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FULL-LENGTH ORIGINAL RESEARCH

Autoimmune epilepsy in children: Case series and proposed guidelines for identification

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Summary

Purpose: Antibodies against neuronal surface proteins are increasingly recognized in autoimmune central nervous system (CNS) disorders in which seizures are the main or an important feature. The disorders include antibody-associated limbic encephalitis and *N*-methyl-D-aspartate receptor (NMDAR) encephalitis; however, seizures of autoimmune etiology may exist beyond the spectrum of these recognized syndromes. Because these seizures are potentially treatable with immune therapy, guidelines are needed to help in their early recognition.

Methods: We describe 13 representative children seen at our tertiary institution over a period of 3.5 years with suspected autoimmune epilepsy. Autoimmune epilepsy was suspected clinically when there was any of the following: (1) recognizable syndromes such as NMDAR encephalitis or limbic encephalitis, (2) evidence of CNS inflammation in cerebrospinal fluid or on magnetic resonance imaging (MRI), (3) the presence of other autoimmune diseases, or (4) positive response to immunotherapy. We tested these patients for neuronal surface antibodies (voltage gated potassium channel [VGKC]-complex, leucine rich glioma inactivated 1 [LGI1], contactin-associated protein-like 2 [CASPR2], and NMDAR) and glutamic acid decarboxylase (GAD) antibodies. We modified the *J Neurol Neurosurg Psychiatry*, 83, 2012, 638 guidelines that were designed to classify adults with neuronal surface antibody syndromes (NSAS), to be more appropriate for children with suspected autoimmune epilepsy. Using the modified guidelines, the 13 patients were classified into definite, probable, possible, unlikely, or unknown autoimmune epilepsy according to the presence of neuronal surface or GAD antibodies, and the response to immune therapy when given.

Key Findings: Of the 13 patients, 11 were females, and the mean age was 6 years (range 1–13 years). Three patients had classical NMDAR encephalitis, two had VGKC encephalitis, two had limbic encephalitis with negative antibodies, three had epilepsy with other autoimmune diseases (one with high titer GAD antibodies), two had fever-induced refractory epileptic encephalopathy in school-aged children (FIRES), and one epileptic encephalopathy associated with VGKC antibodies. Seven patients of the 13 children with suspected autoimmune epilepsy were positive for neuronal surface antibodies (NMDAR, n = 3; VGKC-complex, n = 3; and GAD, n = 1). Immunotherapy was given to nine cases, and a positive response was more common in patients with positive neuronal surface antibodies (5/5) compared to those with negative antibodies (2/4). Applying the proposed guidelines, the classification of autoimmune epilepsy was definite in five, probable in one, possible in three, unlikely in two, and unknown in two patients.

Significance: Neuronal surface antibodies and GAD antibodies are present in a proportion of children with suspected autoimmune epilepsy and may define a treatable subgroup of childhood epilepsy. The proposed guidelines can be useful in the recognition of children with seizures of autoimmune etiology.

KEY WORDS: Epilepsy, Autoimmune, Antibodies, FIRES, VGKC, NMDAR, GAD, Pediatrics.

The association between autoantibodies and central nervous system (CNS) disease is increasingly recognized. Serum and cerebrospinal fluid (CSF) antibodies that bind to neuronal cell surface proteins including channels and receptors have the potential to be pathogenic and cause CNS disease. By contrast onconeuronal antibodies are typically targeted against intracellular antigens and not thought to be directly pathogenic (Vincent et al., 2011; Bien et al., 2012). Recently antibodies that bind extracellularly and are associated with CNS disorders have been called "neuronal surface antibodies" (NSAbs) and the disorders associated with these NSAbs are called "neuronal surface antibody syndromes" (NSAS) (Zuliani et al., 2012). There are well-defined CNS syndromes associated with NSAbs where seizures are an

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important feature. Examples include *N*-methyl-D-aspartate receptor (NMDAR) encephalitis in which 76–83% of patients will have focal, focal dyscognitive, or generalized seizures (Dalmau et al., 2007, 2008, 2011; Irani & Vincent, 2011), and voltage-gated potassium channel (VGKC)-complex antibody associated autoimmune limbic encephalitis (including leucine rich glioma inactivated 1 [LGI1] and contactin-associated protein-like 2 [CASPR2] antibodies) in which patients often have temporal lobe seizures (Irani et al., 2010; Lai et al., 2010). In addition, faciobrachial dystonic seizures are seen in adults in association with LGI1 antibodies and often precede the onset of the limbic encephalitis (Irani et al., 2011). Other NSAbs are less frequently found in adults with limbic encephalitis such as alpha amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and γ-aminobutyric acid B ($GABA_B$) receptor antibodies (Lai et al., 2009; Lancaster et al., 2010; Boronat et al., 2011). Antibodies to glutamic acid decarboxylase (GAD) have been associated with limbic encephalitis (Malter et al., 2010). Although GAD is an intracellular antigen and therefore GAD Abs themselves may not be pathogenic, it is possible that unrecognized NSAbs coexist with GAD Abs (Zuliani et al., 2012).

