each delta wave, is seen more commonly in severely affected

patients with recurrent seizures/status epilepticus, but may be a helpful guide to diagnosis and treatment in some patients [19, 20].

VGKC-complex antibodies and limbic encephalitis

VGKC-complex antibodies have been reported in patients with limbic encephalitis, often with seizures as the presenting feature, from 2001 [21]. This form of limbic encephalitis is not often paraneoplastic and the patients often respond well to immunotherapies, with marked reductions in antibody levels and modified Rankin Scale scores [22]. MRI hyperintensities in the temporal lobes and hyponatraemia are common at first presentation. It is now clear that the VGKC-complex antibodies are mainly directed against other components of the complex such as LGI1 and CASPR2. LGI1 antibodies are most commonly associated with limbic encephalitis [23, 24] and with a recently defined form of epileptic event.

Facio-bracial dystonic seizures (FBDS)

LGI1 antibodies are highly associated with FBDS, a disorder characterized by brief, dystonic episodes that can precede the onset of or occur within the symptomatology of limbic encephalitis [25]. In the initial stages of FBDS, patients can have normal sodium levels, brain MRI, and the scalp EEG is also normal in the majority of patients; some describe the features of tonic seizures [5, 25, 26]. Anti-epileptic drugs (AEDs) are often ineffective, and intriguingly often associated with severe cutaneous reactions in up to 41% of patients [25]. Immunotherapy, particularly oral steroids, produces a clear reduction in seizures, and has been shown to prevent subsequent development of poor cognitive outcome in a few patients [5].

Whether these events represent an autoimmune epileptic encephalopathy or are indeed a movement disorder has been the subject of debate as MRI studies have also described T2 hyperintensities, FDG-PET hypermetabolism and T1 hyperintensity in the basal ganglia [5, 25, 27, 28]. Moreover, a recent retrospective study of LGI1-Ab FBDS found that scalp EEGs were normal in 20/23 assessed, however T1 and T2 basal ganglia signal abnormalities were detected in 42% [29], and mesial temporal abnormalities were significantly less common than in LGI1-Ab positive patients without FBDS. Nevertheless, as previously described, patients responded more frequently and more completely to immunotherapy than anti-epileptic drugs, and the former should be the first-line treatment of these episodes regardless of their cortical or subcortical origin [29]. Recognition of the characteristic semiology and the presence of basal ganglia T1 hyperintensity in particular, should alert the clinician to an immunotherapy responsive syndrome even in the presence of a normal EEG, and absence of mesial temporal MRI changes.

Other antibody mediated clinical presentations

The AMPA receptor (AMPA) is an ionotropic transmembrane glutamate receptor that mediates the majority of fast synaptic transmission throughout the CNS. Autoantibodies to this receptor are rare; in 2009 a case series of ten patients all presented with a form of LE, four patients had seizures, and seven had an underlying malignancy [30]. Nine received immunotherapy and responded to this treatment alongside oncological therapy when

required. There was a tendency towards frequent relapse. A recent case series of a further 21 patients demonstrated a higher prevalence of psychiatric symptoms (~30%) and although 71% patients responded to immunotherapy or tumour removal, the relatively common co-existence of onconeural antibodies predicted a poor outcome [2].

Antibodies to the GluA3 subunit were identified in early research studies investigating the pathogenesis underlying Rasmussen's encephalitis [31], a rare neurological disorder characterized by progressive unihemispheric inflammation of the cerebral cortex causing cognitive deterioration, hemiplegia, hemianopia and drug-resistant focal epilepsy [32]. Further studies were unable to reproduce this finding of potentially pathogenic GluA3 receptors [33] and given the lack of response to PLEX seen in patients with this disease, it is unlikely that CNS autoantibodies are causative in this condition.

GABA receptors are the main inhibitory receptors throughout the CNS. The G-protein coupled GABA_B receptors are composed of two subunits GABA_{B1} and GABA_{B2}, and mediate pre- and post-synaptic inhibition. Autoantibodies to the GABA_B receptor have been reported in a number of case series [3, 34, 35]. Patients presented with symptoms of LE, and in one series all patients had early or prominent seizures [34]. EEG revealed encephalopathy, partly with epileptiform discharges in some patients [35]. Up to 50% of all cases had an underlying SCLC. Response to immunotherapy and oncological treatment was variable with full or partial improvement reported to be between 20-83% [3, 35]. In another recent case series of five patients, four patients had small-cell lung cancer; in three, the identification of the lung cancer was *after* the diagnosis of GABA_B encephalitis, the antibody positivity prompting the search for this specific tumour [36]. Overall the GABA_BR-Ab patients who respond best to immunotherapy are those with LE in the context of SCLC [37].

