The recognition and treatment of autoimmune epilepsy in children

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This article is commented on by Wright and Lim on pages 402–403 of this issue.

PUBLICATION DATA
Accepted for publication 31st October 2014.
Published online 8th December 2014.

ABBREVIATIONS

$GABA_AR$	γ-Aminobutyric acid type A receptor
$GABA_BR$	γ-Aminobutyric acid type B receptor
GAD	Glutamic acid decarboxylase
NMDAR	*N*-methyl-D-aspartate receptor
PERM	Progressive encephalomyelitis with rigidity and myoclonus
VGKC	Voltage-gated potassium channel

There is emerging interest in autoimmune epilepsy, which represents a small but potentially treatable form of epilepsy. Most insights into autoimmune epilepsy derive from the recent descriptions of autoimmune encephalitis that takes two general forms: a focal encephalitis (such as limbic) or a diffuse encephalitis (such as anti-*N*-methyl-D-aspartate receptor [NMDAR] encephalitis). The features of autoimmune epilepsy include acute or subacute onset of seizures, usually in the context of encephalopathy, and inflammation of the central nervous system on testing cerebrospinal fluid or magnetic resonance imaging. Neuronal antibodies associated with autoimmune encephalitis and seizures in children include NMDAR, voltage-gated potassium channel complex, glycine receptor, γ-Aminobutyric acid type A receptor ($GABA_AR$), γ-Aminobutyric acid type B receptor ($GABA_BR$), and glutamic acid decarboxylase antibodies. These antibodies support the diagnosis of autoimmune epilepsy, but are not essential for diagnosis. When autoimmune epilepsy is suspected, first-line immune therapy with corticosteroids in addition to intravenous immunoglobulin or plasma exchange should be considered. Second-line therapy with rituximab or cyclophosphamide can be considered if the syndrome is severe. A response to immune therapy supports the diagnosis of autoimmune epilepsy. Neuronal antibodies are increasingly found in patients with focal epilepsy of unknown cause who do not have 'encephalitis'. Recent epidemiological studies support the link between epilepsy and autoimmune diseases. Future studies need to define the spectrum of autoimmune epilepsy and focus on early identification and treatment.

Activation of the immune system is observed in many disease processes of the central nervous system (CNS), although discriminating a primary (causal) immune response from a secondary (reactive) immune response to tissue damage is not straightforward. There is a large and complex literature describing the presence of inflammation and immune activation in seizures and epilepsy.[1] For example, inflammation caused by fever and infections can trigger seizures through the release of proinflammatory chemokines and cytokines, which can cause activation of ion channels and neuronal hyperexcitability. On the other hand, seizures themselves can lead to activation of cytokine networks, which then cause inflammation and damage to the blood–brain barrier, allowing extravasation of peripheral immune cells or molecules. This leads in many cases to potentiation of seizures and inflammation.[1–3] Defining an acquired autoimmune aetiology is important because these patients may benefit from immune suppression. The confident diagnosis of autoimmune encephalitis and epilepsy has improved substantially owing to the discovery of pathogenic autoantibodies that seem to be discriminating biomarkers of disease. The term 'autoimmune epilepsy' is now used in conditions where the 'specific' or adaptive immune system is involved in the pathogenesis of epilepsy. 'Autoimmune seizures' often do not respond to conventional antiepileptic treatment but might respond to immunotherapy, and therefore are important to recognize. In this paper we aim to review autoimmune seizures and epilepsy in children, and to discuss emerging concepts, challenges, and potential future directions.

AUTOIMMUNE ENCEPHALITIS WITH SEIZURES

Seizures are a common feature of autoimmune encephalitis, where patients characteristically have other clinical features such as encephalopathy, behavioural alteration, and movement disorders, in addition to seizures.

Recognition of autoimmune encephalitis in patients with seizures

Neuronal autoantibodies are important diagnostic markers of autoimmune encephalitis; however, these biomarkers are only present in a proportion of patients with immune-therapy-responsive encephalitis. Therefore the suspicion of autoimmune encephalitis should be predominantly based upon clinical characteristics and supportive investigations, rather than solely on biomarkers. We therefore start by describing the clinical and investigation characteristics of autoimmune encephalitis, which can be broadly separated into focal, multifocal, or diffuse processes.

