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Seizures and risk of epilepsy in autoimmune and other inflammatory encephalitis

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Abstract

Purpose of review—To assess the seizure manifestations and risk of epilepsy in encephalitis associated to antibodies against neuronal cell-surface (AE) or myelin-associated antigens, and to review several chronic epileptic disorders including, Rasmussen's encephalitis (RE), fever-induced refractory epileptic syndromes (FIRES), and new-onset refractory status epilepticus (NORSE).

Recent findings—Seizures are a frequent manifestation of AE. Some AE may associate with characteristic features: faciobrachial dystonic seizures (anti-LGI1 encephalitis), EEG extreme delta brush (anti-NMDAR), or multifocal FLAIR-MRI abnormalities (anti-$GABA_AR$). In anti-LGI1 encephalitis, cortical, limbic, and basal ganglia dysfunction results in different types of seizures. AE or myelin-antibody associated syndromes are often immunotherapy-responsive and appear to have a low risk for chronic epilepsy. In contrast patients with seizures related to GAD65-antibodies (an intracellular antigen) frequently develop epilepsy and have suboptimal response to treatment (including surgery). RE or FIRES may occur with autoantibodies of unclear significance and rarely respond to immunotherapy. A study of patients with NORSE showed that 30% developed chronic epilepsy.

Summary—Although seizures are frequent in all types of AE, the risk for chronic epilepsy is dependent on the antigen: lower if located on the cell-surface, and higher if intracellular. For other disorders (RE, FIRES, NORSE) the prognosis remains poor.

Keywords

neuroinflammation; seizures; encephalitis; neuronal antibodies; demyelinating syndromes

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Conflicts of interest

Dr Dalmau receives royalties from Athena Diagnostics for the use of Ma-2 as an autoantibody test and from Euroimmun for the use of NMDAR, $GABA_BR$, $GABA_AR$, DPPX and IgLON5 as autoantibody tests; he has received an unrestricted research grant from Euroimmun.

INTRODUCTION

Epilepsy is a chronic neurological disease defined by the occurrence of at least one unprovoked seizure and the enduring predisposition to seizure recurrence.[1] The hypothesis that inflammation plays a role in epileptogenesis has long been suggested.[2*] This hypothesis has been reinforced by the identification of several autoimmune encephalitis (AE) that associate with seizures and occur with antibodies against neuronal cell-surface or myelin-related proteins. The study of these disorders has provided new insights into the relationship between neuroinflammation, autoimmunity, and seizure generation, giving rise to the concept of “autoimmune epilepsy”. In the context of AE, the development of seizures and status epilepticus usually represents an acute, symptomatic, manifestation of the brain inflammatory process, but little is known about the risk of developing chronic epilepsy. Chronic epilepsy might potentially result from an ongoing inflammatory process that persists after the acute phase of encephalitis, or from irreversible changes that alter neuronal networks and persist after the inflammatory process resolves. Therefore, although neuroinflammation may trigger symptomatic seizures, this does not necessarily imply that the subsequent development of chronic seizures is inflammation-dependent. Likewise, herpes simplex encephalitis may cause acute seizures, but the subsequent development of chronic epilepsy is not defined as “infectious epilepsy”.

In this review we first discuss recent developments on the role of neuroinflammation in epileptogenesis. Then, we focus on seizure manifestations and risk of epilepsy in AE and acute demyelinating syndromes, and discuss several chronic epileptic disorders for which there is evidence that autoimmunity plays a pathogenic role such as Rasmussen’s encephalitis (RE), fever-induced refractory epileptic syndromes (FIRES), and new-onset refractory status epilepticus (NORSE).

Inflammation, autoimmunity, and epileptogenesis

A number of clinical observations have suggested that inflammatory pathways are involved in epileptogenesis[3,4] including, 1) the anticonvulsant effect of steroids in some pediatric forms of epilepsy, [5] 2) the role of fever in triggering febrile-related epilepsies, [6,7] 3) the higher frequency of epilepsy in systemic autoimmune diseases (e.g., systemic lupus erythematosus and others), [8–19] 4) the increased prevalence of serum autoantibodies in chronic epilepsy (e.g., antinuclear and antiphospholipid antibodies), [20,21] and 5) the involvement of immune-related genes in some types of epilepsy and febrile-seizure susceptibility.[22]

On the other hand, seizures and status epilepticus can cause neuroinflammation through several mechanisms including among others, 1) activation of the interleukin (IL)-1β system by microglia, resulting in a cascade of inflammatory processes involving neurons, endothelial cells, and astrocytes, and likely responsible for blood-brain barrier breakdown and neuronal dysfunction, with alteration of the balance between excitatory and inhibitory neurotransmission, [23,24*] and 2) the involvement of the high-mobility-group box 1 (HMGB1), a danger signal that results in activation of downstream inflammatory pathways through interaction with its receptor (Toll-like receptor 4).[2*]

The immune system, and in particular its adaptive arm, may contribute to epileptogenesis[2*] as suggested by experimental studies with antibodies from patients with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis.[25*] Autoantibodies targeting this and other neuronal antigens have been infrequently identified in adults or children with chronic epilepsy (0–9%) or status epilepticus (< 3%), [26–31,32*,33] and were found at higher frequency (15–37%) when the seizures were refractory to antiepileptic treatment. [34,35] However, with the exception of glutamic acid decarboxylase 65(GAD65) antibodies, the significance of antibodies in chronic epilepsy is unclear because they are usually identified only in serum and may disappear over time despite seizure recurrence.[31] Careful consideration should be given to the interpretation of antibodies against proteins interacting with voltage-gated potassium channels (VGKC complex). These antibodies are in fact directed against two neuronal cell-surface proteins, leucine-rich glioma inactivated-1 (LGI1) and contactin-associated protein-2 receptor (CASPR2), [36,37] and several unknown (probably intracellular) proteins. Whereas LGI1 or CASPR2 antibodies associate with several syndromes that often occur with seizures (e.g., limbic encephalitis, Morvan syndrome), [38**,39*,40**,41*] the detection of VGKC-complex antibodies negative for LGI1 and CASPR2 has unclear clinical utility.[42,43**]

Autoimmune encephalitis with neuronal cell-surface antibodies

Seizures are a frequent manifestation of AE. The risk of developing chronic epilepsy as sequelae of AE is largely unknown because studies rarely provide this information and the patients follow-up is often short considering that some AE recover very slowly.[38**,44] The AE that most frequently manifest with seizures and status epilepticus are those mediated by antibodies against the γ-aminobutyric acid receptor A ($GABA_AR$), $GABA_BR$ and LGI1. [37,45–47, 48**,49,50*,51,52*] However, seizures can occur with any form of AE including those with antibodies against NMDAR, [44,53–55] α-amino-3-hydroxy-5methyl-4-isoxazolepropionic acid receptor (AMPAR), [56,57*] CASPR2, [39*,40**] dipeptidyl-peptidase-like protein-6 (DPPX), [58–60] metabotropic glutamate receptor 5 (mGluR5), [61–63] glycine receptor (GlyR)[64,65] and neurexin3α.[66*] Although seizures are not always the presenting symptom, they occur in the majority of patients during the acute or early stages of the disease (Table 1).[38**,44,53] In most AE, seizures occur in association with other symptoms including among other cognitive dysfunction, altered behavior, decreased level of consciousness, movement and sleep disorders, or dysautonomia.