The GABA_A receptor mediates most of the fast inhibitory transmission in the brain and is the pharmacological target for many anti-epileptic drugs; loss of synaptic GABA_A receptors by internalization is thought to underlie the resistance seen to benzodiazepines in refractory status epilepticus [38]. Recently, high titres of GABA_A antibodies binding different alpha, beta or gamma subunits were identified in patients with refractory seizures and status epilepticus with extensive MRI cortical/subcortical FLAIR changes [6]. The majority of cases treated with immunotherapy made a full or partial recovery [6, 39]. Another series, identified by the presence of this antibody in sera negative for NMDAR-antibodies, found a seizure predominance in presentation (47%) along with memory impairment (47%), hallucinations (33%) and anxiety (20%), but because of the lack of a clear limbic phenotype, most patients had not been given immunotherapies [39]. Two patients in the third series had invasive thymoma, cognitive impairment and multifocal abnormal MRI brain scans, but only one had seizures/status epilepticus [40]. GABA_A receptor antibodies have all the hallmarks of pathogenicity (see below) but it is not yet clear whether they define a highly specific syndrome.

Further neuronal antibodies associated with the clinical presentation of autoimmune epileptic encephalopathy are listed in table 1.

New-onset refractory status epilepticus (NORSE)

NORSE is a rare and devastating condition defined as treatment resistant status epilepticus in otherwise healthy individuals with no pre-existing history of epilepsy, and no obvious aetiological factors [41–43]. The most recent study, a retrospective review of 130 cases, found that the most common aetiology was autoimmune in 48% of cases (non-paraneoplastic (19%) and paraneoplastic (18%)); NMDAR-Abs were the most frequent neuronal antibody identified [44]. Immunotherapy response could not be evaluated as treatment onset/regimes were highly variable, but other case reports have described dramatic responses to plasma exchange and immunotherapy, even in the absence of neuronal antibodies [41, 45, 46]. Further collaborative and prospective studies are required to evaluate the roles of specific antibodies and of immunotherapy in this challenging condition, where early immune therapy may be beneficial.

Neuronal antibodies in adult and paediatric epilepsy cohort studies

A few recent studies have looked for antibodies in cohorts of adult and paediatric epilepsy patients [47–49]. The overall incidence of antibodies to any of the antigens described above is usually around 10% of the patients, and these antibodies are more common in patients with focal seizures of unknown aetiology, suggesting that they might play a role. However, immunotherapies were used variably and without prior knowledge of any antibodies, and the relevance of these relatively low titre antibodies is not yet clear.

Treatment of autoimmune epileptic encephalopathy

There are currently no consensus guidelines on the treatment of autoimmune epileptic encephalopathy. Broadly speaking, most centres advocate “first-line treatment” in the form of pulsed intravenous high dose steroids followed by high dose oral corticosteroids, and intravenous immunoglobulin and/or plasma exchange; second-line immunotherapy options include rituximab, cyclophosphamide, azathioprine, mycophenolate mofetil and methotrexate [8, 50–52]. Patients respond well to immunotherapy with the best therapeutic responses seen in those diagnosed and treated early, and with tumour removal, if applicable [15, 53].

Response to a trial of immunotherapy has also been explored as a diagnostic aid if an autoimmune epileptic encephalopathy is suspected in refractory cases of epilepsy [10]. The most likely to respond were those patients with neuronal autoantibodies (87.5%), although 33% (2/6) patients without detectable antibodies also responded.

Historically, unlike paediatric epilepsy patients, adults have rarely been treated for epilepsy or epileptic encephalopathy with immunotherapy. In paediatrics, West syndrome and patients with electrical status epilepticus in sleep (ESES) respond to immunotherapy although these are not labelled “autoimmune epileptic encephalopathy”, as they are more likely to have another aetiology such as genetic mutations [54]. Therefore caution must be ascribed to assuming that a immunotherapy response indicates an autoimmune condition; this can distract from the actual cause, and chronic immunosuppression may cause harm.