Focal autoimmune encephalitis: limbic encephalitis

The most clearly described focal autoimmune encephalitis is autoimmune limbic encephalitis. Limbic encephalitis is a syndrome that is characterized by inflammation of the limbic areas of the brain. Patients have memory and cognitive disturbance, temporal lobe seizures, behavioural and personality changes, as well as sleep disturbance.[4–6] The classic radiological features of limbic encephalitis include high T_2 or fluid-attenuated inversion recovery signals in the medial temporal structures. Classically limbic encephalitis was described in adults as a paraneoplastic syndrome with associated onconeuronal antibodies (such as anti-Hu antibodies), which are probably markers of the underlying neoplasm.[7] Paraneoplastic limbic encephalitis associated with onconeuronal antibodies generally has a poor prognosis and poor response to immunotherapy. By contrast, autoimmune limbic encephalitis, which is often associated with cell-surface neuronal autoantibodies, has a better prognosis than paraneoplastic limbic encephalitis, with good response to immunotherapy or even spontaneous resolution. Autoimmune limbic encephalitis can be paraneoplastic or 'idiopathic' in adults, but is rarer in children, although it is probably under-recognized, and is rarely paraneoplastic.

Other focal or multifocal autoimmune encephalitis

There are probably other focal autoimmune encephalitis syndromes that are yet to be recognized. Rasmussen encephalitis is another focal encephalitis syndrome, although it is not autoantibody associated and therefore not described further here.[8] The best example of multifocal encephalitis is anti-γ-aminobutyric acid type A receptor ($GABA_AR$) encephalitis, which has been reported in a few adults and children.[9] The clinical and radiological features of anti-$GABA_AR$ encephalitis reveal multifocal enhancing inflammatory lesions involving the cortical and subcortical structures.[9]

Diffuse autoimmune encephalitis

The best example of diffuse autoimmune encephalitis is anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis, which in its fully evolved form shows generalized CNS dysfunction with features of cortical, subcortical, and brainstem dysfunction.[10–12]

Overlapping syndromes

Although the above separation is useful to aid the approach to a patient with suspected autoimmune encephalitis, many patients do not fit neatly into a single category, and have overlapping features.

Suspecting and diagnosing autoimmune encephalitis in children

The following clinical characteristics are seen in autoimmune encephalitis, and are summarized in Table I.

What this paper adds

- An overview of the clinical syndromes, investigation, and treatment of autoimmune epilepsy in children.
- It discusses the important challenges in this rapidly evolving area.

Clinical and demographic features

Seizure onset and clinical associations. Typically, autoimmune encephalitis affects previously neurologically normal children. Although the seizure onset is variable and can be insidious, in many patients it is explosive with rapid evolution into status epilepticus or severe seizure clusters. The seizures are focal in most cases, with temporal and extratemporal seizures described. One of the main suggestive features of an 'encephalitic' process would be the presence of other CNS dysfunctions, particularly cognitive alteration, encephalopathy (personality or behavioural changes, or an altered level of consciousness), movement disorders, and autonomic dysfunction.[9,13–18] An emerging theme is that seizures of autoimmune aetiology are often resistant to conventional antiepileptic drugs.[16,19–21]

Predisposing factors including other autoimmune disease. It is very likely that there is a genetic vulnerability to the development of autoimmune encephalitis. There is a clear ethnic predisposition, and a clear female predisposition (in adolescents but not young children) to anti-NMDAR encephalitis.[10] There is emerging evidence that patients with one autoimmune disease are more likely to develop another autoimmune disease, and patients with one autoantibody are more likely to produce another autoantibody.[22,23] Therefore the presence of a personal history of autoimmune disease, or a first-degree family history of autoimmune disease, in a patient with seizures is a 'clinical flag' that the epilepsy could have an autoimmune aetiology.

Evidence of CNS inflammation: cerebrospinal fluid

Study of cerebrospinal fluid (CSF) is important in providing evidence of CNS inflammation. CSF pleocytosis is found in approximately two-thirds of patients with anti-NMDAR encephalitis; however, pleocytosis is rarely present in voltage-gated potassium channel (VGKC)-complex antibody-associated encephalitis, and the absence of pleocytosis does not exclude an autoimmune aetiology. Likewise pleocytosis is not specific to autoimmune encephalitis, and is obviously seen in infectious syndromes and febrile infection-related epilepsy syndrome. Elevated CSF protein is a non-specific but potentially useful marker of CNS inflammation. More specifically, quantitative assessments of albumin and immunoglobulin G (IgG) index can be useful markers of CNS inflammation.[24] The presence of oligoclonal bands implies clonal expansion of IgG species in CSF alone (intrathecal bands), or both CSF and serum (mirrored oligoclonal bands). Oligoclonal bands are not specific to autoimmune aetiologies,[25] although they are commonly seen in anti-NMDAR encephalitis, particularly in established disease. CSF neopterin is a sensitive marker of acute and active CNS inflammation, but is elevated in primary

