

Autoimmune epilepsies

Sarosh R. Irani^a, Christian G. Bien^b and Bethan Lang^a

^aDepartment of Clinical Neurosciences (Clinical Neurology), Oxford University, Oxford, UK and

^bDepartment of Epileptology, University of Bonn, Bonn, Germany

Correspondence to Dr Bethan Lang, Nuffield Department of Clinical Neurosciences (Clinical Neurology), West Wing Level 5/6, John Radcliffe Hospital, University of Oxford, Oxford OX3 9DU, UK
Tel: +44 1865 234531; fax: +44 1865 222402;
e-mail: bethan.lang@clneuro.ox.ac.uk

Current Opinion in Neurology 2011, 24:146–153

Purpose of review

To review the recent literature describing the detection and clinical importance of serum antibodies in patients with various epilepsies and other seizure-related disorders.

Recent findings

Auto-antibodies to the NMDA, GABA_B and AMPA receptors and to LGI1, CASPR2 and Contactin-2, components of the voltage-gated potassium channel complex, have been detected in the serum of patients with seizures. These antigenic targets are ion channels, receptors and accessory proteins important in both cellular homeostasis and governing the electrical activity of the brain. Antibodies to glutamic acid decarboxylase (GAD) have been found in patients with temporal lobe epilepsy. Antibodies to LGI1 have been described in around 90% of patients with the newly described epileptic syndrome of faciobrachial dystonic seizures.

Summary

An increasing number of antibodies have been described in the epilepsies and other seizure-related disorders. Evidence of direct pathogenicity comes from the extracellular domain targeted by all of these antibodies (other than GAD) and the often dramatic clinical and serological response to immunotherapies, when antiepileptic drugs may be ineffective. Definitive proof as to the pathological relevance of these antibodies will be achieved in the generation of an animal model that demonstrates the clinical phenotype of these antibody-mediated disorders.

Keywords

auto-antibodies, CASPR2, epilepsy, GAD, LGI1, NMDA, VGKC

Curr Opin Neurol 24:146–153
© 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins
1350-7540

Introduction

Epilepsy is the most common serious neurological disorder, affecting between 1 and 3% of the population. ‘Structural/metabolic’ and ‘genetic’ causes of epilepsy are regularly being identified; however, the majority of epilepsies are classified as having an ‘unknown cause’ [1^{••},2]. Autoimmune processes have been hypothesized as a potential cause of these etiologically undefined epilepsies (for reviews see [3–5]). There is now accumulating evidence that specific neuronal auto-antibodies with pathogenic potential may be present in a subset of patients with epilepsy. Importantly, it has recently been shown that some patients with these serum auto-antibodies are often refractory to treatment with standard anti-epileptic drugs (AEDs) and, in contrast, may respond well to immunomodulatory therapies. A link between (often antibody-defined) limbic encephalitis and chronic epilepsy is offered by the observation that in a quarter to a half of patients with adult-onset temporal lobe epilepsy (TLE) and hippocampal sclerosis, limbic encephalitis is the likely precipitating injury [6].

Following the major descriptions of the association of antibodies to voltage-gated potassium channel (VGKC)-

complexes with a treatment-responsive form of limbic encephalitis [7,8], there has been an explosion of reports in the literature associating central nervous system (CNS) disorders with serum antibodies directed against a number of surface-expressed neuronal proteins, including ion channels (NMDA, GABA_B, AMPA receptors, and, rarely, Kv1s) and ion channel-associated molecules (LGI1, CASPR2, Contactin-2). In this article, we will review the syndromes with epilepsy as a prominent feature that are associated with antibodies directed against these functionally important molecules, and will discuss recent evidence regarding their diagnosis and therapy.

Autoimmune encephalitis with seizures

The autoimmune encephalitides are a group of syndromes with subacute onset of amnesia, confusion and often prominent seizures.

Syndromes associated with antibodies to the VGKC-complex

Voltage-gated potassium channel antibodies were first described in the serum of patients with neuromyotonia, characterized by nerve terminal hyperexcitability. They were determined using a radioimmunoassay that detected

patient IgG binding to brain VGKCs labelled with iodinated dendrotoxin, a snake toxin specific for some subtypes of the Kv1 family of potassium channels. Subsequently these antibodies were recognized in a predominantly nonparaneoplastic, immunotherapy-responsive form of limbic encephalitis that frequently included seizures [7,8]. Patients typically presented with an acute or subacute onset of seizures, confusion and amnesia. Generalized and temporal lobe seizures were commonly reported. In around 60% of cases, brain MRI showed medial temporal lobe high signal and serum sodium levels were low [7,8,9^{••},10]. The cerebrospinal fluid (CSF) was usually acellular, without oligoclonal bands and VGKC-complex antibodies were often undetectable in CSF [7,8]. There was some evidence for steroids as the preferred first-line therapy and antibody levels correlated closely with clinical outcomes [7]. Furthermore, it has been suggested that the hippocampal atrophy which develops in some patients with these antibodies may be prevented with early immunotherapies [6]. More recently, some patients with isolated seizure syndromes, including drug-resistant epilepsy and TLE, have been shown to have lower titre VGKC-complex antibodies in their sera [11,12].

