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Clinical Study

Characterisation of a syndrome of autoimmune adult onset focal epilepsy and encephalitis

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ABSTRACT

We report a series of patients with a clinical syndrome characterised by the explosive onset in adulthood of recurrent focal seizures of frontotemporal onset and features suggestive of autoimmune encephalitis. We propose that this presentation of "autoimmune adult onset focal epilepsy and encephalitis" is a recognisable clinical syndrome, and provide evidence it may be associated with heterogeneous immunological targets. Between 2008 and 2011 we encountered six patients with new-onset epilepsy in whom we suspected an autoimmune aetiology. We first characterised the clinical, electroencephalographic, cerebrospinal fluid (CSF), imaging, and pathological findings of this syndrome. We subsequently tested them for antibodies against both intracellular and neuronal cell surface antigens. All patients presented with recurrent seizures with focal frontotemporal onset, refractory to multiple anticonvulsants. Four had focal T2-weighted hyperintensities on MRI. CSF mononuclear cells were variably elevated with positive oligoclonal bands in four. Brain biopsy in one patient demonstrated perivascular lymphocytic infiltration. Two were treated with immunosuppression and went on to achieve complete seizure control and return to baseline cognition. Three of four patients who received only pulsed steroids or no treatment had ongoing frequent seizures, with two dying of sudden unexpected death in epilepsy. Subsequently, three had antibodies identified against neuronal cell surface antigens including N-methyl-D-aspartate receptor and leucine-rich glioma inactivated 1. We suggest that patients with such a presentation should be carefully evaluated for a suspected autoimmune aetiology targeting cell surface antigens and have a therapeutic trial of immunosuppression as this may improve their long-term outcome.

1. Introduction

There is a recognised association between encephalitis and epilepsy. Previously, this was best illustrated by limbic encephalitis (LE) first described in the 1960s, with features of memory loss, epileptic seizures of temporal semiology or affective disturbances [1,2]. LE is often associated with onconeural antibodies targeting intracellular antigens such as Hu, Ma, and Ri [1]. Traditionally, LE is paraneoplastic, associated with various malignancies, including small cell lung cancer, and tends to be progressive. The prognosis can be guarded and management is primarily directed at the malignancy, with neuronal cell death thought to be secondary to T cell-mediated cytotoxicity [3,4]. Onconeural antibodies are thought to be biomarkers of associated tumours rather than directly pathogenic [5].

It is increasingly recognised that autoantibodies targeting extracellular epitopes of cell surface receptors and trans-synaptic protein complexes are responsible for a number of presentations of encephalitis [3]. Identified targets include components of the voltage-gated potassium channel complex (VGKC) such as leucine-rich glioma inactivated 1 (Lgi1) and contactin-associated protein-like 2 (Caspr2); the N-methyl-D-aspartate receptor (NMDAR); the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR);

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and the γ-aminobutyric acid receptor ($GABA_BR$) [2,3]. Autoimmune encephalitis associated with antibodies against cell surface antigens appears to have a higher incidence and a better prognosis than those associated with antibodies to intracellular antigens. The former patients have a less frequent association with an underlying malignancy, may have a relapsing course, and are often responsive to immunomodulatory therapy [3,4]. Autoantibodies, such as those targeting the NMDAR, are thought to be directly pathogenic [5]. Serum autoantibodies targeting neuronal cell surface antigens such as the VGKC complex, the NMDAR, and glutamic acid decarboxylase (GAD) have been found in a variable proportion of unselected patients presenting with both newly diagnosed and refractory drug resistant epilepsy, with quoted percentages ranging from 2% to 16% in different studies [6–14]. Antibody mediated epilepsy has also been recognised as being an uncommon cause of status epilepticus [12]. Descriptions of new clinical phenotypes with a specific association to certain autoantibodies, such as faciobrachial dystonic seizures and Lgi1 antibodies, are emerging [11].