In anti-NMDAR encephalitis, seizures are more often the first clinical manifestation in men than in women, and in children younger than 12 years.[67,68] Age-related clinical differences have also been reported in anti-$GABA_AR$ encephalitis in which children are more likely to develop generalized seizures compared to adults who predominantly develop focal seizures.[47,52*] Although there is substantial clinical overlap among different AE, some symptoms, EEG or MRI findings may suggest the autoantigen. For instance, the EEG pattern named extreme delta brush has been found in children and adults with anti-NMDAR encephalitis and is highly characteristic of this disorder although it is only detectable in a subgroup of patients.[54,69] Extensive multifocal cortical-subcortical T2/FLAIR MRI abnormalities occur in approximately 80% of patients with anti-$GABA_AR$ encephalitis, but rarely occur in other AE.[47,52*]

Facio-brachial dystonic seizures (FBDS) typically precede the development of anti-LGI1 encephalitis, which often occurs in association with other seizures. FBDS are brief (typically 1–2 sec) uni- or bilateral motor seizures, affecting the limbs and face, with a frequency that can be over 100 times per day (median 40/day).[38**] Studies suggest that the type of seizures may change during the course of anti-LGI1 encephalitis with an initial predominance of FBDS and focal seizures (25–30% of the patients) and at later stages a predominance of focal or generalized seizures and impairment of consciousness (60–80% of the patients).[38**,41*,70**,71] Prompt recognition and treatment of FBDS may prevent the development of a full-blown limbic encephalitis.[71,72] A study using EEG, MRI, and FDG-PET suggested that FBDS originate in the motor cortex, while other seizure types and cognitive impairment result from involvement of mesio-temporal regions.[70**] Another study demonstrated that 42% of patients with FBDS have MRI FLAIR and T1 changes in the basal ganglia suggesting that dysfunction at this level might contribute to these seizures.[48**]

In patients with AE generalized seizures and status epilepticus substantially contribute to morbidity and mortality.[38**,44–46,53,52*] Overall, 70–80% of patients with AE respond to immunotherapy.[38**,44,46,47,57*,52*] Residual deficits may include cognitive dysfunction and persistent seizures. Among patients with anti-LGI1 encephalitis, 70–80% have residual cognitive deficits, and 30% of them are left with moderate to severe disability.[38**,41*,49] In most patients the seizures improved or resolved prior to improvement of cognitive functions; indeed, after a follow-up of 2 years, 85% of patients were seizure-free (71% without treatment, and 14% with antiepileptics) while 15% continued to have seizures despite antiepileptics.[38**,49] Similar findings have been reported in patients with anti-$GABA_AR$ encephalitis.[52*]

In more than 70% of patients with AE the associated seizures are successfully treated with immunotherapy and antiepileptics, and most do not require chronic antiepileptic medication.[29,49,73,74] A study on AE associated with antibodies against neuronal cell-surface or intracellular antigens reported good seizure response to rituximab in cases refractory to corticosteroids, intravenous immunoglobulins and plasma exchange.[74] Overall, the risk of developing chronic epilepsy after AE appears low (10–15%) and varies according to the target autoantigen.[38**,49,52*] For example, in two cohorts of patients with anti-AMPAR and anti-$GABA_BR$ encephalitis none of the survivors had persistent seizures.[45,56] Patients with anti-NMDAR encephalitis may have residual cognitive and behavioral deficits but rarely develop chronic seizures.[53]

In patients with anti-LGI1 encephalitis, a high seizure frequency associates with the development of mesial temporal lobe sclerosis (MTS).[75] In these patients the degree of hippocampal atrophy correlates with memory deficits and delay in implementing immunotherapy.[49,50*] In contrast, patients with anti-NMDAR encephalitis may develop hippocampal atrophy, which correlates with disease severity and long-term cognitive deficits, but rarely develop MTS.[76**]

Patients who have AE triggered by herpes simplex encephalitis frequently harbor NMDAR antibodies along with other antibodies against neuronal cell-surface antigens ($GABA_AR$,

dopamine 2 receptor), and their outcome is worse (more frequent residual deficits and seizures) than that of patients with anti-NMDAR encephalitis unrelated to herpes simplex encephalitis.[52*,77,78*]

In patients with AE and seizures who do not respond to immunotherapy, epilepsy surgery has been suggested as an alternative treatment, however, this appears to be less effective than in patients with epilepsy unrelated to AE.[79–81]

Autoimmune demyelinating syndromes and MOG antibodies

Seizures occur in 11–43% of patients with acute disseminated encephalomyelitis (ADEM), including generalized (40%) and focal (< 20%) seizures, and in 0–14% of patients with clinically-isolated syndromes (CIS, mostly generalized seizures).[82–89,90*,91] There is limited information about the risk of chronic epilepsy in these patients. In a recent study, 3 of 8 children with ADEM had seizures at disease onset, and one developed epilepsy; however, the interval between ADEM and onset of epilepsy was 15 years, making it unclear if there was a link between the diseases.[88]

Antibodies against myelin oligodendrocyte glycoprotein (MOG) have been identified in about 40% of patients with ADEM and 0–38% of CIS, as well as in a variety of other demyelinating disorders that do not manifest with seizures.[82–89,90*] In patients with ADEM, the presence of MOG antibodies seems to predict a monophasic course and associates with younger age, larger bilateral brain MRI abnormalities, and better outcome.[84] Future studies should assess the long-term risk of epilepsy in ADEM and CIS, and investigate whether MOG antibodies segregate with a higher or lower risk of epilepsy.

Epilepsy associated with GAD65 antibodies

High titers of GAD65 antibodies may be found in patients with seizures in the context of limbic encephalitis, [92,93] and in patients with chronic epileptic syndromes without clinical or MRI evidence of active CNS inflammation.[92–95] In particular, GAD65 antibodies have been reported in 2–3% of adults and 6–7% of children with chronic epilepsy.[94,96] An important consideration in assessing the relationship of GAD65 antibodies with epilepsy and other neurological syndromes is that these antibodies also occur in 1% of healthy people and 80% of patients with type 1 diabetes mellitus.[97,98] Compared with healthy people or patients with diabetes, patients with neurological symptoms have substantially higher titers of serum antibodies (~100–1000 times higher), and the antibodies are detectable in CSF.[92,93,99]

Since GAD65 is an intracellular antigen and is not accessible to circulating antibodies, the pathogenic role of GAD65 antibodies is controversial. It is thought that other mechanisms, such as T-cell mediated processes or additional antibodies to yet unknown antigens might be involved.[100*] Patients with epilepsy and GAD65 antibodies show poor response to immunotherapy. In a retrospective study of 13 patients, only one patient remained seizure-free after discontinuation of immunotherapy, and similar results were obtained in another study.[101,102]