Zuliani et al. proposed guidelines for the recognition, testing, and treatment of suspected autoimmune CNS disorders. They used clinical criteria, supportive features, neuronal antibody testing, and the response to immune therapy to classify patients into categories of definite, probable, and possible NSAS (Zuliani et al., 2012). Lancaster and Dalmau have proposed an alternative laboratory-based algorithm for identification and assessment of antibodies to neuronal cell-surface antigens using cell based assays as well as rat brain immunohistochemistry and cultures of neurons for serum and CSF antibody binding (Lancaster & Dalmau, 2012).

In children, NMDAR encephalitis is well described (Florance et al., 2009), whereas limbic encephalitis has been described in association with a number of different autoantibodies including VGKC-complex Abs (Haberlandt et al., 2011; Suleiman et al., 2011a). In children there are other epileptic conditions where immune-mediated mechanisms are suspected such as febrile infection-related epilepsy syndrome (van Baalen et al., 2010) or fever-induced refractory epileptic encephalopathy in school-aged children (Nabbout et al., 2010, 2011), both called fever-induced refractory epileptic encephalopathy in school-aged children (FIRES). Previous terms used to describe similar syndromes include devastating epileptic encephalopathy in school-aged children (DESC) (Mikaeloff et al., 2006) and acute encephalitis with refractory repetitive partial seizures (AERRPS) (Sakuma, 2009). These conditions are characterized by new-onset refractory focal status epilepticus, preceded by fever or infection in previously normal children, followed by a chronic phase of refractory focal epilepsy and severe neurologic impairment (Sakuma et al., 2010). The cause of these conditions is unknown and underlying immune mechanisms have been proposed (Sakuma et al., 2010; Specchio et al., 2010; Nabbout et al., 2011) but not proven.

Herein we present a representative case series of 13 children suspected to have an autoimmune basis for their epilepsies. We propose modified guidelines for the recognition of autoimmune epilepsy and apply these guidelines to the 13 children with suspected autoimmune epilepsy to test their utility.

Methods

Cases identification

Through our clinical practice at The Children Hospital at Westmead (CHW) we identified cases with seizures that may have an autoimmune etiology. The neurology department at CHW is a busy tertiary children's hospital that sees 300–400 children with new onset seizures per year, as well as other acute and chronic neurologic diseases in children. The patients presented in this cohort were discussed in detail by JS and RCD as they were suspected to have an autoimmune cause of their epilepsy (as defined below), and were investigated for neuronal surface antibodies. This cohort does not represent all children with encephalitis (of all etiologies) seen during this time (n = 33) and are currently being tested in a separate study at this hospital. It is also likely that other autoimmune epilepsies were missed by the investigating team and were not tested for antibodies. Instead this cohort should be considered a representative sample of children with suspected autoimmune epilepsy, which were used to test the utility of the modified guidelines.

We suspected autoimmune epilepsy in children with acute or subacute onset of seizures once other causes (infection, structural, metabolic, or genetic) were excluded, and when any of the features described in Table 1 were present.

Herein we describe 13 representative patients seen over a three and a half year period (late 2008 to mid-2012), who we suspected may have an autoimmune cause for their epilepsy, and who had serum available for testing for neuronal antibodies. No patients have been previously reported except for case 5 (Suleiman et al., 2011a) and case 10 (Suleiman et al., 2011b), and these two cases were included as they test the utility of the guidelines. This study was approved by the hospital ethics committee.

Ten patients had serum testing in the acute phase of their illness, whereas in three the serum was from the chronic symptomatic phase. All samples were taken before immune therapy, if given. Antibody assays were all performed in Oxford, United Kingdom using previously published methods (Irani et al., 2010), apart from case 3, for which the assay was performed in National NMDAR antibody referral laboratory (Brisbane, Qld, Australia).