(causal) and secondary (reactive) inflammation, and is a biomarker that is not broadly available.[26] There is an urgent need for other CSF biomarkers of inflammation. Different cytokines and chemokines are found in the setting of CNS inflammation and may be potential CSF biomarkers; however, their role requires further study.[27]

Evidence of CNS inflammation: neuroimaging

Radiological evidence of limbic encephalitis might be seen on magnetic resonance imaging (MRI) with signal abnormalities in the mesotemporal lobes.[18,28,29] In addition, signal abnormalities in other areas have been reported in autoimmune encephalitis, including cortical and subcortical regions, and basal ganglia.[9,13] However, in many patients conventional MRI is normal, particularly in initial studies. Functional neuroimaging such as positron emission tomography (PET) has a significant role in adult neurology and can show limbic hypermetabolism in limbic encephalitis. PET is often abnormal in anti-NMDAR encephalitis, and striatal hypermetabolism and cortical (particularly posterior) hypometabolism is often observed.[30,31] Although PET hypermetabolism suggests inflammation, the hypometabolism observed in anti-NMDAR encephalitis is probably related to neuronal hypofunction caused by endocytosis of NMDA receptor.[32,33] PET has not been significantly investigated outside anti-NMDAR encephalitis in children.

Other evidence of CNS inflammation: histopathology

An immunohistopathological study of 17 adult cases (autopsy or biopsy samples) with encephalitis and antibodies to intracellular or surface antigens showed histopathological inflammatory changes that varied in the different antibody-associated syndromes.[34] Histopathological reports are rare in children. One child with limbic encephalitis with high-titre glutamic acid decarboxylase (GAD) and low-titre VGKC underwent temporal lobe surgery, and histopathological studies showed chronic lymphocytic–microglial infiltrate consistent with inflammation.[29] Although autoantibodies have reduced the need for invasive procedures, biopsies still have a role in the context of inflammatory brain disease, particularly when small-vessel CNS vasculitis is a diagnostic consideration.

Electroencephalography features in autoimmune encephalitis

Electroencephalography (EEG) features are usually not specific, including encephalopathy and epileptic discharges. Independent bi-temporal epileptic discharges and electrical seizures have been described in some children with VGKC encephalitis.[18,35] In anti-NMDAR encephalitis, generalized slowing is often seen and rarely epileptic discharges. 'Extreme delta brush' on EEG has been described in adults with anti-NMDAR encephalitis,[36] although this is mostly observed during the comatose period. Other characteristic electrographic features have been described in some children with anti-NMDAR encephalitis including excess theta and alpha frequencies in non-rapid eye movement sleep as well as preservation of background rhythm in the awake state with focal or unilateral slowing.[37] Children with these EEG findings had better outcomes than those with diffuse slowing.[37]

AUTOANTIBODY BIOMARKERS OF AUTOIMMUNE ENCEPHALITIS WITH SEIZURES

Cell surface antibodies

Autoantibodies to the following neuronal proteins and receptors have been described in autoimmune encephalitis associated with seizures in children (Table II).

VGKC complex including leucine-rich, glioma inactivated 1 and contactin-associated protein-2

VGKC antibodies were initially described in adults with limbic encephalitis.[4,5,38] The target antigens for VGKC antibodies were later found to be other proteins tightly

Table I: Clinical and other features suggestive of autoimmune encephalitis in patients with seizures

Clinical features
Focal seizures, particularly focal motor and focal dyscognitive, secondary generalized seizures[a]
Seizure clusters: status epilepticus
Seizures and epilepsy of 'unknown' cause
Refractory seizures
Associated features: encephalopathy, movement disorders, neuropsychiatric symptoms, cognitive or memory impairment
History of other autoimmune diseases (personal or family)
Imaging and other investigations
Positive CSF findings suggestive of inflammation (pleocytosis, elevated neopterin, oligoclonal bands)
Inflammatory MRI changes of high T_2 or FLAIR signal in medial temporal structures, cortical or subcortical areas, as well as cerebellum and basal ganglia
Focal (or multifocal) electrographic changes including slowing and/or epileptiform activity, particularly involving temporal lobe(s)
Histopathological findings compatible with inflammation (such as lymphocytic infiltrates) on biopsy
Positive cell-surface neuronal autoantibodies (serum or CSF)
Treatment response
Resistance to conventional antiepileptic drugs
Response to immunotherapy (including steroids, immunoglobulin, and immunosuppressive agents)
No other explanation

[a]Generalized seizures alone are less likely to be associated with autoimmune encephalitis. CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery.