Epilepsy in Rasmussen's encephalitis (RE)

RE is a rare chronic epileptic syndrome that predominantly affects previously healthy children but in rare instances may also occur in adults.[103–106] Patients develop frequent, unilateral motor seizures that evolve to intractable epilepsia partialis continua, hemiplegia, and cognitive decline, accompanied by progressive unilateral hemispheric atrophy.[107–109] Younger patients are more likely to develop more severe disease and a higher degree of hemispheric atrophy.[107] The cause of this disorder is unclear but cytotoxic T-cell mechanisms are thought to be involved.[110–113] Although a number of autoantibodies have been reported in patients with RE, [114–117] their pathogenic significance and clinical utility are uncertain. For example, antibodies against the GluA3 (or GluR3) subunit of AMPAR have been reported in 4–25% of patients with RE but also in 40–60% of patients with focal or generalized epilepsy unrelated to RE.[114–117] Antibodies against the GluN2 subunit of the NMDAR, as well as other neuronal proteins, have been inconsistently identified in some patients with RE.[115,118–121] Importantly, the AMPAR and NMDAR antibodies identified in RE are different from those associated with anti-AMPAR or NMDAR encephalitis: the target subunits are different (GluA1/GluA2 in anti-AMPAR encephalitis and GluN1 in anti-NMDAR encephalitis), the epitopes in RE are linear instead of conformational and are located in the intracellular and not extracellular domain of the receptors.[53,120,122,123] Moreover, the appearance of these antibodies in patients with RE is often delayed from the time of seizure onset, [124] and the findings are not reproducible across different laboratories.

Seizure control in RE is challenging: antiepileptics are inefficient and the response to immunotherapies is often poor or transient.[125–127] Natalizumab or rituximab have shown some efficacy, but these treatments have not been tested in controlled trials.[128–130] Functional hemispherectomy is the only therapeutic option to achieve long-term seizure control; it is efficacious in 70–80% of the patients but at the expense of irreversible loss of neurological functions.[131]

Fever-induced refractory epileptic syndrome (FIRES) and new onset refractory status epilepticus (NORSE)

FIRES is a devastating epileptic syndrome occurring in previously healthy children around the age of 5–12 years.[132] It is characterized by frequent seizures developing in the context of a nonspecific febrile episode that rapidly evolve to status epilepticus and chronic pharmacoresistant epilepsy associated with severe neurodevelopmental delay.[132–134] The brain MRI is initially normal but as the disease progresses, mesio-temporal T2/FLAIR hyperintensities become apparent and almost all patients eventually develop cerebral atrophy and MTS.[135] Due to the refractoriness of status epilepticus, patients frequently need pharmacologically-induced coma. Anesthetics are often inefficient and their prolonged use seems to negatively influence cognitive outcome.[136]

The etiology of FIRES is unclear.[133,134,137,138] Although inflammation is thought to play a pathogenic role, the evidence is inconclusive. CSF oligoclonal bands and testing for neuronal autoantibodies are usually negative.[133,134,139] A few patients have been reported with antibodies against VGKC complex (unknown antigen), GAD65, or GluA3, but

these findings were not confirmed in other studies.[133,139] Immunotherapy is usually ineffective.[133,134,136]

NORSE is a descriptive term used to indicate the onset of refractory status epilepticus in adults or children without a previous history of epilepsy.[140] A multicenter study on patients with NORSE for whom the underlying etiology could not be determined during the first 48 hours of presentation, found that in 40% the cause was autoimmune and in the other 60% the cause remained unknown.[34] In recent reports, the use of immunotherapy improved the outcome of 42–75% of patients with NORSE but approximately 30% developed chronic epilepsy.[141,142]

CONCLUSIONS

In patients with AE and seizures associated to antibodies against neuronal cell-surface proteins, the response to immunotherapy is substantially better than in those with CNS disorders that appear to be related to T-cell mediated mechanisms, such as RE or GAD65 antibody-associated epilepsy. The long-term risk to develop epilepsy is low in neuronal cell-surface antibody-associated AE (<15%) and moderate in NORSE (30%). Future studies should assess whether early recognition of these disorders and prompt immunotherapy decrease the risk of chronic epilepsy, and whether T-cell targeted immunotherapies may have a role in some disorders. A better understanding of the inflammatory processes underlying chronic epileptogenesis is critical for developing novel treatments.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest,

** of outstanding interest.

1. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE Official Report: A practical clinical definition of epilepsy. Epilepsia. 2014; 55:475–482. [PubMed: 24730690]

2*. Vezzani A, Fujinami RS, White HS, et al. Infections, inflammation and epilepsy. Acta Neuropathol. 2016; 131:211–234. Review of infectious and non-infectious inflammatory causes of seizures and epilepsy, focusing on the inflammatory pathways involved in seizure generation and epileptogenesis. [PubMed: 26423537]

3. Pernot F, Heinrich C, Barbier L, et al. Inflammatory changes during epileptogenesis and spontaneous seizures in a mouse model of mesiotemporal lobe epilepsy. Epilepsia. 2011; 52:2315–2325. [PubMed: 21955106]

4. Matin N, Tabatabaie O, Falsaperla R, et al. Epilepsy and innate immune system: A possible immunogenic predisposition and related therapeutic implications. Hum Vaccin Immunother. 2015; 11:2021–9. [PubMed: 26260962]

5. Verhelst H, Boon P, Buyse G, et al. Steroids in intractable childhood epilepsy: Clinical experience and review of the literature. Seizure. 2005; 14:412–421. [PubMed: 16087358]

6. Dubé CM, Brewster AL, Baram TZ. Febrile seizures: Mechanisms and relationship to epilepsy. Brain Dev. 2009; 31:366–371. [PubMed: 19232478]

7. Cross JH. Fever and fever-related epilepsies. Epilepsia. 2012; 53:3–8.

8. Shoenfeld Y, Lev S, Blatt I, et al. Features associated with epilepsy in the antiphospholipid syndrome. J Rheumatol. 2004; 31:1344–8. [PubMed: 15229954]

9. Harboe E, Tjensvoll AB, Maroni S, et al. Neuropsychiatric syndromes in patients with systemic lupus erythematosus and primary Sjögren syndrome: a comparative population-based study. Ann Rheum Dis. 2009; 68:1541–1546. [PubMed: 18930990]

10. Delalande S, de Seze J, Fauchais A-L, et al. Neurologic Manifestations in Primary Sjögren Syndrome. Medicine (Baltimore). 2004; 83:280–291. [PubMed: 15342972]

11. Aykutlu E, Baykan B, Serdarolu P, et al. Epileptic seizures in Behçet disease. Epilepsia. 2002; 43:832–835. [PubMed: 12181001]

12. Benavente L, Morís G. Neurologic disorders associated with inflammatory bowel disease. Eur J Neurol. 2011; 18:138–143. [PubMed: 20500801]

13. Ludvigsson JF, Zingone F, Tomson T, et al. Increased risk of epilepsy in biopsy-verified celiac disease: A population-based cohort study. Neurology. 2012; 78:1401–1407. [PubMed: 22517096]