Pathogenicity and epileptogenicity of neuronal antibodies

As well as the favourable clinical response to immunotherapy, *in vitro* and *in vivo* studies provide further evidence of the pathogenicity of NMDAR-Abs. Incubation of dissociated rodent hippocampal neurons with patient NMDAR-Abs *in vitro* causes a selective reduction in surface membrane NMDARs, resulting in “NMDAR hypofunction” [55]. This is reversible on removal of the NMDAR-Abs, and mediated by autoantibody cross-linking of the receptors and internalization [56]. Similarly, a recent study on the pathogenicity of AMPA receptor antibodies showed that human antibodies internalize and degrade surface AMPAR clusters and decrease AMPAR-mediated currents *in-vitro*, leading to increased intrinsic excitability [57]. Unlike the glutamate receptor antibodies, there was no reduction of GABA_BR levels on *in vitro* hippocampal neurons exposed to GABA_BR antibodies [34], but GABA_AR antibodies do reduce surface levels of GABA_AR's [6, 39], and selectively reduced miniature IPSC amplitude and frequency without affecting miniature EPSCs in one electrophysiological study [40].

Ex-vivo electrophysiology studies have shown that one patient's IgG containing LGI1 antibodies induced epileptiform activity in CA3 pyramidal cells in rat hippocampal slices, similar to that induced by the VGKC inhibitor dendrotoxin [58]. A more detailed *in vitro* study found that LGI1 autoantibodies inhibited the interaction of LGI1 with ADAM22 and caused synaptic AMPAR reduction [59], a potentially pathogenic and epileptogenic effect. Both pre- and postsynaptic mechanisms are likely to play a role in LE.

The pathogenicity of NMDAR antibodies has been demonstrated in two recent reports. Spontaneous seizures were not observed in either study. Cognitive and memory deficits were seen in mice after 14 days of CSF infusion with human CSF containing NMDAR antibodies [60]. Post-mortem analysis revealed a progressive decrease of total and synaptic NMDAR clusters. Lowered seizure threshold was found when purified serum IgG containing NMDAR-Abs was injected into mice implanted with wireless EEG transmitters [61] and given a sub-convulsive dose of PTZ. In this case, unexpectedly, there was no apparent loss of NMDAR expression overall, but it is possible that loss of the receptors in a population of inhibitory interneurons, which would cause an overall increase in network excitability, was involved (Figure 1[62]).

Spontaneous models of antibody-mediated diseases

VGKC-complex/LGI1-Abs were found in cats with “feline complex partial seizures with orofacial movement (FEPSO)” [63], which is now thought to be a form of limbic encephalitis. Similar to humans with VGKC-complex antibodies associated with limbic encephalitis [64] post-mortem hippocampal lesions showed marked IgG infiltration and complement deposition, confirming the same potential pathogenic mechanism [65] and suggesting that immunotherapies should be used in this now well-recognised feline syndrome.

Finally, a recent report found that Knut, the polar bear of the Berlin Zoological Garden who drowned in 2011 following seizures that were observed by many visitors, had high levels of

NMDAR-Abs in his serum and CSF making him the first non-human case of NMDAR-ab encephalitis, and suggesting that this antibody-mediated autoimmunity may also be of clinical relevance to veterinary practice [66].

Conclusions

Autoimmune epileptic encephalopathy is a recognizable and potentially treatable neurological syndrome which often present with seizures, often focal but sometimes generalised. The discovery of new antigens has broadened the clinical spectrum, and clinicians must be alert to search for an autoimmune cause in refractory cases as immunotherapy may be beneficial even in the absence of a specific neuronal antibody. Having demonstrated the pathogenicity of neuronal antibodies, further basic science research into the underlying cellular mechanisms should focus on new pharmacological treatments that might preserve inhibitory neuronal function or restore receptor function.