Epileptic syndromes following a febrile illness have been described in the paediatric literature under various nomenclatures including idiopathic catastrophic epileptic encephalopathy [15], severe refractory status epilepticus owing to presumed encephalitis [16], devastating epilepsy in school-age children [17], and acute encephalitis with refractory repetitive partial seizures (AERRPS) [18]. This clinical entity has been most recently termed febrile illness-related epilepsy syndrome or fever-induced refractory epileptic encephalopathy in school-aged children (FIRES) [19–23]. There are also descriptions of acute onset epilepsy syndromes in the adult population. Wilder-Smith et al. proposed an entity termed new-onset refractory status epilepticus (NORSE) in 2005 [24]. This was characterised in previously well young adults who presented after an antecedent febrile illness with prolonged status epilepticus. Their clinical course was catastrophic with five of seven dying and two surviving in a vegetative state with refractory epilepsy. Patients described as having a "malignant status epilepticus syndrome" share similar features with NORSE [25]. An immune-mediated pathogenesis for some of these syndromes has been postulated [26–28]. Antibodies against the N-methyl-D-aspartate (NMDA)-type-glutamate receptor (GluR) ε2 subunit have been described in patients with AERRPS and Rasmussen's encephalitis although the disease specificity and pathogenicity of these antibodies are yet to be established [27,28]. Generally in FIRES and NORSE, there are no defining antibodies, either biomarker or pathogenic.

2. Methods

We identified six patients who presented to three tertiary hospitals in Sydney, Australia, over 4 years (2008–2011) in whom we had suspected new onset epilepsy of autoimmune origin based on their clinical presentation and/or cerebrospinal fluid (CSF) findings, prior to any cell surface antibody testing. Inclusion criteria were patients who presented with an explosive onset of epilepsy, with clinical and electrical evidence of recurrent focal seizures of frontotemporal onset refractory to therapy with anticonvulsants, who also had either CSF changes suggestive of an inflammatory aetiology or imaging suggestive of focal pathology. Exclusion criteria included risk factors for epilepsy such as chronic structural lesions, birth complications, cerebral infections, prior head injury or a positive family history for epilepsy. Ethics approval and informed consent was obtained. As a number of antibodies were not available for testing when some of our patients first presented, we contacted patients in January 2012 and arranged for current serum samples to be tested for antibodies against NMDAR, AMPAR, $GABA_BR$, Lgi1 and Caspr2. Anti-GAD antibodies, although targeting intracellular antigens, were also tested given previous descriptions of an association with epilepsy [6]. Time from initial presentation to testing varied between patients (mean 1.9 years, range 0.5–3.6 years). Testing was performed by the Clinical Neuroimmunology Laboratory Oxford University Radcliffe Hospitals Trust in Oxford with cell based assays as previously described [11].

3. Results

3.1. Illustrative patient

This illustrative patient (Patient 2) outlines the features of this syndrome of suspected autoimmune adult onset focal epilepsy and encephalitis (AAFEE) (Table 1). This patient was a 34-year-old right-handed construction worker of Chinese ethnicity, who was previously well with no risk factors for epilepsy. He presented in 2009 with a 1 week history of a viral prodrome, and his first generalised seizure. In the following week he developed intermittent expressive dysphasia, episodes of "blank staring" during which he was unresponsive, auditory hallucinations, and right arm and facial paraesthesia and jerking. Eight days after his initial seizure, he had three secondarily generalised seizures prompting admission. A typical focal seizure was often triggered by speaking or eating. He would stop chewing, develop posturing of his mouth with jaw opening and of his right hand, and have semi-purposeful movements of his left hand. He would be unable to speak or move his right hand on command. During his admission, he was noted to have similar recurrent focal seizures which were initially occurring at a frequency of more than 20 per day. An interictal electroencephalogram (EEG) demonstrated left frontocentral slowing. Numerous EEG seizures that originated in the left frontocentral region were recorded, with phase reversal at C3 (Supp. Fig. 1). His CSF examination demonstrated a mild lymphocytic pleocytosis with 6×10^6/L (normal range 0–5×10^6/L) mononuclear cells and was positive for oligoclonal bands in the CSF but not the serum. A vasculitic screen and antineuronal antibodies were negative. Whole body imaging did not reveal an underlying malignancy. MRI demonstrated left frontotemporal cortical hyperintensity and swelling with faint increased signal on diffusion weighted imaging, which colocalised with left perisylvian cerebral hypermetabolism on a positron emission tomography (PET) scan (Supp. Fig. 2).