14. Nishino H, Rubino FA, DeRemee RA, et al. Neurological involvement in Wegener's granulomatosis: An analysis of 324 consecutive patients at the Mayo Clinic. Ann Neurol. 1993; 33:4–9. [PubMed: 8388187]

15. Baumann RJ, Robertson WC. Neurosarcoid presents differently in children than in adults. Pediatrics. 2003; 112:e480–6. [PubMed: 14654650]

16. Nowak DA, Widenka DC. Neurosarcoidosis: a review of its intracranial manifestation. J Neurol. 2001; 248:363–72. [PubMed: 11437156]

17. Ong M-S, Kohane IS, Cai T, et al. Population-Level Evidence for an Autoimmune Etiology of Epilepsy. JAMA Neurol. 2014; 71:569. [PubMed: 24687183]

18. Appenzeller S, Cendes F, Costallat LTL. Epileptic seizures in systemic lupus erythematosus. Neurology. 2004; 63:1808–12. [PubMed: 15557494]

19. Hanly JG, Urowitz MB, Su L, et al. Seizure disorders in systemic lupus erythematosus results from an international, prospective, inception cohort study. Ann Rheum Dis. 2012; 71:1502–1509. [PubMed: 22492779]

20. Eriksson K, Peltola J, Keränen T, et al. High prevalence of antiphospholipid antibodies in children with epilepsy: A controlled study of 50 cases. Epilepsy Res. 2001; 46:129–137. [PubMed: 11463514]

21. Peltola JT, Haapala A, Isojärvi JI, et al. Antiphospholipid and antinuclear antibodies in patients with epilepsy or new-onset seizure disorders. Am J Med. 2000; 109:712–7. [PubMed: 11137486]

22. Emsley HCA, Appleton RE, Whitmore CL, et al. Variations in inflammation-related genes may be associated with childhood febrile seizure susceptibility. Seizure. 2014; 23:457–61. [PubMed: 24703484]

23. Turrin NP, Rivest S. Innate immune reaction in response to seizures: Implications for the neuropathology associated with epilepsy. Neurobiol Dis. 2004; 16:321–334. [PubMed: 15193289]

24*. Gorter JA, Van Vliet EA, Aronica E. Status epilepticus, blood-brain barrier disruption, inflammation, and epileptogenesis. Epilepsy Behav. 2015; 49:13–16. Review on the mechanisms of disruption of the blood-brain barrier induced by status epilepticus and their relevance to epileptogenesis. [PubMed: 25958228]

25*. Wright S, Hashemi K, Stasiak L, et al. Epileptogenic effects of NMDAR antibodies in a passive transfer mouse model. Brain. 2015; 138:3159–3167. The authors show that mice receiving a single cerebroventricular injection of total serum IgG from patients with anti-NMDAR encephalitis showed a diminished threshold for pentylenetetrazol-induced seizures. [PubMed: 26373601]

26. Brenner T, Sills GJ, Hart Y, et al. Prevalence of neurologic autoantibodies in cohorts of patients with new and established epilepsy. Epilepsia. 2013; 54:1028–1035. [PubMed: 23464826]
27. Lilleker JB, Jones MS, Mohanraj R. VGKC complex antibodies in epilepsy: diagnostic yield and therapeutic implications. Seizure. 2013; 22:776–9. [PubMed: 23838087]
28. Liimatainen S, Peltola J, Hietaharju A, et al. Lack of antibodies to NMDAR or VGKC-complex in GAD and cardiolipin antibody-positive refractory epilepsy. Epilepsy Res. 2014; 108:592–596. [PubMed: 24447612]
29. Quek AML, Britton JW, McKeon A, et al. Autoimmune epilepsy: clinical characteristics and response to immunotherapy. Arch Neurol. 2012; 69:582–93. [PubMed: 22451162]
30. Suleiman J, Wright S, Gill D, et al. Autoantibodies to neuronal antigens in children with new-onset seizures classified according to the revised ILAE organization of seizures and epilepsies. Epilepsia. 2013; 54:2091–2100. [PubMed: 24151870]
31. Wright S, Geerts AT, Jol-Van Der Zijde CM, et al. Neuronal antibodies in pediatric epilepsy: Clinical features and long-term outcomes of a historical cohort not treated with immunotherapy. Epilepsia. 2016; 57:823–831. [PubMed: 26996997]
32*. Spatola M, Novy J, Du Pasquier R, et al. Status epilepticus of inflammatory etiology. Neurology. 2015; 85:464–470. Restrospective study of 570 patients with status epilepticus of all causes (except anoxia). Only 6% of the patients had an inflammatory cause; inflammatory disorders predominated in younger patients, and their seizures were often refractory to initial antiepileptic treatment. [PubMed: 26092915]
33. Holzer FJ, Rossetti AO, Heritier-Barras A-C, et al. Antibody-mediated status epilepticus: a retrospective multicenter survey. Eur Neurol. 2012; 68:310–7. [PubMed: 23051892]
34. Gaspard N, Foreman BP, Alvarez V, et al. New-onset refractory status epilepticus. Neurology. 2015; 85:1604–1613. [PubMed: 26296517]
35. Holtkamp M, Othman J, Buchheim K, Meierkord H. Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. J Neurol Neurosurg Psychiatry. 2005; 76:534–539. [PubMed: 15774441]
36. Irani SR, Alexander S, Waters P, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain. 2010; 133:2734–2748. [PubMed: 20663977]
37. Lai M, Huijbers MG, Lancaster E, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol. 2010; 9:776–785. [PubMed: 20580615]
38**. Van Sonderen A, Thijs RD, Coenders EC, et al. Anti-LGI1 encephalitis: Clinical syndrome and long-term follow-up. Neurology. 2016; 87:1449–1456. Nationwide study of the clinical manifestations of LGI1-antibody associated encephalitis focusing on the long-term outcome, residual seizures, and cognitive dysfunction. [PubMed: 27590293]
39*. Van Sonderen A, Ariño H, Petit-Pedrol M, et al. The clinical spectrum of Caspr2 antibody-associated disease. Neurology. 2016; 87:521–528. Clinical and immunological characterization of a large cohort of patients with CASPR2 antibody-associated neurological disorders. [PubMed: 27371488]
40**. Joubert B, Saint-Martin M, Noraz N, et al. Characterization of a Subtype of Autoimmune Encephalitis With Anti-Contactin-Associated Protein-like 2 Antibodies in the Cerebrospinal Fluid, Prominent Limbic Symptoms, and Seizures. JAMA Neurol. 2016; 73:1–10. Retrospective study on patients with CASPR2-antibody associated disorders showing that patients with CSF antibodies were more likely to develop limbic encephalitis, whereas those with serum antibodies were more likely to have Morvan syndrome and neuromyotonia.
41*. Ariño H, Armangué T, Petit-Pedrol M, et al. Anti-LGI1–associated cognitive impairment. Neurology. 2016; 87:759–765. Retrospective study focused on residual cognitive deficits in patients with LGI1-antibody associated disorders. [PubMed: 27466467]
42. Graus F, Gorman MP. Voltage-gated potassium channel antibodies. Neurology. 2016; 86:1657–1658. [PubMed: 27037235]