Antibodies to the VGKC-complex proteins LGI1, CASPR2 and Contactin-2

It has been difficult to explain why patients with apparently the same antibody exhibited such varied clinical manifestations. Within the last year, a series of papers have gone some way to explain this phenomenon [9^{••},13^{••},14,15[•]]. The dendrotoxin-labelled VGKCs immunoprecipitated by patient antibodies now appear to be a complex of at least three accessory proteins: the 'VGKC-complex'. So far, antibodies specifically directed against three proteins within the VGKC-complex, namely CASPR2, LGI1 and Contactin-2, have been described. Rarely patients may actually have antibodies directed against Kv1 channels [9^{••}]. These antibodies have been detected using an immunofluorescence cell-based assay which detects the binding of patients' sera to the surface of cells transfected with cDNA encoding the relevant accessory proteins (for example see Fig. 1c) [13^{••}].

CASPR2 antibodies have mainly been found in patients with Morvan's syndrome or neuromyotonia, many of whom have a paraneoplastic, often thymomatous, association without prominent seizures. A small proportion of patients with mediotemporal lobe epilepsy related to limbic encephalitis also have CASPR2 antibodies [9^{••},14]. The majority of patients with mediotemporal lobe epilepsy related to limbic encephalitis have LGI1 antibodies without an associated tumour [9^{••},15[•]]. Antigenic specificities are awaited in the cohorts of patients previously found to have VGKC-complex antibodies and drug-resistant epilepsy [11,12].

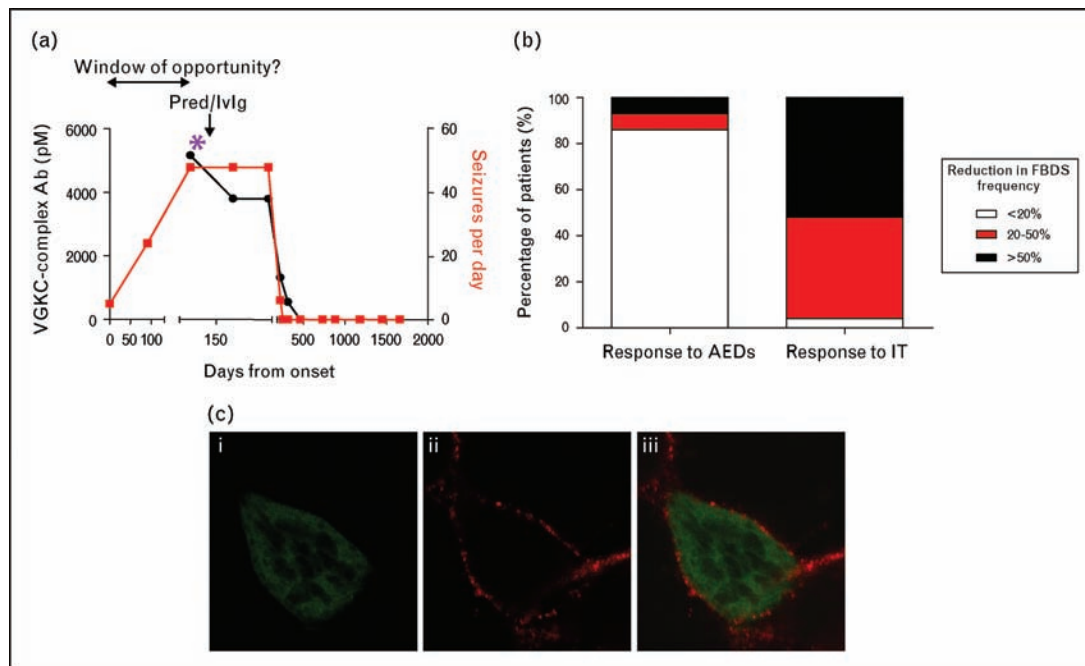
Key points

- An autoimmune cause should be considered in patients with an acute or subacute onset of seizures, especially when associated with cognitive decline and personality changes.
- Antibodies to different ion channels and receptors (NMDA, AMPA, GABA_{B1} receptors) and proteins associated with VGKCs (LGI1, CASPR2 and Contactin-2) have been found in the serum and cerebrospinal fluid of patients with seizures.
- A new clinically distinct syndrome – faciobrachial dystonic seizures (FBDS) – has been described in association with antibodies to LGI1.
- Patients, in whom antibodies to clinically relevant neuronal proteins have been detected, can respond very well to immunomodulatory therapy.