Despite a combination of maximum doses of four antiepileptic agents he continued to have between five and 20 focal seizures a day. He was empirically treated with 3 days of pulsed methylprednisolone 2 weeks after presentation. Although it was recognised that his focal MRI and PET abnormalities could have been secondary to his seizures, because of his lack of response to therapy the decision was made to proceed to a brain biopsy to exclude an underlying neoplastic or vasculitic process. The biopsy demonstrated foci of perivascular lymphocytic infiltration, suggestive of an immune mediated process (Supp. Fig. 3). The lymphocytes were predominantly CD3+ T cells.

Over a period of 2 weeks after methylprednisolone and with titration of his anticonvulsants, he demonstrated improvement in seizure frequency. He was discharged home 7 weeks after presentation, with complete seizure control. He had persistent mild aphasia and difficulties with concentration in the absence of ongoing EEG epileptiform activity. Six month clinical and neuropsychological follow-up demonstrated a return to baseline function.

3.2. Clinical presentation and seizure semiology

Clinical data from five female and one male patient are summarised in Table 1. They were all under the age of 50 and had a preceding viral prodrome. Fevers were not documented during this prodromal phase or their inpatient admission. The most striking

Table 1
Clinical, laboratory and imaging results and clinical response to treatment

	Time of presentation	Age, years	Sex	Risk factors for epilepsy	Viral prodrome (headache, myalgia)	Clinical presentation suggestive of focal seizures	Associated Features	Secondarily GTCS	Seizure frequency	EEG features	Anticonvulsant regime	CSF mononuclear cell count (× 10^6/L)	CSF oligoclonal bands	Imaging characteristics	Immunomodulatory treatment trials	Response and clinical outcome	Neuronal cell surface antigen (tested January 2012)
Patient 1	June 2008	23	Female	No	Yes	Right facial twitching, jerking of right arm and right leg, NCSE requiring ICU	Encephalopathy with confusion, requiring management in the ICU for NCSE	Yes	Initially 4–6 focal seizures per day, admitted to ICU in NCSE, later 1–4/day	Left frontotemporal seizure onset, occasional right frontotemporal discharges, encephalopathic background; follow-up EEG showing bilateral frontotemporal seizure onset	LEV 1 g tds, TPM 125 mg bd, CNZ 0.5 mg bd	0	Absent	MRI: no focal abnormality, PET: mild bilateral inferior frontal and bitemporal hypometabolism	3 days of IV methylprednisone, then oral taper of prednisone	Ongoing seizures, frequency 1/week–1/fortnight, SUDEP 2012	Negative
Patient 2	May 2009	34	Male	No	Yes	Aphasia, right face and arm paraesthesia	Features of global language dysfunction, impaired attention and short term memory	Yes	5–20/day	Left frontotemporal seizure onset, encephalopathic background	LEV 1.5 g bd. TPM 150 mg bd, CNZ 0.5 mg qid, PHT 300 mg od	6	Present	MRI: left frontal T2-weighted hyperintensity and swelling, PET: left perisylvian cerebral hypermetabolism	3 days of IV methylprednisone	Cessation of seizures, complete recovery	Negative
Patient 3	May 2009	23	Female	No	Yes	Onset 22 weeks gestation, head and eye deviation to left, left hemiparaesthesia, left facial and upper limb jerking, NCSE requiring ICU	Encephalopathy with confusion, requiring management in the ICU for NCSE	Yes	Initially focal seizures with subsequent GTCS, NCSE in ICU, later 4–7/day	Right frontotemporal seizure onset, occasional left frontal discharges, encephalopathic background; follow-up EEG showing bilateral frontotemporal seizure onset	CBZ 600 mg mane 800 mg nocte, VAL 1.5 g bd, TPM 200 mg bd, CNZ 1 mg tds	2–10 on repeat CSF	Present	MRI: right temporal T2-weighted hyperintensity and swelling, PET post delivery: mild bitemporal (right > left) hypometabolism	5 days of IV methylprednisone, second trial of pulse steroids 4 months later	Ongoing seizures, frequency 1/fortnight, SUDEP November 2012	Negative
Patient 4	August 2010	41	Female	No	Yes	Head and eye deviation to right, right facial twitching	Impaired attention, impaired short term memory, personality changes including irritability	Yes	2–3/day	Rhythmic left frontotemporal slowing, encephalopathic background	LEV 1 g bd, VAL 1 g bd, TPM 100 mg bd	0	Present	MRI: no focal abnormality	None	Ongoing seizures, frequency 1/fortnight–1/month, residual executive dysfunction on neuropsychological assessment	NMDAR
Patient 5	June 2011	44	Female	No	Yes	Recurrent aphasia, right sided visual disturbance	Aphasia, mild difficulty reading	Yes	2–3/day	Left frontotemporal slowing and sharp waves, encephalopathic background	CBZ 200 mg bd, LEV 1.5 g bd	23	Absent	MRI: left temporoparietal hyperintensity/swelling	5 days of IV methylprednisone, 5 days of induction of IVIg, then maintenance with monthly IVIg	Cessation of seizures, complete recovery	Lgi1
Patient 6	July 2011	46	Female	No	Yes	Aphasic, disorientated, amnestic	Fatuous affect, disinhibition, severely impaired memory	No	5–10/day	Left frontotemporal seizure onset	PHT 300 mg od, LEV 750 mg bd	6	Present	MRI: left frontotemporal hyperintensity	5 days of IV methylprednisone, followed by maintenance with oral prednisone and azathioprine	Cessation of seizures, good recovery	NMDAR