43**. Van Sonderen A, Schreurs MWJ, De Bruijn MAAM, et al. The relevance of VGKC positivity in the absence of LGI1 and Caspr2 antibodies. Neurology. 2016; 86:1692–1699. Study showing that determination of VGKC-complex antibodies have very limited clinical utility unless they associate with antibodies against LGI1 or CASPR2. [PubMed: 27037230]

44. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013; 12:157–165. [PubMed: 23290630]

45. Lancaster E, Lai M, Peng X, et al. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. Lancet Neurol. 2010; 9:67–76. [PubMed: 19962348]

46. Höftberger R, Titulaer MJ, Sabater L, et al. Encephalitis and GABAB receptor antibodies: Novel findings in a new case series of 20 patients. Neurology. 2013; 81:1500–1506. [PubMed: 24068784]

47. Petit-Pedrol M, Armangue T, Peng X, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. Lancet Neurol. 2014; 13:276–86. [PubMed: 24462240]

48**. Flanagan EP, Kotsenas AL, Britton JW, et al. Basal ganglia T1 hyperintensity in LGI1-autoantibody faciobrachial dystonic Seizures. Neurology. 2015; 2:e161. Study showing that patients with LGI1-antibody associated facio-brachial-dystonic seizures often have T1 MRI abnormalities in the basal ganglia.

49. Malter MP, Frisch C, Schoene-Bake JC, et al. Outcome of limbic encephalitis with VGKC-complex antibodies: relation to antigenic specificity. J Neurol. 2014; 261:1695–1705. [PubMed: 24935858]

50*. Finke C, Prüss H, Heine J, et al. Evaluation of Cognitive Deficits and Structural Hippocampal Damage in Encephalitis With Leucine-Rich, Glioma-Inactivated 1 Antibodies. JAMA Neurol. 2016; 74:50–59. High-resolution MRI study on 30 patients with anti-LGI1 encephalitis, showing that hippocampal atrophy and microstructural changes correlate with verbal and visuo-spatial memory residual deficits, as well as longer delay to immunotherapy initiation.

51. Pettingill P, Kramer HB, Coebergh JA, et al. Antibodies to GABAA receptor α1 and γ2 subunits: clinical and serologic characterization. Neurology. 2015; 84:1233–41. [PubMed: 25636713]

52*. Spatola M, Petit-Pedrol M, Simabukuro MM, et al. Investigations in GABA A receptor antibody-associated encephalitis. Neurology. in press. Case series of 26 patients describing the clinical manifestations and triggers of the disease in children and adults; most patients had multifocal MRI abnormalities.

53. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 2008; 7:1091–1098. [PubMed: 18851928]

54. Haberlandt E, Ensslen M, Gruber-Sedlmayr U, et al. Epileptic Phenotypes, Electroclinical Features and Clinical Characteristics in 17 Children with Anti-NMDAR Encephalitis. Eur J Paediatr Neurol. 2016; doi: 10.1016/j.ejpn.2016.11.016

55. Irani SR, Bera K, Waters P, et al. N-methyl-d-aspartate antibody encephalitis: Temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain. 2010; 133:1655–1667. [PubMed: 20511282]

56. Lai M, Hughes EG, Peng X, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol. 2009; 65:424–34. [PubMed: 19338055]

57*. Höftberger R, van Sonderen A, Leypoldt F, et al. Encephalitis and AMPA receptor antibodies: Novel findings in a case series of 22 patients. Neurology. 2015; 84:2403–12. Case series of 22 patients with anti-AMPAR encephalitis, expanding the clinical spectrum, tumor association, and response to immunotherapy. The long-term outcome was found influenced by presence of a tumor and onconeuronal antibodies. [PubMed: 25979696]

58. Tobin WO, Lennon VA, Komorowski L, et al. DPPX potassium channel antibody: Frequency, clinical accompaniments, and outcomes in 20 patients. Neurology. 2014:83.

59. Hara M, Ariño H, Petit-pedrol M, et al. DPPX-antibody associated encephalitis: main syndrome and antibody effects. Neurology. in press.

60. Boronat A, Gelfand JM, Gresa-Arribas N, et al. Encephalitis and antibodies to dipeptidyl-peptidase-like protein-6, a subunit of Kv4. 2 potassium channels. Ann Neurol. 2013; 73:120–128. [PubMed: 23225603]

61. Lancaster E, Martinez-Hernandez E, Titulaer MJ, et al. Antibodies to metabotropic glutamate receptor 5 in the Ophelia syndrome. Neurology. 2011; 77:1698–1701. [PubMed: 22013185]

62. Mat A, Adler H, Merwick A, et al. Ophelia syndrome with metabotropic glutamate receptor 5 antibodies in CSF. Neurology. 2013; 42:7–8.

63. Pruss H, Rothkirch M, Kopp U, et al. Limbic encephalitis with mGluR5 antibodies and immunotherapy-responsive prosopagnosia. Neurology. 2014; 83:1384–1386. [PubMed: 25194012]

64. Carvajal-González A, Leite MI, Waters P, et al. Glycine receptor antibodies in PERM and related syndromes: Characteristics, clinical features and outcomes. Brain. 2014; 137:2178–2192. [PubMed: 24951641]

65. Zuliani L, Ferlazzo E, Andrigo C, et al. Glycine receptor antibodies in 2 cases of new, adult-onset epilepsy. Neurol Neuroimmunol Neuroinflammation. 2014; 1:e16.

66*. Gresa-Arribas N, Planagumà J, Petit-Pedrol M, et al. Human neurexin-3α antibodies associate with encephalitis and alter synapse development. Neurology. 2016; 86:2235–42. Description of a novel neuronal antibody associated with autoimmune encephalitis and its pathogenic effects in cultured neurons. [PubMed: 27170573]

67. Viaccoz A, Desestret V, Ducray F, et al. Clinical specificities of adult male patients with NMDA receptor antibodies encephalitis. Neurology. 2014; 82:556–563. [PubMed: 24443452]

68. Titulaer MJ, Dalmau J. Seizures as first symptom of anti-NMDA receptor encephalitis are more common in men. Neurology. 2014; 82:550–551. [PubMed: 24443450]

69. Schmitt SE, Pargeon K, Frechette ES, et al. Extreme delta brush; A unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology. 2012; 79:1094–1100. [PubMed: 22933737]

70**. Navarro V, Kas A, Apartis E, et al. Motor cortex and hippocampus are the two main cortical targets in LGI1-antibody encephalitis. Brain. 2016; 139:1079–1093. Study combining EEG, MRI and PET analysis in patients with LGI1-antibody associated encephalitis, suggesting that progressive changes in seizures and cognitive impairment during the course of the disease correspond to different involvement of specific brain regions. [PubMed: 26945884]

71. Irani SR, Michell AW, Lang B, et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Ann Neurol. 2011; 69:892–900. [PubMed: 21416487]