Table II: Neuronal antibodies associated with encephalitis complicated by seizures in children[a]

Antibody type	Encephalitis association in adults	Encephalitis association in children	Seizure types (adults and children)	Typical associated features	Tumour association[b]	MRI features	References
VGKC complex	Limbic encephalitis Morvan syndrome	Limbic encephalitis Encephalitis with status epilepticus	Focal (or multifocal) seizures (mostly temporal lobe) Mixed seizure types Faciobrachial dystonic seizures (LGI1)	Fever Encephalopathy Behavioural changes Memory and cognitive impairment	Rare, thymus, lung	Normal High signal in medial temporal lobes White matter signal abnormalities, high signal in basal ganglia	4, 5, 18, 29, 38, 41, 78
NMDAR	Encephalitis with movement disorder, psychiatric disturbances, aphasia, autonomic dysfunction, and seizures	Encephalitis with movement disorder, psychiatric disturbances, aphasia, autonomic dysfunction, and seizures	Focal seizures (motor and dyscognitive), mostly extra-temporal Mixed seizure types Status epilepticus/EPC	Encephalopathy Movement disorder Psychiatric disturbance Autonomic instability	Ovarian teratoma, (females, increases >13y of age)	Normal High signal medial temporal lobe, and other regions	14, 15, 49, 79
$GABA_BR$	Limbic encephalitis	Limbic encephalitis	Focal seizures (temporal lobe) Generalized seizures (primary and secondary) Status epilepticus	Memory disturbance Movement disorder (dystonia, chorea), opsoclonus, ataxia	30–60%, lung, thymus	Normal High signal medial temporal lobes, and other regions	17, 51–53
$GABA_AR$	Encephalitis with seizures or status epilepticus (multifocal encephalitis)	Encephalitis with seizures or status epilepticus (multifocal encephalitis)	Focal seizures (temporal and extratemporal) Mixed seizure types Status epilepticus/EPC	Memory and cognitive impairment Behavioural changes, psychosis Movement disorder (dystonia chorea) Other autoimmune disorders	Rare, Hodgkin's lymphoma, thymus	High-signal cortical –subcortical lesions (multifocal) High-signal temporal lobes	9
Glycine receptor	Other spinal and brain stem disorders (stiff person syndrome, PERM) Limbic encephalitis	PERM Focal encephalitis with seizures	Myoclonic jerks (cortical or subcortical) Hyperekplexia Temporal lobe seizures and status epilepticus	Rigidity (startle induced) Cognitive impairments	Rare, lung, thymus	Normal	55–58
GAD	Limbic encephalitis Stiff person syndrome	Limbic encephalitis	Focal seizures (mostly temporal) Secondary generalized seizures EPC (multifocal)	Memory, cognitive impairment, ataxia Autoimmune disorders or immune deficiency	Rare, lung	Normal Lesions in hippocampus, cortex or cerebellum	29, 59, 60, 62

[a]Autoantibodies associated with encephalitis that have not been observed in children are not presented (LGI1, CASPR2, and AMPA-R antibodies). [b]These tumours are mostly reported in adults. VGKC, voltage-gated potassium channel; LGI1, leucine-rich, glioma inactivated 1; NMDAR, *N*-methyl-D-aspartate receptor; EPC, epilepsia partialis continua; $GABA_BR$, γ-aminobutyric acid type B receptor; $GABA_AR$, γ-aminobutyric acid type A receptor; PERM, progressive encephalomyelitis with rigidity and myoclonus; GAD, glutamic acid decarboxylase.