bd = twice daily, Caspr2 = contactin associated protein-like 2, CBZ = carbamazepine, CNZ = clonazepam, CSF = cerebrospinal fluid, GTCS = generalised tonic clonic seizure, ICU = intensive care unit, IVIg = intravenous immunoglobulin, LEV = levetiracetam, Lgi1 = leucine-rich glioma inactivated 1, mane = in the morning, NCSE = nonconvulsive status epilepticus, NMDAR = N-methyl D-aspartate receptor, nocte = in the evening, od = once daily, PHT = phenytoin, qid = four times daily, SUDEP = sudden unexpected death in epilepsy, tds = three times daily, TPM = topiramate, VAL = sodium valproate.

clinical feature was the explosive onset of multiple daily seizures of focal onset refractory to multiple anticonvulsants. The seizures were stereotyped and of focal onset with semiology consistent with frontotemporal involvement such as aphasia or unilateral limb movement. Each individual initially had a single seizure type (for example, Patient 2 had five to 20 daily episodes of recurrent aphasic seizures associated with right upper limb motor arrest, whereas Patient 4 had two to three daily episodes of head and eye deviation to the right and right facial twitching). Three patients had EEG seizures arising from a unilateral frontotemporal focus, with a fourth demonstrating rhythmic left frontotemporal slowing. Two patients demonstrated primarily unilateral frontotemporal seizure onset with occasional interictal discharges from the contralateral frontotemporal region. The patients evolved to develop an encephalopathic picture with confusion and generalised theta and delta slowing on the EEG, with two requiring management in the intensive care unit for nonconvulsive focal status epilepticus. Five developed secondarily generalised tonic clonic seizures. None had faciobrachial dystonic seizures.

3.3. Investigations

Four patients had variable CSF lymphocytosis (ranging from 0–23 $\times$ 10^6/L mononuclear cells). Infectious aetiologies were excluded, with four being empirically treated with acyclovir until herpes simplex virus polymerase chain reaction testing was confirmed to be negative. Four patients were positive for oligoclonal bands isolated to CSF. Four patients had focal T2-weighted hyperintensity on MRI corresponding to the location of seizure onset on EEG. Patient 2 underwent a brain biopsy which revealed perivascular lymphocytic infiltration, characterised as CD3+ T cells.

3.4. Immunomodulatory therapy trialed and patient outcomes

Five patients were treated empirically with pulsed steroids while one (Patient 4) did not receive any therapy apart from anticonvulsants. Two were treated proactively with immunosuppression: Patient 5 received induction and maintenance immunoglobulin and Patient 6 was maintained on prednisone and azathioprine after pulsed methylprednisolone. These two patients went on to demonstrate complete control of seizures implying treatment responsiveness. In contrast, three of the four who received only pulsed steroids or no treatment have had ongoing frequent seizures and residual cognitive impairment with two patients being unable to return to employment. Subsequent to their inclusion in this study two patients (Patient 1 and 3) died unexpectedly in 2012 at 45 and 42 months after their initial presentation, respectively, at a time where ongoing seizure frequency was one seizure every 1 to 2 weeks, with their deaths attributed to sudden unexpected death in epilepsy (SUDEP).