Faciobrachial dystonic seizures and LGI1 antibodies

Recently, a clinically distinctive seizure semiology has been described in adult patients with high levels of VGKC-complex antibodies and multiple, brief (<3 s) episodes of simultaneous facial grimacing and ipsilateral arm dystonia [10]. Following on from this original article, a further 26 patients with a similar seizure semiology have been reported, again with a high frequency of attacks. Overall, ictal electroencephalography (EEG) abnormalities were detectable in 24% of cases and revealed rhythmic frontotemporal spikes. This clinically distinctive syndrome has been termed faciobrachial dystonic seizures (FBDS) [13^{••}]. Many of these patients had unexplained falls and, in addition, most patients developed the full-blown picture of limbic encephalitis with amnesia and typical medial temporal lobe seizures and some generalized tonic-clonic seizures. All patients tested during their illness had high levels of VGKC-complex antibodies; the specific target was LGI1 in 90% of cases. Similar patients have been described in a detailed case report [16], with facial 'spasms' in a paper about VGKC-antibody limbic encephalitis mimicking Creutzfeldt-Jakob disease [17]; and 40% of the patients described in a separate LGI1-antibody series had 'myoclonus', which may also represent FBDS [15[•]].

The timing of the FBDS was especially interesting (Fig. 1a). In three of the 29 cases, FBDS were observed in isolation with no cognitive impairment. These three patients were treated with immunotherapies with excellent resolution [13^{••}]. In the other 26 cases, cognitive impairment was noted. In 77% of these cases, FBDS preceded the onset of limbic encephalitis (defined by amnesia and confusion). In the remaining six cases, limbic encephalitis appeared before FBDS. During the period in which only FBDS were present, serum sodium levels and MRI were normal. In contrast, when FBDS were accompanied by amnesia/confusion, 88% of patients

Figure 1 Clinical and serological responses to immunotherapy in faciobrachial dystonic seizures

(a) Patient with faciobrachial dystonic seizures (FBDS). At the onset of amnesia/confusion (*), antibodies (Ab) to the voltage-gated potassium complex (VGKC-complex) are first measured and the patient is treated with prednisolone (Pred) and intravenous immunoglobulins (Ivlg). It is hypothesized that if the patient had been treated earlier, the cognitive effects may have been avoided: 'window of opportunity'. (b) The response of FBDS after treatment with anti-epileptic drugs (AEDs) and/or immunotherapies (IT). The reduction of FBDS in patients treated with either AEDs and/or immunotherapy is shown as a percentage of the total patients in each group. (c) Binding of FBDS patient IgG to the surface of cells transfected with LGI1 cDNA: (i) LGI1/EGFP (green)-transfected human embryonic kidney cell, (ii) incubated with FBDS patient IgG (red), and (iii) merged to show binding to the cell surface. Magnification $\times 5000$. Modified from [13**].

had hyponatraemia and 54% had abnormal MRIs, commonly medial temporal high signal. Few patients responded well to AEDs, and in 41% of cases AEDs caused adverse reactions including life-threatening complications. In marked contrast, immunotherapies produced a clear and often dramatic and prompt reduction in seizure frequency (see Fig. 1a and b).

These reports suggest that FBDS may provide an early clinical clue to the presence of an immunotherapy-responsive syndrome, often associated with LGI1 antibodies, and it would be of interest to assess whether early immunotherapy during the period of FBDS alone may prevent or postpone the onset of amnesia. The question is raised: Are FBDS a potential therapeutic window of opportunity?

Antibodies to N-methyl-D-aspartate receptors

Antibodies to the NMDA receptor (NMDAR) were originally described in association with a purely paraneoplastic panencephalopathy of young women where the underlying ovarian teratoma expressed the NMDAR [18]. More recently, it has become clear that these antibodies are associated with a predominantly non-paraneoplastic disease and that both adult males and children are commonly affected [19,20**,21]. The typical

syndrome consisted of seizures and neuropsychiatric features followed by a characteristic choreoathetoid movement disorder, dysautonomia and reduction in consciousness. Seizures were seen in around 80% of these patients and a study examining the seizures in detail concluded these were usually of extratemporal origin [22]. In addition, by analogy with VGKC-complex antibodies, up to 5% of patients with NMDAR antibodies have a pure seizure disorder without prominent neuropsychiatric involvement [5]. Nonconvulsive status epilepticus and frequent drug-refractory TLE in association with NMDAR antibodies has also been observed [5,20**,23*].