72. Irani SR, Stagg CJ, Schott JM, et al. Faciobrachial dystonic seizures: The influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. Brain. 2013; 136:3151–3162. [PubMed: 24014519]

73. Toledano M, Britton JW, McKeon a, et al. Utility of an immunotherapy trial in evaluating patients with presumed autoimmune epilepsy. Neurology. 2014; 82:1578–86. [PubMed: 24706013]

74. Byun JI, Lee ST, Jung KH, et al. Effect of immunotherapy on seizure outcome in patients with autoimmune encephalitis: A prospective observational registry study. PLoS One. 2016; 11:e0146455. [PubMed: 26771547]

75. 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. Am J Neuroradiol. 2014; 35:84–89. [PubMed: 23868165]

76**. Finke C, Kopp UA, Pajkert A, et al. Structural Hippocampal Damage Following Anti-N-Methyl-D-Aspartate Receptor Encephalitis. Biol Psychiatry. 2014; 79:727–734. This MRI study shows that hippocampal structural damage and decreased volume associate with disease duration, severity, and residual memory deficits in anti-NMDAR encephalitis.

77. Mohammad SS, Sinclair K, Pillai S, et al. Herpes simplex encephalitis relapse with chorea is associated with autoantibodies to N-Methyl-D-aspartate receptor or dopamine-2 receptor. Mov Disord. 2014; 29:117–122. [PubMed: 24115338]

78*. Armangue T, Moris G, Cantarín-Extremera V, et al. Autoimmune post-herpes simplex encephalitis of adults and teenagers. Neurology. 2015; 85:1736–43. Prospective study of 14 young adults with autoimmune encephalitis triggered by herpes simplex encephalitis, focusing on the clinical, CSF and MRI differences between adults and previously reported children. [PubMed: 26491084]

79. Almeida V, Pimentel J, Campos A, et al. Surgical control of limbic encephalitis associated with LGI1 antibodies. Epileptic Disord. 2012; 14:345–348. [PubMed: 22940785]
80. Carreño M, Bien C, Asadi-Pooya A, et al. Epilepsy surgery in drug resistant temporal lobe epilepsy associated with neuronal antibodies. Epilepsy Res. in press.
81. Mathon B, Bédos Ulvin L, Adam C, et al. Surgical treatment for mesial temporal lobe epilepsy associated with hippocampal sclerosis. Rev Neurol (Paris). 2015; 171:315–325. [PubMed: 25746582]
82. O'Connor KC, McLaughlin KA, De Jager PL, et al. Self-antigen tetramers discriminate between myelin autoantibodies to native or denatured protein. Nat Med. 2007; 13:211–217. [PubMed: 17237795]
83. Pröbstel AK, Dornmair K, Bittner R, et al. Antibodies to MOG are transient in childhood acute disseminated encephalomyelitis. Neurology. 2011; 77:580–8. [PubMed: 21795651]
84. Baumann M, Sahin K, Lechner C, et al. Clinical and neuroradiological differences of paediatric acute disseminating encephalomyelitis with and without antibodies to the myelin oligodendrocyte glycoprotein. J Neurol Neurosurg Psychiatry. 2015; 86:265–272. [PubMed: 25121570]
85. Hacohen Y, Absoud M, Deiva K, et al. Myelin oligodendrocyte glycoprotein antibodies are associated with a non-MS course in children. Neurol Neuroimmunol Neuroinflammation. 2015; 2:e81.
86. Hacohen Y, Nishimoto Y, Fukami Y, et al. Paediatric brainstem encephalitis associated with glial and neuronal autoantibodies. Dev Med Child Neurol. 2016; 58:836–841. [PubMed: 26918533]
87. Spadaro M, Gerdes LA, Krumbholz M, et al. Autoantibodies to MOG in a distinct subgroup of adult multiple sclerosis. Neurol Neuroimmunol Neuroinflammation. 2016; 3:e257.
88. Hino-Fukuyo N, Haginoya K, Nakashima I, et al. Clinical features and long-term outcome of a group of Japanese children with inflammatory central nervous system disorders and seropositivity to myelin-oligodendrocyte glycoprotein antibodies. Brain Dev. 2015; 37:849–852. [PubMed: 25748628]
89. Di Pauli F, Mader S, Rostasy K, et al. Temporal dynamics of anti-MOG antibodies in CNS demyelinating diseases. Clin Immunol. 2011; 138:247–254. [PubMed: 21169067]
90*. Fernandez-Carbonell C, Vargas-Lowy D, Musallam A, et al. Clinical and MRI phenotype of children with MOG antibodies. Mult Scler. 2016; 22:174–84. In this study 17% of children with demyelinating syndromes had MOG antibodies. Patients with MOG antibodies were younger, did not have MRI lesions in the corpus callosum, and had similar relapse rate and disability scores compared with seronegative patients. [PubMed: 26041801]
91. Kitley J, Woodhall M, Waters P, et al. Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype. Neurology. 2012; 79:1273–1277. [PubMed: 22914827]
92. Saiz A, Blanco Y, Sabater L, et al. Spectrum of neurological syndromes associated with glutamic acid decarboxylase antibodies: diagnostic clues for this association. Brain. 2008; 131:2553–2563. [PubMed: 18687732]
93. Malter MP, Helmstaedter C, Urbach H, et al. Antibodies to glutamic acid decarboxylase define a form of limbic encephalitis. Ann Neurol. 2010; 67:470–478. [PubMed: 20437582]
94. Liimatainen S, Peltola M, Sabater L, et al. Clinical significance of glutamic acid decarboxylase antibodies in patients with epilepsy. Epilepsia. 2010; 51:760–767. [PubMed: 19817821]
95. Peltola J, Kulmala P, Isojärvi J, et al. Autoantibodies to glutamic acid decarboxylase in patients with therapy-resistant epilepsy. Neurology. 2000; 55:46–50. [PubMed: 10891904]
96. Veri K, Uibo O, Talvik T, et al. Newly-diagnosed pediatric epilepsy is associated with elevated autoantibodies to glutamic acid decarboxylase but not cardiolipin. Epilepsy Res. 2013; 105:86–91. [PubMed: 23538270]
97. Baekkeskov S, Aanstoot HJ, Christgau S, et al. Identification of the 64K autoantigen in insulin-dependent diabetes as the GABA-synthesizing enzyme glutamic acid decarboxylase. Nature. 1990; 347:151–156. [PubMed: 1697648]
98. Petersen JS, Hejnæs KR, Moody A, et al. Detection of GAD65 antibodies in diabetes and other autoimmune diseases using a simple radioligand assay. Diabetes. 1994; 43:459–467. [PubMed: 8314020]

99. Meinck HM, Faber L, Morgenthaler N, et al. Antibodies against glutamic acid decarboxylase: prevalence in neurological diseases. J Neurol Neurosurg Psychiatry. 2001; 71:100–3. [PubMed: 11413272]