Table 1. Criteria and supportive features to suspect autoimmune epilepsy in children with seizures

The following two clinical criteria are used to suspect autoimmune epilepsy associated with NSAbs and GAD antibodies (both are needed)

1 Acute or subacute (<12 weeks) onset of symptoms.

2 Exclusion of other causes (CNS infection, trauma, toxic, tumor, metabolic, previous CNS disease).

The following supportive features would strengthen the suspicion of autoimmune epilepsy (patients should have at least 1 of the following):

1 The presence of a well-defined clinical syndrome such as NMDAR or limbic encephalitis

2 CNS inflammation manifested by at least one of:

- a CSF pleocytosis (defined as >5 white cells/mm^3) or presence of oligoclonal bands, elevated IgG index, or elevated neopterin (defined as >30 nM)
- b MRI abnormality compatible with an inflammatory or autoimmune encephalitis including increased signal in the mesiotemporal lobe (LE – like syndrome)
- c Inflammatory neuropathology on biopsy

3 History of other antibody mediated condition (e.g., myasthenia gravis), organ specific autoimmunity or other autoimmune disorders.[a]

4 Response to immunotherapy

[a]It is recognized that epilepsy is more common in many autoimmune disorders including multiple sclerosis, systemic lupus erythematosus, type 1 diabetes mellitus (T1DM), celiac disease, and autoimmune thyroid disease (Vincent & Crino, 2011).

Table 2. Classification categories of suspected autoimmune epilepsy in children identified using the criteria and supportive features in Table 1 (Zuliani et al., modified)

Classification categories expressing the likelihood of autoimmune epilepsy based on the presence of NSAbs and GAD Abs and the response to immunotherapy (see Fig. 1):

Definite autoimmune epilepsy is present if:
Known NSAbs are present in serum or CSF
AND there is response to immunotherapy

Probable autoimmune epilepsy is present if
Known NSAbs are present and no immunotherapy responsiveness demonstrated (immunotherapy unsuccessful or not given)
OR GAD antibodies are present AND there is response to immunotherapy

Possible autoimmune epilepsy is present if known NSAbs are negative and
GAD antibodies are present and no immunotherapy responsiveness demonstrated (unsuccessful or not given)
OR GAD antibodies are negative and there is a response to immunotherapy

Unlikely autoimmune epilepsy is present if
Known NSAbs and GAD are negative and there is no response to immunotherapy

Unknown autoimmune epilepsy[a] is present if
Known NSAbs and GAD are negative and immunotherapy is not given

[a]Patients in this category may move to a different category if they receive immunotherapy, such as "possible" if they respond or "unlikely" if they did not respond to immunotherapy.

Proposed modified guidelines

To improve recognition and diagnosis of children with suspected autoimmune epilepsy, we modified the guidelines proposed by Zuliani et al. for identification of children with neuronal surface antibodies syndromes (Table 1). Then, based on antibody testing and the response to immunotherapy (when given), we proposed five categories for classification (in descending order of likelihood of autoimmune epilepsy) including definite, probable, possible, unlikely, or unknown autoimmune epilepsy (Table 2, Fig. 1). We applied the modified guidelines to our 13 cases to test their usefulness (Table 3).

The main differences to the Zuliani et al. guidelines for adults include the following:

1 In children a paraneoplastic cause of epilepsy is very rare, and testing for onconeural antibodies is rarely necessary. However; children with positive NMDAR Abs should be screened for ovarian teratomas.

2 In children fever and intercurrent infections are common and less likely to be a supportive feature for an autoimmune process as has been proposed in adults, so this was not used as one of the supportive features (Zuliani et al., 2012).

3 We used elevated CSF neopterin as an additional marker of CNS inflammation (Dale et al., 2009).

4 In Zuliani et al., abnormalities on functional imaging including hypermetabolism on positron emission tomography or hyperperfusion on single proton computed tomography were used as features to suggest CNS inflammation. However, there is inadequate research to demonstrate their ability to discriminate epilepsy etiologies in children and therefore we did not include these features.