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References

- (* , special interest) A comprehensive review of the concept of ‘autoimmune epilepsy’ in adult epilepsy patients with diagnostic and treatment algorithm
- (** , special interest) A large retrospective cohort of the clinical entity known as NORSE
- (*** , special interest) An acute passive transfer model, demonstrating the epileptogenicity of NMDAR-Abs using a novel wireless telemetry system for long-term analysis
- (\$, special interest) Largest reported cohort of patients with NMDAR-Ab encephalitis to date detailing clinical presentation, responses to immunotherapy and outcomes of affected patients
- (∅ , special interest) Comprehensive review of autoimmune encephalitides in children
- (**** , outstanding interest) A fascinating and stimulating article describing the history, clinical features and histopathological investigation/diagnosis of the first non-human mammalian case of NMDAR-Ab mediated autoimmune epileptic encephalopathy
- (€ , outstanding interest) A passive transfer study of NMDAR-Abs confirming the pathogenicity of cell-surface antibodies in vitro after chronic exposure, providing a disease model on which treatments may be tried in future experiments
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Key points

- Autoimmune epileptic encephalopathy classically presents with seizures, neuropsychiatric features, abnormal movements and cognitive decline
- Seizures may be the presenting feature in males with NMDAR-antibodies
- FBDS is a specific form of epileptic syndrome, strongly associated with LGI1 antibodies and responsive to immunotherapies
- EEG and MRI may have specific features such as “extreme delta brush” in NMDAR-Ab encephalitis and basal ganglia T1 hyperintensity in FBDS giving a diagnostic clue
- A trial of immunotherapy in patients with severe epilepsy without an identified antibody may still be of clinical and diagnostic benefit