100*. Gresa-Arribas N, Ariño H, Martinez-Hernandez E, et al. Antibodies to inhibitory synaptic proteins in neurological syndromes associated with glutamic acid decarboxylase autoimmunity. PLoS One. 2015; 10:e0121364. Study of serum and CSF from 106 patients with anti-GAD65 associated neurological disorders showing no syndrome-epitope specificity; CSF antibody titers were found higher in patients with cerebellar ataxia and limbic encephalitis, and lower in stiff-person syndrome. [PubMed: 25774787]

101. Hansen N, Widman G, Witt JA, et al. Seizure control and cognitive improvement via immunotherapy in late onset epilepsy patients with paraneoplastic versus GAD65 autoantibody-associated limbic encephalitis. Epilepsy Behav. 2016; 65:18–24. [PubMed: 27855355]

102. Malter MP, Frisch C, Zeitler H, et al. Treatment of immune-mediated temporal lobe epilepsy with GAD antibodies. Seizure. 2015; 30:57–63. [PubMed: 26216686]

103. Kupila L, Jutila L, Immonen A, et al. Late-onset Rasmussen's encephalitis and long-term remission. Epileptic Disord. 2011; 13:88–91. [PubMed: 21393098]

104. Sanfilippo C, Giuliano L, Fatuzzo D, et al. Late onset Rasmussen encephalitis: complete remission after one session of plasmapheresis. Eur J Neurol. 2016; 23:e15–e16. [PubMed: 26918748]

105. Hunter GR, Donat J, Pryse-Phillips W, et al. Rasmussen's encephalitis in a 58-year-old female: still a variant? Can J Neurol Sci. 2006; 33:302–305. [PubMed: 17001818]

106. Lamb K, Scott W, Mensah A. Prevalence and clinical outcome of Rasmussen encephalitis in children from the United Kingdom. Dev Med Child Neuorlogy. 2013; 55:1–14.

107. Wagner J, Schoene-Bake JC, Bien CG, et al. Automated 3D MRI volumetry reveals regional atrophy differences in Rasmussen encephalitis. Epilepsia. 2012; 53:613–621. [PubMed: 22309137]

108. Bien CG, Urbach H, Deckert M, et al. Diagnosis and staging of Rasmussen's encephalitis by serial MRI and histopathology. Neurology. 2002; 58:250–257. [PubMed: 11805253]

109. Freeman JM. Rasmussen's syndrome: Progressive autoimmune multi-focal encephalopathy. Pediatr Neurol. 2005; 32:295–299. [PubMed: 15866428]

110. Bien CG, Bauer J, Deckwerth TL, et al. Destruction of neurons by cytotoxic T cells: A new pathogenic mechanism in Rasmussen's encephalitis. Ann Neurol. 2002; 51:311–318. [PubMed: 11891826]

111. Pardo CA, Vining EPG, Guo L, et al. The Pathology of Rasmussen Syndrome: Stages of Cortical Involvement and Neuropathological Studies in 45 Hemispherectomies. Epilepsia. 2004; 45:516–526. [PubMed: 15101833]

112. Li Y, Uccelli A, Laxer KD, et al. Local-clonal expansion of infiltrating T lymphocytes in chronic encephalitis of Rasmussen. J Immunol. 1997; 158:1428–37. [PubMed: 9013988]

113. Baranzini SE, Laxer K, Saketkhoo R, et al. Analysis of antibody gene rearrangement, usage, and specificity in chronic focal encephalitis. Neurology. 2002; 58:709–716. [PubMed: 11889232]

114. Rogers SW, Andrews PI, Gahring LC, et al. Autoantibodies to glutamate receptor GluR3 in Rasmussen's encephalitis. Science. 1994; 265:648–51. [PubMed: 8036512]

115. Nibber A, Clover L, Pettingill P, et al. Antibodies to AMPA receptors in Rasmussen's encephalitis. Eur J Paediatr Neurol. 2016; 20:222–227. [PubMed: 26785913]

116. Wiendl H, Bien CG, Bernasconi P, et al. GluR3 antibodies: prevalence in focal epilepsy but no specificity for Rasmussen's encephalitis. Neurology. 2001; 57:1511–4. [PubMed: 11673604]

117. Mantegazza R, Bernasconi P, Baggi F, et al. Antibodies against GluR3 peptides are not specific for Rasmussen's encephalitis but are also present in epilepsy patients with severe, early onset disease and intractable seizures. J Neuroimmunol. 2002; 131:179–85. [PubMed: 12458050]

118. Watson R, Jepson JEC, Bermudez I, et al. Alpha7-Acetylcholine receptor antibodies in two patients with Rasmussen encephalitis. Neurology. 2005; 65:1802–1804. [PubMed: 16344526]

119. Yang R, Puranam RS, Butler LS, et al. Autoimmunity to munc-18 in Rasmussen's encephalitis. Neuron. 2000; 28:375–83. [PubMed: 11144349]

120. Takahashi Y, Mori H, Mishina M, et al. Autoantibodies and cell-mediated autoimmunity to NMDA-type GluRε2 in patients with Rasmussen's encephalitis and chronic progressive epilepsia partialis continua. Epilepsia. 2005; 46:152–158. [PubMed: 15987271]

121. Samanci B, Tektürk P, Tüzün E, et al. Neuronal autoantibodies in patients with Rasmussen's encephalitis. Epileptic Disord. 2016; 18:204–10. [PubMed: 27248684]

122. Takahashi Y, Mori H, Mishina M, et al. Autoantibodies to NMDA receptor in patients with chronic forms of epilepsia partialis continua. Neurology. 2003; 61:891–6. [PubMed: 14557555]

123. Gleichman AJ, Panzer JA, Baumann BH, et al. Antigenic and mechanistic characterization of anti-AMPA receptor encephalitis. Ann Clin Transl Neurol. 2014; 1:180–189. [PubMed: 24707504]

124. Fukuyama T, Takahashi Y, Kubota Y, et al. Semi-quantitative analyses of antibodies to N-methyl-d-aspartate type glutamate receptor subunits (GluN2B & GluN1) in the clinical course of Rasmussen syndrome. Epilepsy Res. 2015; 113:34–43. [PubMed: 25986190]

125. Granata T, Fusco L, Gobbi G, et al. Experience with immunomodulatory treatments in Rasmussen's encephalitis. Neurology. 2003; 61:1807–1810. [PubMed: 14694056]

126. Takahashi Y, Yamazaki E, Mine J, et al. Immunomodulatory therapy versus surgery for Rasmussen syndrome in early childhood. Brain Dev. 2013; 35:778–785. [PubMed: 23433490]

127. Bien CG, Gleissner U, Sassen R, et al. An open study of tacrolimus therapy in Rasmussen encephalitis. Neurology. 2004; 62:2106–2109. [PubMed: 15184626]

128. Laxer K, Wilfong A, Morris G, Andermann F. Pilot study of Rituximab to treat chronic focal encephalitis. Epilepsia. 2008; 49:121.