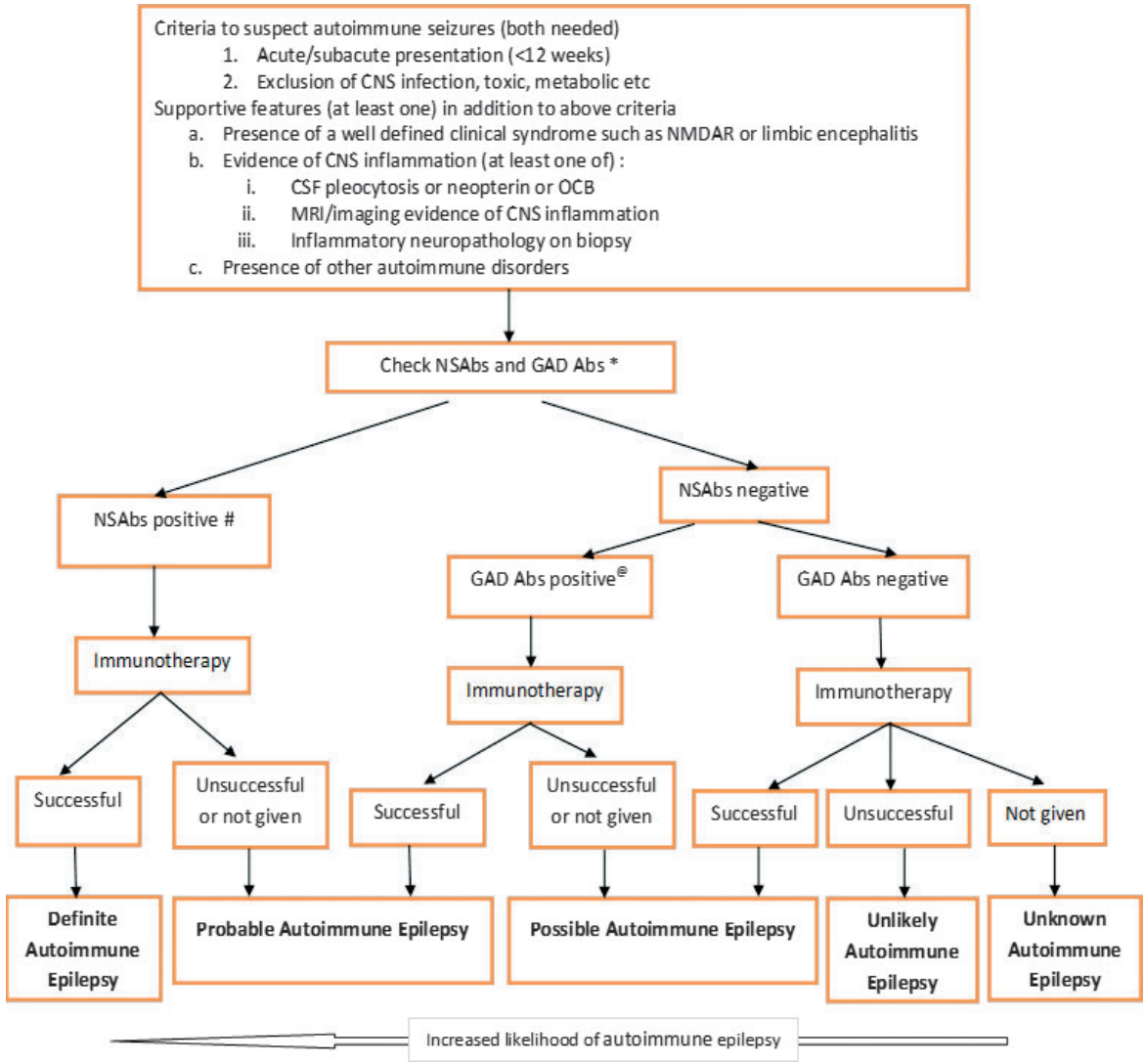

Figure 1.
Flow chart for approach to children with seizures of suspected autoimmune etiology (modified from Zuliani et al., 2012). OCB, oligoclonal bands; *, onconeuronal Abs testing is rarely necessary in children; #, if NMDAR, look for ovarian teratoma in females; @, GAD positivity is defined as >1,000 u/ml. Immunotherapy refers to high-dose steroids and/or intravenous immunoglobulins.
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5 Antibodies included in the guidelines are those available at international laboratories including antibodies against VGKC-complex proteins, LGI1 and CASPR2, NMDAR, and GAD. We did not include neuronal binding or neuropil antibody testing (using immunohistochemistry or immunofluorescence on rat brain tissue) for recognizable staining patterns (Lancaster & Dalmau, 2012), as these are done in research settings and are less available to clinicians routinely.

6 Response to immunotherapy was defined as significant clinical improvement of encephalopathy or reduction of seizures as judged by the treating clinicians. We accept the subjective nature of this, and the fact that there are a number of confounders that could be responsible for improvements such as the concomitant change in antiepileptic drugs.

7 We incorporated patients who did not receive immunotherapy into the classification either because an immune-mediated mechanism was not initially suspected or because of spontaneous improvement.