3.5. Immunological characterisation

All patients tested negative for the standard intracellular onconeural antibody screen both at initial presentation and follow-up. Extensive investigation with whole body CT and PET scans failed to reveal an underlying malignancy in all patients. Three of our six patients were negative for antibodies to known cell surface antigens. The other three (50%) were found to be positive for serum antibodies to NMDAR and Lgi1 (Table 1).

4. Discussion

We describe a series of patients with a clinical syndrome that has not been previously well-characterised in the adult literature. Although these patients demonstrated some features previously described in the field of autoimmune encephalitides, they shared a distinct constellation of clinical and investigation findings on presentation which we feel should be highlighted as a recognisable clinical syndrome [29]. We propose to label this syndrome "autoimmune adult onset focal epilepsy and encephalitis" (AAFEE), to emphasise the key clinical features. These include:

- Previously well adults with no risk factors for epilepsy.
- A preceding viral prodrome.
- The explosive onset of multiple daily focal seizures of frontotemporal semiology (±secondarily generalised seizures) refractory to anticonvulsants alone but responsive to immunosuppression.
- An associated encephalopathy.
- Clinical and EEG evidence supporting a focal frontotemporal seizure onset at presentation, with or without the presence of multifocal discharges as their seizures continue.
- Variable CSF lymphocytosis and/or positive oligoclonal bands.
- Focal imaging abnormalities.

AAFEE may well be a subpopulation of patients previously characterised as NORSE, however we believe there are a number of distinct differences between these two groups of patients which have been outlined in Table 2. AAFEE is characterised by recurrent focal seizures at presentation that are clinically evident by signs such as aphasia or unilateral facial or limb twitching, arising mainly from frontotemporal foci on EEG, and sometimes associated with focal cortical swelling and hyperintensity on MRI. Two patients (Patient 1 and 3) with refractory seizures went on to demonstrate bilateral frontotemporal foci of seizure onset over the course of their admission, but their initial presentation was notably focal. In contrast, clinically evident focal seizures are not common in NORSE and epileptiform activity on EEG is primarily described as being multifocal or generalised from the onset of the clinical presentation [24,30].

While all our patients with AAFEE had a viral prodrome prior to their presentation with seizures, recurrent fever was not a documented phenomenon in any, differentiating this syndrome from both FIRES and NORSE. Four patients had oligoclonal bands in the CSF without matching bands in the serum, contrary to patients with FIRES or NORSE in whom CSF oligoclonal bands are usually absent [2,30,31]. Furthermore, the histopathology of NORSE is often nonspecific changes with reactive gliosis [24,30]. In contrast, the single patient in our series who underwent a brain biopsy had perivascular lymphocytic infiltration implying an antigen-specific immune reaction (Fig. 3). Imaging in FIRES and NORSE is typically normal at onset, although mesial temporal signal changes may be present in later stages due to seizure activity, as well as generalised atrophy in the case of FIRES [30,31]. In contrast, four of our six patients demonstrated focal areas of MRI and/or PET scan abnormalities.

Previous reports of NORSE and FIRES document that only a minority of patients were treated with immunomodulatory therapy, with largely negative results [22,24,32]. The prognosis in NORSE and the paediatric equivalent, FIRES, is catastrophic, with death following status epilepticus, or refractory epilepsy, as a sequelae in the majority of patients [19,30]. While our patient cohort is small, two patients were treated with substantial immunomodulatory therapy (Patient 5 and 6). They were both subsequently found to be positive for cell surface antigens (Lgi1 and NMDAR), and demonstrated significant clinical improvement coincident with immunomodulatory therapy resulting in seizure cessation and a return to baseline cognitive function. This rapid and complete response is significantly different to previous reports of patients with NORSE or FIRES, lending further weight to the proposition that AAFEE is a distinct and potentially treatable clinical syndrome, and of suspected immune-mediated aetiology.