complexed with the potassium channel rather than the channel itself, including leucine-rich, glioma inactivated 1 (LGI1), contactin-associated protein-2 (CASPR2), and contactin 2.[39,40] Most adults who tested positive for VGKC antibodies were positive for antibodies to one or more of those antigens[39,40] although some cases were negative.[20,40] A specific seizure syndrome called 'faciobracial dystonic seizures' has been described in association with LGI1 antibodies.[41] These characteristic, short-lived, 'spasm-like' events are almost pathognomic of LGI1-antibody-associated encephalitis, and often predate the limbic encephalitis. Early recognition and steroid treatment of these patients can prevent the full-blown cognitive phenotype associated with limbic encephalitis, and improve outcome.[42] These patients are typically refractory to conventional antiepileptic drugs, but respond well to corticosteroids.[41–43] There are no reported children with positive LGI1 antibodies, suggesting this is an adult-specific antibody syndrome. CASPR2 antibodies are found in adults with Morvan syndrome and limbic encephalitis, although CASPR2 antibodies are more typically found in patients with peripheral disease such as autoimmune neuromyotonia.[40,44] Limbic encephalitis associated with VGKC-complex antibodies (acute or remote) may result in adult-onset temporal lobe epilepsy and mesotemporal sclerosis.[45–47]

VGKC complex antibodies have been reported in children with limbic encephalitis as well as encephalitis with status epilepticus.[18,29] In these children, temporal lobe seizures were common.

In the early descriptions of VGKC antibodies, a positive result was more than 100picomolar (pM). Recently a scale has been developed for use in children. A titre of <100pM is considered negative; 100 to 150pM is 'low positive'; 150 to 400pM is 'positive'; >400pM is 'high positive'.[29] The 'lower-titre' antibodies of <400pM are less significant than antibodies >400pM in adults, and it is likely that a similar association is true for children. Therefore the significance of lower titre VGKC-complex antibodies should be interpreted with caution. Children with VGKC-complex antibodies are often negative for antibodies against LGI1 and CASPR2.[13,18,48] This suggests that VGKC antibodies in children might bind other antigenic targets within the potassium channel complex that are 'yet to be identified'. In addition, VGKC-complex antibodies are measured using radioimmunoassay, rather than a cell-based assay, which is typically used to detect cell surface autoantibodies. It is possible that some intracellular antigens are part of the VGKC complex, and therefore some antibodies that bind to VGKC complex may not be 'cell surface antibodies', so their clinical importance is less clear.

NMDAR

Encephalitis associated with antibodies to the glutamate receptor NMDAR is a well characterized syndrome and was initially described in females with ovarian teratoma,[49] but is now described in young children too. The characteristic features are similar in children and adults and include psychiatric disorders, movement disorders, autonomic disturbance, as well as seizures. Children are more likely to have seizures as the presenting symptom than adults.[12] Seizures in anti-NMDAR encephalitis are often focal, but can be secondary generalized or generalized. Anti-NMDAR encephalitis is rarely associated with tumours in children (except for ovarian teratoma in adolescent females). Incomplete syndromes can occasionally occur in which one feature predominates including seizures, movement disorder, or psychosis, although these incomplete syndromes are uncommon.[50]

$GABA_bR$

Antibodies against γ-Aminobutyric acid type B receptor ($GABA_BR$) have been identified in adults with limbic encephalitis, many of whom had an associated neoplasm.[51,52] One patient out of a series of 20 with limbic encephalitis associated with $GABA_BR$ was a 16-year-old female who responded to immunotherapy with complete recovery.[53] A recent report of a 3-year-old child with encephalitis and high-titre $GABA_BR$ antibodies[17] described a complex syndrome of lethargy, movement disorder, opsoclonus, ataxia, and seizures. Seizures were focal with secondary generalization and were resistant to treatment including immunotherapy. MRI showed diffuse changes in cortical and subcortical structures. The patient died of sepsis 4 weeks into his illness.

$GABA_aR$

Recently antibodies against $GABA_AR$ were identified in 18 out of 140 patients with refractory seizures, status epilepticus, or encephalitis who had antibodies to unknown neuropil antigens, including seven children (three females, age range 2–16y).[9] Seizures were often dominant in these encephalitic patients, and were often refractory, including epilepsia partialis continua. Five of the $GABA_AR$-positive children had antibodies to other neuronal antigens (GAD, n=2; NMDAR, n=1; $GABA_BR$, n=1). MRI showed multifocal cortical and subcortical lesions. Five of these seven children received immunotherapy; the outcome was variable, including full recovery, partial response, and persistent epilepsy and cognitive deficit.