Results

The 13 patients with seizures of suspected autoimmune origin (11 female, age range 1–13 years, mean age 6 years) are presented in Table 3. All patients had other potential causes for their seizures excluded. All 13 patients had new-onset seizures and at least one supportive feature of CNS

Table 3. Patients with suspected autoimmune epilepsy: clinical criteria, supportive features, and classification as per guidelines (see Fig. 1)

Case	Age (years)/ sex	Epilepsy diagnosis	Acute or sub-acute onset	Seizure type	Associated features	CSF inflammation (pleocytosis/ OCB/ neopterin)	MRI inflammatory changes	Presence of autoimmune/ Ab mediated disease	NSAbs/ GAD Abs	Response to immune therapy	Outcome	Guideline classification
1	3/F	NMDAR encephalitis	+	Focal dyscognitive	Encephalopathy, aphasia, dystonia, emotional lability, relapse	−/+/+	−	−	NMDAR CSF and serum	+ (steroid, IVIG, mycophenolate)	Relapse, normal in between	Definite
2	6/M	NMDAR encephalitis	+	Focal dyscognitive	Encephalopathy, agitation, chorea, dystonia	+/−/+	−	−	NMDAR CSF and serum	+ (steroid and IVIG)	Recovery	Definite
3	7/F	NMDAR encephalitis	+	Focal dyscognitive	Encephalopathy, agitation, irritability, dyskinesia, fever	+/− /ND	+	−	NMDAR CSF and serum	+ (steroids, IVIG)	Recovery	Definite
4	1/F	VGKC encephalitis	+	Focal dyscognitive, focal motor with automatism	Encephalopathy, fever, respiratory infection	+/ND/+	+	−	VGKC serum (421 pM)	Not given	Recovery	Probable
5	15/F	VGKC encephalitis	+	Focal, secondary generalized tonic–clonic, status epilepticus,	Encephalopathy, memory deficit, fever	+/−/+	−	−	VGKC serum (640 pM)	+ (steroids, IVIG)	Relapse, normal in between	Definite
6	12/F	Limbic encephalitis	+	Focal dyscognitive	Encephalopathy, lethargy, behavioral alteration	ND	+	+/− (ANA)	Negative	Not given	Cognitive, psychiatric impairment	Unknown
7	15/F	Limbic encephalitis	+	Focal dyscognitive, secondary generalized tonic–clonic	Encephalopathy, cognitive deficits, fever	+/−/+	−	−	Negative	+ (steroid)	Recovery	Possible

Continued

Table 3. Continued.

Case	Age (years)/ sex	Epilepsy diagnosis	Acute or sub-acute onset	Seizure type	Associated features	CSF inflammation (pleocytosis/ OCB/ neopterin)	MRI inflammatory changes	Presence of autoimmune/ Ab mediated disease	NSAbs/ GAD Abs	Response to immune therapy	Outcome	Guideline classification
8	3/M	FIRES	+	Focal, status epilepticus	Encephalopathy, irritability, fever, rash,	−/−/+	−	−	Negative	− (steroids, IVIG, rituximab)	Severe neurologic disability, refractory epilepsy	Unlikely
9	8/F	FIRES	+	Focal, secondary generalized	Encephalopathy, headache, confusion, fever	+/−/+	+/−	−	Negative	− (steroids)	Severe neurologic disability, refractory epilepsy	Unlikely
10	1/F	Epileptic encephalopathy	+	Epileptic spasms	Encephalopathy, developmental delay	−/+/+	−	−	VGKC serum (201 pM)	+ (steroids)	Developmental delay	Definite
11	13/F	Suspected autoimmune epilepsy	+	Myoclonic, generalized tonic–clonic (JME)	Hyperthyroidism	ND	−	+ (Grave's disease and T1DM)	Negative	Not given	Ongoing epilepsy	Unknown
12	3/F	Suspected autoimmune epilepsy	+	Focal dyscognitive	Myasthenia	ND	−	+ (MG)	Negative	+ (steroids)	Steroid dependent myasthenia	Possible
13	4/F	Suspected autoimmune epilepsy	+	Absence	Ataxia	−/ND/ND	No	+ (T1DM)	GAD (3,000 U/ml)	Not given	Cognitive impairment, ongoing epilepsy	Possible

FIRES, fever-induced refractory epileptic encephalopathy in school-aged children; JME, juvenile myoclonic epilepsy; OCB, oligoclonal bands; ND, not done; T1DM, type 1 diabetes mellitus; MG, myasthenia gravis; NSAb, neuronal surface antibody.

Encephalopathy is defined by the presence of acquired reduction in consciousness, cognitive dysfunction, or behavioral change lasting more than 24 h, and not related to the posticital state, +: present or positive, −: absent or negative.