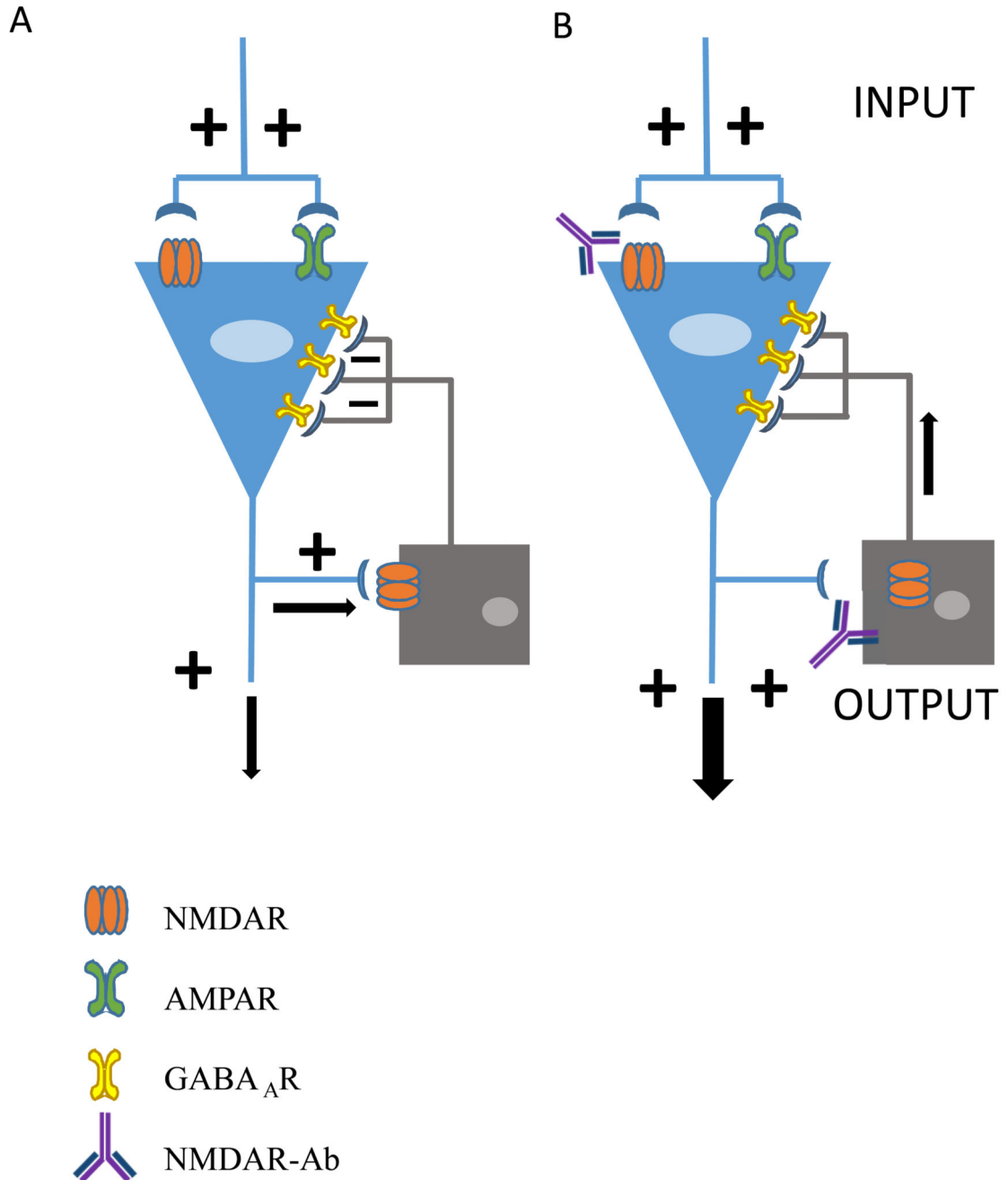


Figure 1. Schematic of how NMDAR-Abs might cause increased neuronal excitability

A. Activation of the pyramidal cell (blue triangle) by AMPAR receptors produces a strong output. The pyramidal cell action potential also exerts stimulates the inhibitory neurons (grey squares) via release of glutamate onto NMDA receptors; these feedback onto the pyramidal cell body providing inhibition via GABA_A receptors. Meanwhile, depolarisation of the pyramidal cell leads to opening of the NMDA receptors which are required for long-term potentiation. **B.** In the presence of NMDAR-Abs, the internalisation of NMDARs on the interneuron disrupts this feedback inhibition resulting in increased excitatory output.

Adapted from Rujescu, D., et al. (2006). "A pharmacological model for psychosis based on N- methyl-D-aspartate receptor hypofunction: molecular, cellular, functional and behavioral abnormalities." Biol Psychiatry59(8): 721-729.

Table 1.
Neuronal targets in autoimmune epileptic encephalopathy, including classical intracellular onconeural proteins less commonly associated with this clinical presentation

Neuronal target	Cell surface or intracellular	Paraneoplastic	Neurological features
NMDAR	Cell-surface	Ovarian teratoma, neuroblastoma, testicular germinoma	Encephalitis, neuropsychiatric features, seizures, movement disorder, dysautonomia
AMPA	Cell-surface	Lung cancer, thymic tumour, breast cancer	Encephalitis, seizures, psychiatric features
GABA _A	Cell-surface	Invasive thymoma	Encephalitis, status epilepticus, refractory seizures
GABA _B	Cell-surface	Small cell lung carcinoma	LE
VGKC-complex and LGI1	Cell-surface	Thymoma, small-cell lung carcinoma, breast, prostate cancer	LE, FBDS
Glycine receptor	Cell-surface	About 15%, thymoma, lymphoma	PERM, SPS, epileptic encephalopathy
DPPX	Cell-surface	Not yet described	Encephalitis, myoclonus, sleep disturbance, GI disturbance
mGluR5	Cell-surface	Hodgkin lymphoma	Ophelia syndrome - limbic encephalitis
GAD65	Intracellular	Not common but occasional thymoma; renal, breast GI tract carcinoma	SPS, LE, refractory seizures (temporal lobe)
Hu	Intracellular	Classically small-cell carcinoma	LE, neuropathy (autonomic, peripheral, sensory), brainstem encephalitis
CRMP-5	Intracellular	Small-cell carcinoma, thymoma, breast cancer	Limbic encephalomyelitis, LEMS, neuropathy, optic neuritis
Ma1, Ma2	Intracellular	Testicular, breast, colon cancer	LE, polyneuropathy, encephalomyelitis
Amphiphysin	Intracellular	Breast and small-cell lung carcinoma	LE, SPS, myelopathy, encephalomyelitis

Abbreviations: DPPX dipeptidyl-peptidase-like protein-6; GI gastrointestinal; LE limbic encephalitis; LEMS Lambert Eaton Myasthenic Syndrome; PERM progressive encephalomyelitis with rigidity and myoclonus; SPS stiff-person syndrome