Variations in clinical features, including response to immunotherapies, corresponded closely to the serum NMDAR-antibody levels. As described for the VGKC-complex antibodies, NMDAR antibodies are found at higher levels in serum than CSF. From the Oxford study, EEG and MRI data suggested a spread of the areas involved from cortex to subcortex. Specifically, early seizures and neuropsychiatric features were associated with cortical MRI changes and EEG spikes but subsequently, subcortical MRI changes and diffuse slowing/intermittent rhythmic delta activity on EEG were observed in conjunction with choreiform movements,

reduction in consciousness and dysautonomia [20**]. In-vitro experiments with neuronal cultures and chronic in-vivo administration have shown that NMDAR antibodies downregulated surface NR1 subunits. Data regarding the behavioural effects of these manipulations are awaited in animal models [24**].

In contrast to patients with VGKC-complex antibodies, however, at least 25% of untreated patients with NMDAR antibodies have disease relapses [19,20**] and preliminary evidence has suggested that recrudescence of antibodies is temporally associated with relapses. As a result of the frequent relapses and the life-threatening nature of the disorder, aggressive early immunotherapies are advocated [20**].

Encephalitis lethargica

The syndrome of encephalitis lethargica traditionally has been associated with the 1917 influenza epidemic. A recent study has recognized that many of the cardinal characteristics of encephalitis lethargica overlap with NMDAR-antibody encephalitis. In a study of 20 patients previously diagnosed with encephalitis lethargica, half of the patients had antibodies to NMDAR [25]. Interestingly, the patients with seizures were all NMDAR antibody positive, suggesting a different, as yet undefined, antigenic specificity in the subgroup without seizures.

Antibodies to GABA_B and AMPA receptors

Some patients with typical limbic encephalitis and a clear immunotherapy response had no auto-antibodies detected (e.g. [26]). Similar patients have recently been reported to have antibodies to the GABA_B receptor and 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid receptor (AMPA) [27**,28].

Antibodies to the extracellular region of the GABA_{B1} receptor have been reported in 15 patients, presenting with prominent drug-refractory seizures as well as other limbic symptoms. Seven of these had tumours, five of which were small cell lung tumours [27**]. Nine of the 10 patients who received immunotherapy and tumour treatment showed a neurological improvement by comparison to none in the untreated group.

In contrast, patients who present with limbic encephalitis in conjunction with antibodies to the AMPAR do not present so frequently with seizures: only 3/10 had seizures as presenting feature with one other patient having seizures after a relapse [28]. These two reports await reproduction by other groups to understand the full clinical spectrum of the diseases and the true paraneoplastic frequencies, but they form useful examples of other seizure-related autoimmune disorders with auto-antibodies targeting cell membrane proteins.

Classical syndromes of probable autoimmune origin

Autoimmunity, both antibody-mediated and cellular, has been associated with a number of clinically distinct syndromes; however, clear proof of pathogenicity is on the whole still lacking.

Rasmussen's encephalitis

Rasmussen's encephalitis is a severe unihemispheric syndrome that commonly starts in childhood [29]. Most patients conform to three classical stages [30] with frequent intractable partial seizures and secondary generalized seizures, followed by progressive cortical inflammation which can eventually destroy the affected hemisphere, and finally fixed neurological deficits, cognitive decline and intractable seizures. Immunomodulatory therapy can be useful early in the course of the disease. However, later on the seizures usually become resistant to treatment and hemispherectomy is often the only alternative. Antibodies to a number of different antigens have been described. However, the role of auto-antibodies in the disease development is unclear.

The role of the cellular arm of the immune system is clearer. Granzyme B-containing T cells directed at the neurones and astrocytes [31,32] have been implicated in the pathogenesis of Rasmussen's encephalitis, and oligoclonal expansions of these particular T cells have been detected both in the brain tissue and in the blood of patients with Rasmussen's encephalitis [33].

So it is surprising that the most encouraging report of a novel treatment for Rasmussen's encephalitis described the use of rituximab (a monoclonal anti-CD20), which causes the depletion of B cells. Thilo and colleagues [34] reported a patient who entered a seizure-free period after being treated with IgG immunoadsorption and intravenous rituximab; hemispherectomy was not required. Although rituximab was designed to selectively act on B cells, there may be an influence of the drug on the T cells, and in Rasmussen's encephalitis this may lead to a treatment that avoids the severe cognitive and motor impairment which result from hemispherectomy.

Temporal lobe epilepsy and glutamic acid decarboxylase antibodies

Auto-antibodies directed against the enzyme glutamic acid decarboxylase (GAD), responsible for synthesis of the inhibitory neurotransmitter GABA, have been reported in a number of patients with various forms of epilepsy. GAD antibodies are found in 60–80% of patients with type 1 diabetes at low levels. However, higher levels (>1000 units/ml) have been demonstrated in patients with various neurological conditions such as cerebellar ataxia and stiff-person syndrome (SPS). In fact,

epilepsy co-exists in up to 30% of the patients with SPS (reviewed in [35]).