Abnormal ranges: Pleocytosis: CSF white blood cells >5 cells/mm^3, Neopterin elevated >30 nM, VGKC serum >100 pM, High titer cutoff for GAD antibodies in neurologic disease is 1,000 U/ml.

inflammation or the presence of other autoimmune diseases (Tables 1 and 2). Three patients had the clinical characteristics of NMDAR encephalitis (all with CSF and serum NMDAR antibodies), two had encephalitis associated with VGKC-complex antibodies, two had features suggestive of limbic encephalitis (with negative antibodies), three had epilepsy in association with other autoimmune diseases (one with GAD antibodies), two had FIRES, and one had epileptic encephalopathy with CNS inflammation (VGKC antibody positive).

Seven patients (53.9%) of the 13 were positive for one of the tested antibodies including NMDAR (n = 3), VGKC-complex (n = 3), and GAD (n = 1). Immunotherapy was given in nine patients: five with positive neuronal antibodies and four negative. The immune therapy was steroids alone (n = 4), steroids and intravenous immunoglobulin (IVIG) (n = 3), steroids, IVIG and mycophenolate (n = 1) and steroids, IVIG, and rituximab (n = 1). All five patients with positive neuronal antibodies who received any immune therapy improved after receiving therapy, whereas only two of four with negative neuronal antibodies improved after receiving immune therapy. Three of the four patients who did not receive immunotherapy had poor outcome including ongoing epilepsy, and cognitive and psychiatric impairment (Table 3).

Patients were classified according to the proposed modified guidelines (Table 2, Fig. 1), and their classification is presented in Table 3. Five patients had definite, one had probable, three had possible, two had unlikely, and two had unknown autoimmune epilepsy.

We present the case histories for 8 of the 13 patients in details in the Data S1 as representative examples.

Discussion

The recognition of immune mechanisms in neurologic disorders is important as this can prompt early treatment and may lead to better outcomes. The identification of specific and potentially pathogenic NSAbs is increasing, and the spectrum of the clinical syndromes associated with NSAbs is widening (Zuliani et al., 2012). Recently guidelines have been developed to help in the diagnosis and management of adults with suspected NSAS (Zuliani et al., 2012). In children the lack of large studies regarding NSAbs and their related syndromes makes it harder to identify these cases; therefore, guidelines may help in the identification of NSAS particularly when seizures are an important feature.

In this paper, we describe 13 representative patients with seizures of suspected autoimmune etiology and we propose features for identification of these pediatric patients, and a classification system testing the strength of evidence of autoimmune epilepsy based on the presence of neuronal antibodies and response to immunotherapy.

There were some general features common to the cohort. Females were over-represented in this cohort, as is often described in autoimmune disorders in general. The seizures were often focal, and generally occurred in association with encephalopathy or other features of CNS dysfunction.

Three cases had typical features of NMDAR encephalitis in children, as represented by case 3 description in the Data S1. The patients with NMDAR encephalitis generally had focal epilepsy, and the presence of psychiatric manifestations, behavior alteration, and movement disorder was a strong indicator of NMDAR encephalitis. However, it is possible that NMDAR Abs are present in children with epilepsy in the absence of the classic phenotype as has been described in adults (Niehusmann et al., 2009), and therefore testing for NMDAR Abs in children with suspected autoimmune seizures may provide further information about the spectrum of NMDAR antibody-associated disease.

Two cases had VGKC-complex Ab-associated encephalitis, characterized by fever-associated focal seizures and status epilepticus; one was previously reported (case 5) and the clinical phenotype of the second case (case 4) was similar to our previously reported pediatric patients with VGKC-complex Ab-associated encephalitis (Suleiman et al., 2011a). The seizure semiology was suggestive of temporal lobe onset, a finding that is commonly seen in both adults and children with this syndrome (Vincent et al., 2004; Suleiman et al., 2011a). In case 4, mycoplasma immunoglobulin M (IgM) was positive and was consistent with acute infection. Mycoplasma infection has been described in association with NMDAR encephalitis in children and may be a trigger of autoimmune CNS disorders (Florance et al., 2009). However, mycoplasma pneumonia is a common respiratory infection in children and positive mycoplasma serology may therefore be incidental in some patients (Waites & Talkington, 2004). Antibodies against LGI1 or CASPR2, which have been identified as the target of VGKC-complex Abs in adults, were negative in this case, a finding that is common in children with positive VGKC-complex Abs. It is possible that in children, VGKC-complex Abs are targeted against other antigens in the VGKC-complex that are yet to be identified. Patients with VGKC-complex Ab-associated encephalitis often respond to immune therapy, but spontaneous improvement can also occur (Irani et al., 2010) as was the case in this patient.