129. Thilo B, Stingele R, Knudsen K, et al. A case of Rasmussen encephalitis treated with rituximab. Nat Rev Neurol. 2009; 5:458–62. [PubMed: 19657347]

130. Bittner S, Simon OJ, Gobel K, et al. Rasmussen encephalitis treated with natalizumab. Neurology. 2013; 81:395–397. [PubMed: 23794679]

131. Bien CG, Schramm J. Treatment of Rasmussen encephalitis half a century after its initial description: Promising prospects and a dilemma. Epilepsy Res. 2009; 86:101–112. [PubMed: 19615863]

132. Van Baalen A, Häusler M, Boor R, et al. Febrile infection-related epilepsy syndrome (FIRES): A nonencephalitic encephalopathy in childhood. Epilepsia. 2010; 51:1323–1328. [PubMed: 20345937]

133. Kramer U, Chi C-S, Lin K-L, et al. Febrile infection-related epilepsy syndrome (FIRES): pathogenesis, treatment, and outcome: a multicenter study on 77 children. Epilepsia. 2011; 52:1956–65. [PubMed: 21883180]

134. Nabbout R, Vezzani A, Dulac O, Chiron C. Acute encephalopathy with inflammation-mediated status epilepticus. Lancet Neurol. 2011; 10:99–108. [PubMed: 21163447]

135. Rivas-Coppola MS, Shah N, Choudhri AF, et al. Chronological Evolution of Magnetic Resonance Imaging Findings in Children with Febrile Infection-Related Epilepsy Syndrome. Pediatr Neurol. 2016; 55:22–29. [PubMed: 26597039]

136. Kramer U, Chi CS, Lin KL, et al. Febrile infection-related epilepsy syndrome (FIRES): Does duration of anesthesia affect outcome? Epilepsia. 2011; 52:28–30.

137. Bindoff LA, Engelsen BA. Mitochondrial diseases and epilepsy. Epilepsia. 2012; 53:92–97. [PubMed: 22946726]

138. Appenzeller S, Helbig I, Stephani U, et al. Febrile infection-related epilepsy syndrome (FIRES) is not caused by SCN1A, POLG, PCDH19 mutations or rare copy number variations. Dev Med Child Neurol. 2012; 54:1144–1148. [PubMed: 23066759]

139. Van Baalen A, Häusler M, Plecko-Startinig B, et al. Febrile infection-related epilepsy syndrome without detectable autoantibodies and response to immunotherapy: A case series and discussion of epileptogenesis in FIRES. Neuropediatrics. 2012; 43:209–216. [PubMed: 22911482]

140. Costello DJ, Kilbride RD, Cole AJ. Cryptogenic New Onset Refractory Status Epilepticus (NORSE) in adults—Infectious or not? J Neurol Sci. 2009; 277:26–31. [PubMed: 19013586]

141. Li J, Saldivar C, Maganti RK. Plasma exchange in cryptogenic new onset refractory status epilepticus. Seizure. 2013; 22:70–73. [PubMed: 23068971]

142. Khawaja AM, DeWolfe JL, Miller DW, Szaflarski JP. New-onset refractory status epilepticus (NORSE) —The potential role for immunotherapy. Epilepsy Behav. 2015; 47:17–23. [PubMed: 26010959]

KEY POINTS

- Most patients with AE associated to antibodies against neuronal cell-surface antigens develop seizures. However, after the encephalitis is successfully treated, the risk of developing chronic epilepsy is low (< 15%).
- The subtypes of AE that more frequently associate with seizures are those related to antibodies against $GABA_AR$, $GABA_BR$, LGI1, CASPR2, AMPAR, and NMDAR. Patients with ADEM or CIS may also develop seizures, and rarely develop epilepsy. Some of these patients have MOG antibodies.
- In AE, the assessment of symptoms, EEG, and MRI may suggest the underlying immune response. For example, FBDS characteristically occur in patients with LGI1 antibodies and often precede the development of a full-blown encephalopathy. The EEG pattern « extreme delta brush» associates with anti-NMDAR encephalitis. The occurrence of multiple cortical-subcortical FLAIR MRI abnormalities suggests anti-$GABA_AR$ encephalitis.
- Patients with seizure disorders associated to antibodies against neuronal cell-surface proteins or receptors, or patients with ADEM, usually respond to immunotherapy. In contrast, patients with seizure disorders without these antibodies (RE, FIRES) or with antibodies against intracellular proteins (GAD65) are much less responsive to immunotherapy.

Table 1

Clinical features and seizure type in autoimmune encephalitis associated with antibodies to neuronal cell-surface antigens.

	LGI1 [38,41*,48**,49,50*]**	**$GABA_AR$ [47,52*,51]**	**$GABA_BR$ [45,46]**	**NMDAR [44,53–55]**	**AMPAR [56,57*]**	**mGluR5 [61–63],§**	**DPPX [59,60]**	**GlyR [64,65]**	**CASPR2 [39*,40**]**	**Neurexin3α [66*]**
Median age (y), Occurs in children, Gender	61 No M≫F	40 Yes F=M	62 No M>F	22 Yes F≫M	61 No F>M	29 Yes F=M	58 Rare M≫F	50 Yes F=M	61 No M≫F	43 No M<F
Seizure frequencyand type (% of all cases)	Any type 90%;FBDS 47%, focal 66%, generalized 63%	Any type 88%; focal 81%, generalized 69%	Any type 90–100%; focal 40%, generalized 93%	Any type 76%; focal 17%, generalized 53%	Any type 36–40%; focal 10%, generalized 30%	Any type 60%;§ focal 10%, generalized 55%	Any type 22%	In patients with encephalitis ~13%	Any type 53%; in patients with LE 90%	Any type 80%
Status epilepticus	Yes	Yes (42%)	Yes (20%)	Yes	Yes	Yes (20%§)	No data	Anecdotal case reports	No data	No data
Other clinical manifestations	LE	Alteration of memory, behavior; dyskinesias	LE	Anti-NMDAR encephalitis	LE	Confusion, memory deficit, altered behavior	Confusion, psychosis, hyperekplexia, tremor, myoclonus, ataxia; GI, weight loss	Progressive encephalomyelitis with rigidity and myoclonus, Stiff-person syndrome,	LE, Morvan syndrome, neuromyotonia	Confusion, decreased level of consciousness, dyskinesias, hypoventilation
Tumor	7–11 %	38%; mostly thymoma	50–58%, mostly SCLC	20–42%, mostly ovarian teratoma	64–70%, thymoma, SCLC, breast	60%§, mostly Hodgkin's lymphoma	10%, B-cell tumors	9%, mostly thymoma	16–19%, mostly thymoma	No
Response to immunotherapy	80%	86%	60%	75–81%	70–90%	90%§	60–78%	77%	73–93%	75%
Risk of epilepsy	15%	15%	29%	Low§§	Low§§	Low§§	No data	No data	No data	No data
Relapse	27–35%	No	No	12%	16–50%	10%§	23%	11–14%	25–37%	No data

F=female; GI= prodromal gastrointestinal symptoms (diarrhea, constipation); LE= limbic encephalitis; M=males; SCLC= small-cell lung cancer.

§Spatola and Dalmau, personal communication;

§§Low = Probably <5%.