Glycine receptor

Glycine receptor alpha-1 antibodies have been described in adult patients with progressive encephalomyelitis with rigidity and myoclonus (PERM) and stiff person syndrome.[54–56] One paediatric case of PERM associated with glycine receptor antibodies in serum and CSF has been reported in a 14-month-old female who developed startle-induced episodes, generalized rigidity, myoclonus, and axial hyperextension without impairment of consciousness.[57] Brain and spinal MRI was normal and EEG showed frequent generalized myoclonus without electrographic correlates. This individual responded to immunotherapy in the form of intravenous immunoglobulin and steroids, but had

multiple relapses. It is likely that these myoclonic episodes in PERM are spinal rather than cortical in origin and hence are not strictly epileptic seizures. A 5-year-old female reported to have explosive-onset epileptic encephalopathy (no rigidity or myoclonus) had positive glycine receptor antibodies in her serum and CSF.[13] The clinical, electrographic, and imaging data for this individual were not described further. Glycine receptor antibodies were found in a 4-year-old male with refractory focal epilepsy, and speech and behavioural disturbance. His CSF and brain MRI were normal. He responded to steroids with complete recovery.[58]

In summary, glycine receptor antibodies are strongly associated with PERM, but can be associated with encephalitis and focal seizures.

Autoantibodies to intracellular antigens

Glutamic acid decarboxylase (GAD) antibodies

Although GAD is an enzyme involved in metabolism of the inhibitory neurotransmitter GABA, it is an intracellular antigen and not a cell surface antigen. In general, GAD antibodies are a useful biomarker of autoimmunity, but are considered unlikely to be pathogenic. It is expected that patients with these antibodies have other cell surface autoantibodies, or the immune process is T-cell mediated. GAD antibodies at 'diabetic' level are considered insignificant in the context of neurological disease, whereas high-level GAD antibodies (>100units/ml) are considered more likely to be significant.[59,60]

GAD antibodies have been reported in children with limbic encephalitis and temporal lobe seizures,[29,61,62] similar to adults. Some cases responded positively to immunotherapy including steroids, immunoglobulins, plasmapheresis, and rituximab with favourable outcome; however, in general, patients with GAD antibodies are more resistant to immune therapy than those with cell surface antibodies.

OTHER ISSUES IN CELL SURFACE ANTIBODY METHODOLOGY

The issue of whether serum or CSF antibodies are preferable for assay testing is still under debate.[63] Although it is clear that many patients with anti-NMDAR encephalitis have intrathecal synthesis of antibodies, this is less true in other cell surface antibody syndromes, although the timing of testing is probably relevant, with hyper-acute testing least likely to demonstrate intrathecal synthesis. In general, serum testing appears adequate, although it is possible that a few cases of anti-NMDAR encephalitis could be missed with this approach. It has been shown that patients without a defined cell surface antibody who are suspected to have autoimmune encephalitis are equally likely to respond to immune therapy.[13] This suggests that there are other cell surface antibodies yet to be discovered, or that there are other inflammatory processes operating. In addition to the discovery of novel specific cell surface autoantibodies, other approaches can be used to demonstrate in principle that the patient harbours a cell surface antibody. 'Neuropil antibodies' is a term that was given to antibodies that bind to the synaptically dense regions (neuropil) in the hippocampus and cerebellum on immunohistochemistry.[64] In addition, IgG binding in serum or CSF against the cell surface of cultured live hippocampal neurons provides a rationale that the patient has a cell surface antibody, although this technique is labour intensive and only available in research laboratories.[65] One of the challenges in the area is the use of the commercial kits that use fixed cells to define 'cell surface antibodies'. By fixing the cells, antibody can access intracellular (as well as extracellular) epitopes; therefore fixed commercial cell lines do not only measure cell surface antibodies.

PATHOGENIC ROLE OF NEURONAL ANTIBODIES

In general the cell surface antibodies have demonstrated pathogenic potential, with downregulation of receptor from the cell surface (internalization) being the dominant pathogenic mechanism.[9,32,52,56,66–68]

However, there are some findings that argue against the pathogenic role of these antibodies. These include the presence of some of these autoantibodies in a proportion of controls, such as VGKC and NMDAR antibodies,[48] as well as the non-specificity of clinical syndromes associated with some of these antibodies, particularly VGKC and GAD antibodies. The presence of these antibodies might be a secondary phenomenon in some patients; nevertheless these autoantibodies are at least markers of immune activation and possible immune therapy responsiveness. It is also possible that when autoantibodies are found in neurologically well controls or patients, rather than representing a 'false-positive' result, they could predict the future development of clinical disease, as previously described in other autoantibody-associated diseases.[69]

TREATMENT OF SUSPECTED AND CONFIRMED AUTOIMMUNE SEIZURES AND EPILEPSY

There is a consensus that early immune treatment of cases with suspected and confirmed autoimmune encephalitis associated with seizures has better outcomes.[20,70] A positive response to immunotherapy is reported in 60 to 80% of adult patients with suspected autoimmune epilepsy (most had positive neuronal antibodies),[20,70] and in adult patients with drug-resistant epilepsy who are positive for neuronal antibodies.[21] Limited data and trials of immunotherapy are available in children.