Case 6 had a syndrome of limbic encephalitis; however, NSAbs and GAD Abs were negative, possibly due to late testing and because the patient received no immunotherapy, the classification was "unknown." Early recognition, testing, and treatment might have improved her outcome. Case 7 had a limbic encephalitis syndrome and was negative for NSAbs but responded to immune therapy (classification possible). Antibodies against AMPAR and $GABA_BR$ (not tested) or other unrecognized NSAbs could be the cause of limbic encephalitis in these patients. The diagnosis of limbic encephalitis can be challenging in children, where its existence is reported but probably underrecognized (Haberlandt et al., 2011). The diagnosis of limbic encephalitis is

partly clinical, with new-onset temporal lobe seizures and cognitive disturbance sometimes associated with radiologic mesial temporal or hippocampal changes. Because hippocampal signal change is described in a proportion of children with febrile status epilepticus (Shinnar et al., 2012), it is difficult to discriminate radiologic seizure-induced hippocampal swelling from limbic encephalitis.

Cases 8 and 9 were typical of "FIRES" (van Baalen et al., 2010; Nabbout et al., 2011). Neuronal antibodies were negative, and there was no response to immunotherapy in both patients. The absence of antibodies and the negative response to immune therapy make an autoimmune etiology "unlikely." Negative response to immunotherapy has been reported in a series of seven cases of FIRES, and NSAbs were negative in the tested patients (three were tested for VGKC-complex Abs and one for NMDAR Abs) (Howell et al., 2012). In addition a series of 12 children with FIRES was negative for neuronal surface antibodies and GAD (van Baalen et al., 2012). There is one report of a boy with positive VGKC antibodies associated with FIRES who benefited from immunotherapy (Illingworth et al., 2011); however, this case did not have a typical course of FIRES and it is possible that the case had VGKC-complex antibody-associated encephalitis instead. The markers of CNS inflammation seen in our two cases (8 and 9) have been reported in the acute phase of FIRES, and may be explained by the extreme high seizure load, seizure-related neuronal injury, or cytokine release (Howell et al., 2012). Rather than an autoimmune epilepsy syndrome, FIRES may be a genetic channelopathy or a chronic epilepsy syndrome with explosive onset (Ismail & Kossoff, 2011; Howell et al., 2012).

Three of our cases had epilepsy in association with other autoimmune diseases including type 1 diabetes mellitus (T1DM) and autoimmune thyroid disease (case 11), anti MuSK myasthenia gravis (case 12), and T1DM and possible autoimmune ataxia (case 13).

T1DM is a T cell–mediated autoimmune disorder, and there is an increased prevalence of epilepsy in children with this disease (Schober et al., 2012).

Seizures can occur in Hashimoto's encephalopathy, which is a rare association of autoimmune Hashimoto's thyroiditis associated with Abs against thyroid peroxidase and thyroglobulin (Castillo et al., 2006). Patients described with Hashimoto encephalopathy present with broad clinical manifestations and are classically reported to be steroid responsive. The role of thyroid antibodies in Hashimoto encephalopathy is uncertain, and the term "steroid responsive encephalopathy associated with autoimmune thyroiditis" (SREAT) has been used to reflect the hypothesis that Hashimoto encephalopathy may be caused by unidentified neuronal autoantibodies (Castillo et al., 2002; Schauble et al., 2003).

Graves' disease is an antibody mediated autoimmune disorder and juvenile myoclonic epilepsy (JME) has been previously associated with Grave's disease, and may be due to thyroxine causing a lower seizure threshold (Su et al., 1993). Our case 11 was diagnosed to have an idiopathic myoclonic epilepsy (JME) based on her age, seizure phenotype, and EEG abnormality. JME is considered to be a genetic epilepsy, and indeed in this case there was limited evidence that the epilepsy was autoimmune despite the presence of other autoimmune diseases, and her classification was "unknown" as she was negative for NSAbs and received no immunotherapy.

Seizures in association with anti MuSK Ab myasthenia gravis are rare but have been reported in an adult patient (Bhagavati et al., 2007). Case 12 had anti-MuSK Ab associated myasthenia gravis and concurrent focal epilepsy. Her seizures did not respond to carbamazepine but improved when high dose steroids were used to treat her myasthenia gravis. It is possible that myasthenia gravis and epilepsy in our patient is a chance association, although both clinical entities presented, remitted and relapsed concurrently.