In a prospective study of 253 patients with epilepsy, 15 (6%) had GAD antibodies compared to 1.5% of controls. Of the seven patients with high antibody levels, six had TLE [36]. Similar results were found in a smaller study [37]. Most intriguingly, a recent report highlighted a subpopulation of recent-onset TLE with inflammation of the mediotemporal lobes and cognitive problems, which together define these patients with a GAD-antibody-associated limbic encephalitis. The most prominent clinical problem was intractable temporal lobe epilepsy. GAD-antibody-associated limbic encephalitis with seizures were approximately as common in patients with antibodies to VGKC-complexes, but with a younger age of onset [38^{••}]. There are some reports describing clinical improvements following immunotherapies (e.g. [39–41]).

It is likely that GAD antibodies act as a marker of an underlying autoimmune disease, as it is difficult to envisage how antibodies to an intracellular enzyme could directly initiate pathological events. The recent papers highlighting the responsiveness of these patients to immunotherapy and association to localization-related forms of epilepsy suggest that antibodies with cell-surface specificities may also be present. This is supported by a functional MRI spectroscopy study in patients with TLE and elevated serum GAD antibody levels who were shown to have significantly lower GABA levels within their cortex compared to matched control patients [42^{*}]. It is interesting that some of the AMPA and GABA_B receptor-antibody-positive patients had GAD antibodies, describing potentially pathogenic antibodies in GAD-antibody-positive sera [28,29].

New syndromes of probable autoimmune origin

Epilepsy in children and adolescents can often adversely influence neurological and cognitive development. Although many of the genetic forms of epilepsy manifest their symptoms during this time, increasingly immunological components are being recognized in some of the childhood cases and immunotherapy is administered in some of these patients.

AERPPS/FIRES/DESC/NORSE: probable postinfectious epileptic syndromes

A number of seizure syndromes have recently been reported as distinct clinical entities: AERPPS (acute encephalitis with refractory, repetitive partial seizures [43]), FIRES (febrile infection-related epilepsy syndrome [44]), DESC (devastating epileptic encephalopathy

in school-aged children [45]) and NORSE (new-onset refractory status epilepticus, [46]).

The development of an acute encephalitis with prominent, often characteristic, seizures, in the context of a preceding febrile illness, has been described by a number of groups in both adult and children from both Asian and European cohorts [43–45]. These cohorts may well correspond to the previously reported acute encephalopathies of obscure origin in infants and children [47]. Although the paediatric reports do show some subtle differences, they broadly report previously well children with an acute onset of recurrent focal or generalized seizures, an associated encephalopathy and, in some, a postencephalitic phase of recurrent seizures. Both the acute and postencephalitic seizure phases are often drug refractory with an inconsistent response to even barbiturates. CSF pleocytosis and MRI abnormalities in the temporal lobes were seen commonly. One important question is whether these abnormalities are purely due to recurrent seizures [48] or whether they are part of an underlying inflammatory disease process. Indeed, glutamate receptor epsilon2 subunit (the NR2B subunit of the NMDA receptor) antibodies were detected in some cases [43]. However, these are only supportive of a more generalized autoimmune response, as they are not known to bind the extracellular domain of natively expressed GluR2 receptors. In fact, brain biopsies obtained from such cases have been noninflammatory in appearance and immunotherapy has rarely been successful. This may indicate the residual presence of a burned-out inflammatory process with gliotic epileptogenic tissue. These are important diseases for future study as the outcome is globally poor.

Conclusion

Recently, there has been an explosion of reports in the literature associating CNS disorders with auto-antibodies that are directed against cell-surface proteins and are likely to be pathogenic. Many of these conditions have seizures as an early and prominent feature (Table 1) [7,8,9^{••},10,13^{••},15^{*},16–19,20^{••},22,25,27^{••},28,29] which are commonly refractory to conventional AEDs. In contrast, a good response is often seen with immunotherapies.

Reports initially came from groups studying paraneoplastic limbic encephalitis. More recently, these antibodies have been identified in the more common forms of nonparaneoplastic encephalitis. Within the last couple of years, a further step has been taken with the identification of these antibodies in patients in whom seizures are the predominant, and in some cases the only feature.

Initial steps have been taken to identify phenotypically distinct epilepsy syndromes that are associated with clearly defined auto-antibodies, for example LGI1-antibodies in

Table 1 Summary of seizures in the main studies describing the specific auto-antibodies (antibodies to cell surface neuronal proteins in encephalitis)