Currently there are limited guidelines for the choice of first-line agents, length of treatment, or indications to switch to a second-line agent. Table III summarizes the generally accepted therapeutic approach. Many factors influence the decision making about second-line treatment and the agent to choose including availability, safety, side-effect profile, efficacy, as well as the severity of the disease.[71] The choice and combination of agents is often guided by the severity of disease, initial clinical response, and clinician familiarity with the therapies.

Table III: Immunotherapy for autoimmune epilepsy in children–recommended regimen

	Treatment and suggested regimen	Comments
(a) *Acute treatment*		
First line	Pulse intravenous methyl prednisolone (30mg/kg/d for 3–5d, maximum 1g/d)[50,70,80]	This can be repeated weekly for 4–6wks[70,80] and is often followed by oral prednisolone (given over weeks to months): see maintenance treatment
	Adjunctive IVIG (2g/kg given in two doses over 2d or 0.4g/kg/d for 5d)[50,80,81]	This treatment (IVIG) can be given as a one-off, or continued monthly for 3mo or longer depending on the syndrome and response
	Plasma exchange can be used as an alternative for IVIG (five to seven exchanges of 50ml/kg on alternate days)[80,81]	Patients who are steroid resistant may instead respond to IVIG or plasma exchange
Second line	Rituximab (375mg/m^2 weekly, four doses, or other regimens)[50,71]	Reserved for severe refractory cases with partial or no response to first-line agents
	Cyclophosphamide (750mg/m^2)[50,82]	Usually given as monthly pulses for 3–6mo, or until clinical recovery is achieved. Indications as for rituximab
(b) *Maintenance therapy*		
	Oral prednisolone (1–2mg/kg/d tapering over a few weeks–months)[81]	
	Monthly IVIG (0.4–1.0g/kg for 1d)	
	Mycophenolate mofetil (600mg/m^2 orally twice daily; maximum 2g/d)[81] or azathioprine (1–3mg/kg orally once a day) (steroid sparing agents)[50]	For steroid dependence, or relapsing course in steroid-responsive patients
	Maintenance rituximab or cyclophosphamide	In severe cases with high risk of relapse

IVIG, intravenous immunoglobulin.

Antibody-positive cases are more likely to receive second-line immunotherapy; however, seronegative cases may also respond to immune therapy.[13]

Although the different syndromes associated with autoantibodies share many common clinical and radiological features, there is emerging evidence that they have different responses to immunotherapy, and different risk of relapse.[34,72] This might suggest that the choice of treatment may need to be driven by the specific antibody and associated syndrome. For example, patients with LGI1-positive limbic encephalitis seem to respond extremely well to steroids, but not as well to rituximab.[72]

In addition to immunotherapy, it is recommended to screen for neoplasms in children with anti-NMDAR encephalitis. The association with tumour is otherwise very rare in children. When tumours are found, they should be removed. When tumours are not found in anti-NMDAR encephalitis, it is recommended that tumour screening is continued every 6 months for some years.

In general there are emerging themes in the treatment of autoimmune CNS disease:

1 Patients identified early and treated early generally do better;
2 Symptomatic management of seizures and other disorders in autoimmune encephalitis is difficult and refractory;
3 In patients who do not respond to a first-line therapy, an alternative first-line therapy should be considered; or second-line therapy if the disease severity warrants such an approach.

GUIDELINES FOR IDENTIFYING AUTOIMMUNE ENCEPHALITIS AND AUTOIMMUNE EPILEPSY

Diagnostic guidelines have been developed to help clinicians deal with patients having suspected autoimmune encephalitis or epilepsy in adults and children.[16,73] These guidelines are clinically oriented and classify patients into different categories of probability of an autoimmune aetiology, including definite, probable, possible, and unknown. The classification is based on many factors including clinical criteria (as described above), the presence of autoantibodies to neuronal surface antigens, and the response to immunotherapy.[16,73] An alternative laboratory-based approach is more 'antibody driven' and recommends that patients with positive cell surface antibodies should have confirmation that these autoantibodies bind to neuronal cell surface (using live cultures of neurons) and to neuropil (using rat brain immunohistochemistry).[74]