Case 13 had seizures in the context of T1DM. This patient had an acute transient ataxia followed by chronic epilepsy, with very high GAD antibodies. GAD antibodies are associated with a variety of CNS syndromes including stiff person syndrome, immune ataxia, epilepsy, and limbic encephalitis (Honnorat et al., 2001; Saiz et al., 2008; Malter et al., 2010). In our patient the immune-mediated ataxia, cognitive impairment, focal epilepsy, and high GAD antibodies were supportive of the autoimmune epilepsy hypothesis.

Patients with epilepsy and other systemic autoimmune diseases may have other as-yet-unidentified NSAbs. However, other explanations for increased epilepsy incidence in systemic autoimmune disorders include incidental coexistence, a common genetic predisposition, or secondary effects of the primary disease (Vincent & Crino, 2011).

One important feature of the adult guidelines is that response to immunotherapy is used as a retrospective feature to help with classification. In other words the "guideline classification" cannot be completed until immunotherapy is used. Our modified guidelines partly address this issue and incorporate patients who did not receive immunotherapy. In our case, series some patients did not receive immunotherapy either because an autoimmune etiology was not initially suspected at presentation or due to spontaneous improvement without the need for immunotherapy. A positive response to immunotherapy was more common in patients who had positive NSAb (five of five given immunotherapy) compared to those who were NSAb negative (two of four). However, in a recent study of 48 children with suspected autoimmune encephalitis, only 21 had specific antibodies detected, and beneficial treatment responses were seen in both antibody-positive and antibody-negative groups (Hacohen et al., 2012).

In our clinical practice over the last few years we have been increasingly using immunotherapy empirically once an underlying immune-mediated disorder is suspected while awaiting the specific investigations. Children suspected of potential autoimmune epilepsy undergo investigations to

exclude infectious, toxic, metabolic, or genetic causes, and neuronal surface and GAD antibodies are requested. While awaiting the results of the neuronal antibodies, empiric immunotherapy may be commenced if the clinical syndrome is severe and impairing. We suggest that immunotherapy be used early in the disease course to optimize its potential effect. The regimen we have been using includes intravenous pulse methylprednisolone at 30 mg/kg/day for 3 days followed by a tapering course of oral prednisolone (variable duration of weeks to months according to the disorder), often in conjunction with intravenous immunoglobulins at 2 g/kg given over 2 days. Patients with partial response or no response after 1–3 weeks may receive further doses of intravenous immunoglobulins or plasma exchange if the condition is severe and concerning, and the autoimmune hypothesis remains possible. Patients who fail to respond or who have a partial response may be considered for second-line therapy, such as rituximab or cyclophosphamide. However the side effect profile of these drugs is more concerning, so a "risk versus benefit" assessment is necessary. In our case series immunotherapy was generally tolerated well, particularly when given short term (such as the NMDAR encephalitis cases). Two patients developed significant side effects attributed to immunotherapy including behavioral alteration with prolonged steroid use (case 12) and prolonged hypogammaglobulinemia requiring IVIG replacement presumed to be secondary to rituximab (case 8), a finding that has been described previously (Makatsori et al., 2012). Some patients with seizures of autoimmune etiology can have complete recovery without immunotherapy (similar to case 4); however, it is hard to predict which cases will spontaneously recover, and therefore early immunotherapy is suggested when the patient is severely impaired. Similar treatment regimens have been used in adults with VGKC Ab-positive encephalitis with good effect (Reid et al., 2009; Wong et al., 2010). Although plasma exchange is used commonly in adults, the use of plasma exchange in children as a modality of immune therapy is limited due to its invasiveness, the need for intensive care treatment, and potential side effects.

Although a positive response to immunotherapy supports immune-mediated mechanisms, steroids (and IVIG to a lesser extent) are used in the treatment of refractory and severe epilepsies that are not proven to be autoimmune.

In conclusion, autoimmune mechanisms play an important role in a proportion of children presenting with seizures. We propose guidelines that may help clinicians in the approach to identify children with suspected autoimmune seizures. Although helpful, the guidelines are not perfect and represent only an attempt to identify and classify these patients. These guidelines do not predict treatment responsiveness or outcome. Future studies may improve the understanding of clinical phenotypes of autoimmune epilepsy in children and help further develop syndrome-specific and treatment-oriented guidelines.

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Disclosure

AV and the Department of Clinical Neurology in Oxford receive royalties and payments for antibody assays, and AV is the named inventor on patent application WO/2010/046716 entitled "Neurological Autoimmune Disorders." The patent has been licensed to Euroimmun AG for the development of assays for LGI1 and other VGKC-complex antibodies. AV and BL are coinventors and may also receive future royalties. None of the other authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Clinical case histories of eight of the patients are described in detail.