Syndrome	Number of patients	Patients with seizures (%)	Antibodies	Seizure details	Comment	Reference
VGKC encephalitis	10	9 (90%)	VGKC-complex (100%)	7 generalized, 6 partial, 3 with both		[7]
	7	6 (86%)	VGKC-complex (100%)	3 generalized, 5 complex partial, 2 simple motor		[8]
	72	42 (58%)	VGKC-complex (100%)	Temporal onset in 13, extratemporal onset in 5, partial with unclear localization in 3, generalized in 11, and unspecified in 10. Generalized seizures observed in 4 patients with temporal seizures and in one with extratemporal seizures	Study includes some patients without CNS features	[49]
Faciobrachial dystonic seizures (FBDS)	15	12 (80%)	VGKC-complex (100%)	Frontotemporal and generalized tonic clonic seizures noted	12/15 had myoclonus, facial tics noted similar to FBDS	[17]
	96	68 (71%)	VGKC-complex (100%); 49 LGI1, 10 CASPR2 and one Contactin-2 positive	4 patients had seizures without other cognitive features	Includes 11 patients with neuromyotonia	[9**]
	57	42 (82%)	VGKC-complex (100%), all LGI1 positive	Data available for 51 patients: focal onset in 95% of 38 patients for whom localization was established; 11% of patients with seizures had convulsive or nonconvulsive status epilepticus	Myoclonus found in 40% may represent FBDS	[15*]
NMDAR encephalitis	3	3 (100%)	VGKC-complex (100%)	Uni- or bilateral arm posturing with facial grimacing	Upto 70/day	[10]
	1	1 (100%)	VGKC-complex (100%)	Involuntary synchronous twitches of shoulder and face	Upto 30/min	[16]
	29	29 (100%)	VGKC-complex (100%) ^a ; 89% LGI1; two of these cases also had CASPR2 antibodies and one also had Contactin-2 antibodies	FBDS (100%). In addition, generalized (13, 45%), complex partial (14, 48%) and simple motor (1, 3%) seizures described	50 (6–360) seizures per day (median, range)	[13**]
NMDAR encephalitis	12 (12F)	11 (92%)	NMDAR (100%)	Generalized or partial complex seizures	All patients had teratomas	[18]
	100 (91F)	76 (76%)	NMDAR (100%)	45 (59%) generalized, 19 (13%) partial complex	Accrual of a large number of NMDAR-antibody positive patients in short time	[19]
	32 (under 13 years, 26F)	23/30 (77%)	NMDAR (100%)	Usually partial motor or complex seizures	Children affected at high frequency	[21]
Encephalitis lethargica	44	36 (82%)	NMDAR (100%)	Generalized 33, complex partial 16, simple partial 12	Males and nonparaneoplastic cases found at higher frequency	[20**]
	5	5 (100%, inclusion criterion)	NMDAR (100%)	All had extratemporal seizures	Anti-NMDAR encephalitis is a relevant differential diagnosis in otherwise unexplained new-onset epilepsies in young females	[22]
	20 children (8F)	10 (50% had NMDAR antibodies)	NMDAR (50%)		None of the patients without NMDAR antibodies had seizures	[25]
AMPAR encephalitis	10 (9F)	4 (40%; 3 at presentation, 1 at relapse)	GluR1/2. All 3 with seizures had GluR2 antibodies, patient relapse GluR1	Focal motor or GTC seizures; patient developed GTC seizures on relapse, died during status epilepticus	3 GluR2 positive patients had tumours (lung or thymus). No tumour found in GluR1-positive patient	[28]
GABA B encephalitis	15 (7F)	15 (100%).	GABA receptor B1 subunit (100%)	Seizures were the presenting symptom (13/15). Most seizures appeared to have a temporal-lobe onset with secondary generalization. Three patients had SE	7 patients had a tumour (6 SCLC)	[27**]

CNS, central nervous system; FBDS, faciobrachial dystonic seizures, GTC, generalized tonic-clonic seizures; SCLC, small cell lung carcinoma; VGKC-complex, voltage-gated potassium channel complex.

^aWhen tested during acute illness.

FBDS. However, definitive proof of pathogenicity is still lacking. Some studies have demonstrated the direct and specific modulation of NMDA and AMPA receptors on cultured rat neurones *in vitro* and *in vivo* after the application of patient IgG [24^{**},28]. More recently, Lalic and colleagues [50] have shown that purified IgG-containing LGI1 antibodies, from a patient with limbic encephalitis, can induce epileptiform activity in cultured hippocampal CA3 pyramidal slices. Further studies need to extend these *in-vitro* studies to whole animal models to establish the epileptogenic capabilities of the antibodies. These models will help inform the mechanisms of action of these antibodies and allow experiments to address our understanding of the optimal modality of treatment in individuals with epilepsy as the predominant feature.

Acknowledgements

SRI is supported by the National Institute for Health Research (NIHR), Department of Health, UK. BL received funding from Epilepsy Research UK (ERUK).

Conflict of interest: a patent application for the use of LGI1, CASPR2 and Contactin-2 antigens in antibody determination from patients' serum samples and CSF as a diagnostic test has been filed by the University of Oxford (SRI, BL). Additionally, the Department of Clinical Neurosciences Oxford received payment for carrying out diagnostic tests for auto-antibodies (BL).

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

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 189).