Table 2
Comparison of clinical and investigation findings in autoimmune adult onset focal epilepsy and encephalitis, new-onset refractory status epilepticus and fever-induced refractory epileptic encephalopathy in school-aged children

	Autoimmune adult onset focal epilepsy and encephalitis	NORSE	FIRES
Age group, sex predisposition	23–46, female:male 5:1	20–50 s, primarily female	Children
Prodrome	Preceding viral prodrome, absence of fevers	Preceding febrile illness	Preceding febrile illness
Seizure semiology	Recurrent focal seizures of a single semiology (e.g. stereotyped aphasia, unilateral limb twitching) with occasional subsequent secondarily generalised seizures	Frequently multifocal or generalised seizures at onset	May start with focal seizures but rapidly progress to become multifocal and generalised
EEG features	Predominantly unifocal frontotemporal seizure focus, 2/6 patients developed bilateral frontotemporal epileptiform discharges on EEG later in disease course	Multifocal or generalised seizure foci	May have focal discharges early on, but rapidly become multifocal or generalised
CSF findings	4/6 patients had CSF (but not serum) oligoclonal bands	Unremarkable, no oligoclonal bands	Variable lymphocytosis, although often unremarkable; no oligoclonal bands
MRI characteristics	4/6 patients had MRI or PET scan features of focal abnormalities corresponding to site of seizure focus	Typically normal at onset	Typically normal at onset
Histopathology	1/6 patients with a biopsy had perivascular lymphocytic infiltration	Nonspecific changes with reactive gliosis, no inflammatory infiltrate	Variable cell loss, mild astrogliosis, no inflammatory infiltrate
Treatment response and prognosis	2/2 patients with significant immunosuppressive therapy recovered to baseline, 2/4 patients treated with either steroids or no therapy had ongoing seizures and died secondary to SUDEP, 1/4 patients without therapy had ongoing seizures	No response to immune therapy; poor prognosis with refractory epilepsy, vegetative state or death	No response to immune therapy; poor prognosis with refractory focal or multifocal epilepsy without a silent period, vegetative or minimally conscious states, or death; only a minority of patients recover free of any neurological sequelae
Detection of neuronal surface antibodies	3/6 patients had antibodies detected to neuronal surface antibodies (NMDAR and Lgi1)	No defining pathogenic or biomarker antibodies have been identified	No defining pathogenic or biomarker antibodies have been identified

CSF = cerebrospinal fluid, EEG = electroencephalogram, FIRES = fever-induced refractory epileptic encephalopathy in school-aged children, Lgi1 = leucine-rich glioma inactivated 1, NMDAR = N-methyl-D-aspartate receptor encephalitis, NORSE = new-onset refractory status epilepticus, PET = positron emission tomography, SUDEP = sudden unexpected death in epilepsy.

It is interesting to note that our antibody positive patients did not have the typical presentation that is described in the literature for these antibodies. Both patients with positive NMDAR antibodies (Patient 4 and 6) did not present with psychosis, orofacial dyskinesias, or develop central hypoventilation [33]. While 40% of patients with Lgi1 antibodies have myoclonic-like movements, and up to 20% of patients with VGKC antibody mediated limbic encephalitis manifest initially as faciobrachial dystonic seizures, neither of these clinical phenotypes were present in our Lgi1 patient (Patient 5) [3,11,34,35].

There are other clinical entities that should be considered in patients with a presentation suggestive of AAFEE. This syndrome is distinguished from LE by its often frontotemporal and frontocentral focus of seizure onset, rather than being limited to medial temporal structures as is the case in LE. It is distinguished from cortical dysplasia by an initial presentation in adulthood rather than childhood or adolescence, its preceding viral prodrome, the association with encephalopathy, and the presence of inflammatory markers such as CSF oligoclonal bands. Biopsy findings in Patient 2 also did not support cortical dysplasia.