EPIDEMIOLOGICAL ASSOCIATION BETWEEN EPILEPSY AND AUTOIMMUNE DISEASE

The association between epilepsy and systemic autoimmune diseases is well known. A recent epidemiological population-based study of 2.5 million people with health care insurance showed a statistically significant relation between epilepsy and 12 different autoimmune disorders, the strongest association being with systemic lupus erythematosis, antiphospholipid syndrome, type 1 diabetes mellitus, and myasthenia gravis.[75] Overall, children with autoimmune diseases had a fivefold increased risk of epilepsy.[75] Although this association does not prove causation, the authors considered potential confounders including medication, and showed that the results were unchanged. It is possible that patients with organ-specific autoimmune disease produce neuronal antibodies resulting in epilepsy. For example, NMDAR antibodies were found in some cases of encephalopathy attributed to autoimmune thyroid disease.[23] Likewise CASPR2 antibodies were found in association with Hashimoto encephalopathy.[76]

AUTOIMMUNE EPILEPSY WITHOUT ENCEPHALITIS

There are now many reports and accumulating data to define a group of patients with an autoimmune basis for their seizures including those without typical 'autoimmune encephalitis' phenotype both in adults and in children. These patients present primarily with seizures in the absence of other features of encephalitis such as encephalopathy, although the seizures and electrographic abnormalities might be severe enough to produce an 'epileptic' encephalopathy.

Neuronal autoantibodies are found in many reports of adults and children with epilepsy, supporting the hypothesis that the epilepsy is 'autoimmune' in these cases. The emerging theme in these reports suggests that autoantibodies are more likely to be found in patients with focal seizures, particularly those who are refractory to antiepileptic drugs, and those previously classified as having 'unknown cause'.[19–21,48,77]

In an adult study of two epilepsy cohorts (established, *n*=235; new onset, *n*=181), neuronal autoantibodies were found in 11% of patients. There were no differences in antibody prevalence between established and new cohorts, or patients with focal or generalized epilepsy. The authors explored the aetiology for patients with focal epilepsy only and found that antibodies were more common in patients with unknown cause than those with a known structural or metabolic cause for their focal epilepsy.[19]

Another adult study investigated the prevalence of neuronal autoantibody in patients with focal epilepsy of unknown cause and in patients with mesial temporal lobe epilepsy with hippocampal sclerosis.[77] Neuronal autoantibodies were found in 13 out of 81 of the total cohort (16%), including 7 out of 55 of the group with focal epilepsy of unknown cause (12.7%) and 6 out of 26 with mesial temporal lobe epilepsy with hippocampal sclerosis (23%).

In a paediatric study of children with new-onset epilepsy (*n*=114), neuronal autoantibodies were found in 9.7% of the total cohort.[48] Neuronal autoantibodies were found more commonly in children with an unknown cause (21%) than in those who had a known structural or metabolic cause (3%). In the antibody-positive patients with unknown cause, the seizures were mostly focal (4/7).[48]

OUTCOME AND PROGNOSIS

The outcome of children with autoimmune seizures has not been studied extensively. Apart from cases of anti-NMDAR encephalitis, in many of the available reports so far, children either received no immunotherapy or therapy was late or incomplete when given. Variable outcomes are described; however, ongoing epilepsy and cognitive and psychiatric impairment are common.[13,18,48] Full recovery is reported, particularly in children who received immunotherapy.[13,53]

CONCLUSION AND FUTURE RESEARCH

Limited research studies are available about autoimmune epilepsy in children. In particular, clinical trials and studies assessing immunotherapies are lacking. The priority should be early identification and early intervention of children with suspected autoimmune epilepsy. To achieve this aim, autoimmunity needs to be considered in the differential diagnosis of new-onset epilepsy, and has recently been added to the International League Against Epilepsy aetiological classification of epilepsies. In addition, clinicians need to perform timely investigations to assess for the presence of CNS inflammation, and be ready to intervene with immune therapy. Although this review has focused on autoantibody-associated epilepsy, other inflammatory mechanisms are probably important, and we need improved biomarkers to identify these patients.

ACKNOWLEDGEMENTS

JS receives funding from the United Arab Emirates University Program for Advanced Research. RCD has funding from the Star Scientific Foundation, Petre Foundation, and a National Health and Medical Research Council Practitioner fellowship. The authors state that they had no interests that might be perceived as posing a conflict or bias.

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