- 1 Berg AT, Berkovic S, Brodie MJ, *et al*. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia* 2010; 51:676–685.
- A thoughtful and simplified approach to the terminology of seizures and seizure disorders.
- 2 Berg AT, Mather GW, Bronen RA, *et al*. Frequency, prognosis and surgical treatment of structural abnormalities seen with magnetic resonance imaging in childhood epilepsy. *Brain* 2009; 132:2785–2797.
- 3 Palace J, Lang B. Epilepsy: an autoimmune disease? *J Neurol Neurosurg Psychiatry* 2000; 69:711–714.
- 4 Bauer J, Bien C. Encephalitis and epilepsy. *Semin Immunopathol* 2009; 31:537–544.
- 5 Vincent A, Irani SR, Lang B. The growing recognition of immunotherapy-responsive seizure disorders with autoantibodies to specific neuronal proteins. *Curr Opin Neurol* 2010; 23:144–150.
- 6 Bien CG, Urbach H, Schramm J, *et al*. Limbic encephalitis as a precipitating event in adult-onset temporal lobe epilepsy. *Neurology* 2007; 69:1236–1244.
- 7 Vincent A, Buckley C, Schott JM, *et al*. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain* 2004; 127:701–712.
- 8 Thieben MJ, Lennon VA, Boeve BF, *et al*. Potentially reversible autoimmune limbic encephalitis with neuronal potassium channel antibody. *Neurology* 2004; 62:1177–1182.
- 9 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.
- Description of antibodies to three VGKC-complex proteins in sera of patients with limbic encephalitis and seizures. LGI1 antibodies were predominantly seen in the patients with limbic encephalitis, whereas CASPR2 antibodies were detected in the patients with neuromyotonia.
- 10 Irani SR, Buckley C, Vincent A, *et al*. Immunotherapy-responsive seizure-like episodes with potassium channel antibodies. *Neurology* 2008; 71:1647–1648.
- 11 McKnight K, Jiang Y, Hart Y, *et al*. Serum antibodies in epilepsy and seizure-associated disorders. *Neurology* 2005; 65:1730–1736.
- 12 Majoie M, de Baets M, Renier W, *et al*. Antibodies to voltage-gated potassium channels in epilepsy. *Epilepsy Res* 2006; 71:135–141.
- 13 Irani SR, Michell AW, Lang B, *et al*. Faciobrachial dystonic seizures precede LGI1-antibody limbic encephalitis. *Ann Neurol* (in press).
- Description of a novel LGI1 antibody-associated form of epilepsy, with late-onset faciobrachial dystonic seizures (FBDS). Antibodies to the VGKC-complex protein LGI1 were found in more than 90% of cases. The FBDS may precede a limbic encephalitis and be a feature specific to VGKC-complex or LGI1 antibodies.
- 14 Vincent A, Irani SR, Caspr2 antibodies in patients with thymomas. *J Thorac Oncol* 2010; 5:S77–S80.
- 15 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.
- All 57 patients with limbic encephalitis and antibodies to the VGKC-complex had LGI1 as the specific antigenic target, and 82% had seizures.
- 16 Barajas RF, Collins E, Cha S, Geschwind MD. Adult-onset drug-refractory seizure disorder associated with antivoltage-gated potassium-channel antibody. *Epilepsia* 2010; 51:473–477.
- 17 Geschwind MD, Tan KM, Lennon VA, *et al*. Voltage-gated potassium channel autoimmunity mimicking Creutzfeldt-Jakob disease. *Arch Neurol* 2008; 65:1341–1346.
- 18 Dalmau J, Tüzün E, Wu HY, *et al*. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007; 61:25–36.
- 19 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.
- 20 Irani SR, Bera K, Waters P, *et al*. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly nonparaneoplastic disorder of both sexes. *Brain* 2010; 133:1655–1667.
- Description of a predominantly nonparaneoplastic cohort of patients with NMDAR-antibodies. NMDAR-antibody levels are shown to correlate with clinical outcomes. Data regarding nonparaneoplastic immunotherapy-responses are provided.
- 21 Florance NR, David RL, Lam C, *et al*. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol* 2009; 66:11–18.
- 22 Niehusmann P, Dalmau J, Rudowski C, *et al*. Diagnostic value of N-methyl-D-aspartate receptor antibodies in women with new-onset epilepsy. *Arch Neurol* 2009; 66:458–464.
- 23 Johnson N, Henry C, Fessle AJ, *et al*. Anti-NMDA receptor encephalitis causing prolonged nonconvulsive status epilepticus. *Neurology* 2010; 75:1480.
- Patient described with refractory nonconvulsive status epilepticus who was refractory to immunosuppressive therapy and made a marked improvement following oophorectomy.
- 24 Hughes EG, Peng X, Gleichman AJ, *et al*. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *J Neurosci* 2010; 30:5866–5875.
- Demonstration of morphological, and electrophysiological effects of NMDAR antibodies *in vitro* and *in vivo*.
- 25 Dale RC, Irani SR, Brilot F, *et al*. NMDA receptor antibodies in pediatric dyskinetic encephalitis lethargica. *Ann Neurol* 2009; 66:704–709.
- 26 Samarasekera SR, Vincent A, Welch JL, *et al*. Course and outcome of acute limbic encephalitis with negative voltage-gated potassium channel antibodies. *J Neurol Neurosurg Psychiatry* 2007; 78:391–394.
- 27 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.
- First description of antibodies to GABA(B) receptors in patients with limbic encephalitis.
- 28 Lai M, Hughes EG, Peng X, *et al*. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. *Ann Neurol* 2009; 65:424–434.
- 29 Bien CG, Granata T, Antozzi C, *et al*. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. *Brain* 2005; 128:454–471.
- 30 Bien CG, Widman G, Urbach H, *et al*. The natural history of Rasmussen's encephalitis. *Brain* 2002; 125:1751–1759.

- 31** 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.
- 32** Bauer J, Elger CE, Hans VH, *et al.* Astrocytes are a specific immunological target in Rasmussen's encephalitis. *Ann Neurol* 2007; 62:67–80.
- 33** Schwab N, Bien CG, Waschbisch A, *et al.* CD8+ T cell clones dominate brain infiltrates in Rasmussen encephalitis and persist in the periphery. *Brain* 2009; 132:1236–1246.
- 34** Thilo B, Stinglee R, Knudsen K, *et al.* A case of Rasmussen encephalitis treated with rituximab. *Nat Rev Neurol* 2009; 5:458–462.
- 35** 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.
- 36** Liimatainen S, Peltola M, Sabater L, *et al.* Clinical significance of glutamic acid decarboxylase antibodies in patients with epilepsy. *Epilepsia* 2010; 51:760–767.
- 37** Errichiello L, Perruolo G, Pascarella A, *et al.* Autoantibodies to glutamic acid decarboxylase (GAD) in focal and generalized epilepsy: a study on 233 patients. *J Neuroimmunol* 2009; 211:20–123.
- 38** 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.
- Of 53 adult patients with limbic encephalitis, nine had high titre GAD antibodies, whereas 10 had antibodies to VGKC-complex proteins. The GAD antibodies defined a younger cohort of nonparaneoplastic limbic encephalitis patients who remained intractable to anticonvulsive treatment.
- 39** Nociti V, Frisullo G, Tartaglione T, *et al.* Refractory generalized seizures and cerebellar ataxia associated with anti-GAD antibodies responsive to immunosuppressive treatment. *Eur J Neurol* 2010; 17:e5.
- 40** Matà S, Muscas GC, Naldi I, *et al.* Nonparaneoplastic limbic encephalitis associated with antiglutamic acid decarboxylase antibodies. *J Neuroimmunol* 2008; 199:155–159.
- 41** Kanter IC, Huttner HB, Staykov D, *et al.* Cyclophosphamide for anti-GAD antibody-positive refractory status epilepticus. *Epilepsia* 2008; 49:914–920.
- 42** Stagg CJ, Lang B, Best JG, *et al.* Autoantibodies to glutamate acid decarboxylase in epilepsy patients are associated with a low cortical GABA levels. *Epilepsia* 2010; 51:1898–1901.
- Using magnetic resonance spectroscopy, a 3T GABA-optimized spectrum was obtained from four patients with high GAD antibodies and 10 controls. The GABA levels in the cortex were found to be considerably lower in the patient group compared to the controls.
- 43** Sakuma H, Awaya Y, Shiomi M, *et al.* Acute encephalitis with refractory, repetitive partial seizures (AERRPS): a peculiar form of childhood encephalitis. *Acta Neurol Scand* 2010; 121:251–256.
- 44** 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.
- 45** Mikaeloff Y, Jambaque I, Hertz-Pannier L, *et al.* Devastating epileptic encephalopathy in school-aged children (DESC): a pseudo-encephalitis. *Epilepsy Res* 2006; 69:67–79.
- 46** Wilder-Smith EP, Lim EC, *et al.* The NORSE (new-onset refractory status epilepticus) syndrome: defining a disease entity. *Ann Acad Med Singapore* 2005; 34:417–420.
- 47** Lyon G, Dodge PR, Adams RD. The acute encephalopathies of obscure origin in infants and children. *Brain* 1961; 84:680–708.
- 48** 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.
- 49** Tan KM, Lennon VA, Klein CJ, *et al.* Clinical spectrum of voltage-gated potassium channel autoimmunity. *Neurology* 2008; 70:1883–1890.
- 50** Lalic T, Pettingill P, Vincent A, Capogna M. Human limbic encephalitis serum enhances hippocampal mossy fibre-CA3 pyramidal cell synaptic transmission. *Epilepsia* 2010 [Epub ahead of print].