The female preponderance, the presence of CSF oligoclonal bands in four patients, and the perivascular lymphocytic infiltrate in the one brain biopsy suggests an immune-mediated pathogenesis underpins AAFEE. We feel the fact that antibodies to known cell surface antigens (NMDAR and Lgi1) were subsequently identified in three of our six (50%) patients and that there was an excellent response to immunomodulatory therapy in two patients supports our contention that this syndrome has a suspected autoimmune basis. Two patients without clear evidence of CSF inflammation (Patient 4 and 5) were nevertheless found to be positive for antibodies against neuronal cell surface antigen (NMDAR and Lgi1). While a lymphocytic pleocytosis and oligoclonal bands in the CSF is suggestive of an inflammatory process, we cannot exclude the possibility that the CSF pleocytosis may be secondary to seizure activity, and importantly, the absence of these features does not exclude the possibility of AAFEE.

Zuliani et al. propose that an immune-mediated aetiology associated with neuronal surface antibodies should be suspected in patients who develop an acute or subacute onset of symptoms (<12 weeks), evidence of central nervous system inflammation either in the CSF (lymphocytic pleocytosis, CSF oligoclonal bands, or elevated immunoglobulin G indices), on imaging (with MRI hyperintensity or functional imaging changes on PET scan), or on biopsy with lymphocytic infiltrates [5]. They suggest supporting features include preceding infectious symptoms, a febrile illness or a viral prodrome, or a history of autoimmunity. All of our patients met these proposed criteria, complementing our notion that AAFEE is likely to be immune-mediated. Lancaster et al. recently proposed an algorithm that incorporates the use of cell based assays, rat brain immunohistochemistry and neuronal cultures to optimise detection of antibodies to cell surface antigens [29].

Quek et al. investigated 32 patients with refractory epilepsy of presumed autoimmune basis [6]. Neural autoantibodies were identified in 27 (91%) patients. A variety of antibodies were identified including both cell surface receptor antigens (NMDAR, Lgi1, Caspr2) and intracellular antigens (GAD65, CRMP5, Ma2). The fact that a similar clinical syndrome is associated with heterogeneous central nervous system targets mirrors our experience with our series of patients. Most patients described by Quek et al. had focal onset seizure types, predominantly arising from the temporal lobe, although a few had extratemporal seizure onset on EEG and accompanying MRI changes, reminiscent of our series of patients [6]. One patient had histopathology demonstrating perivascular inflammatory infiltrates, similar to our illustrative patient. Twenty-one of 27 patients with uncontrolled epilepsy despite multiple anticonvulsants achieved seizure control after initiation of immunomodulatory therapy. In established autoimmune encephalitis associated epilepsy, it is clear that conventional anticonvulsants do not control seizures, and that immunotherapy is required [6]. We believe that the focal autoimmune epilepsy syndrome that we have described as AAFEE should be considered part of the continuum of suspected autoimmune encephalopathy associated with heterogenous autoantibody markers, and that recognition is important as it has therapeutic ramifications.

The retrospective nature of this case series and the relatively small number of patients are inherent limitations of the study design. However, we believe this series highlights an important population of patients in whom recognition of a possible immunological aetiology is essential to focus treatment on the underlying cause and improve clinical outcomes. This is further reinforced by the subsequent death from presumed SUDEP of two of four patients in this series who did not receive immunomodulatory therapy other than steroids.

The lack of diagnosis of a cell surface receptor antibody in three of our six patients deserves comment. We did not identify significant differences in the clinical presentation between patients who were antibody positive as opposed to antibody negative. One limitation of the study design and a possible explanation is the long duration between clinical presentation and peak illness to the testing of serum antibodies. It would have been ideal to have serum from the acute phase of the illness, but some of the autoantibodies had not been described at the time of presentation for the earlier patients, and serum testing was therefore performed during the chronic phase. Other potential explanations for the antibody negative patients include primarily intrathecal production of a known antibody, or the presence of novel antibodies that have not yet been recognised. We hypothesise that a considered regime of immune therapy in these patients might have improved their outcome. Ideally, all patients with a suspected clinical presentation of AAFEE should be tested at the time of initial presentation prior to any immunomodulatory therapy.

We propose that there is a distinct clinical syndrome characterised by the explosive onset in adulthood of recurrent focal frontotemporal seizures refractory to anticonvulsants alone, and features suggestive of suspected autoimmune encephalitis. We believe testing for the full panel of known cell surface antigens (including Lgi1, Caspr2, the VGKC complex, NMDAR, and GAD, and if these are negative considering AMPAR and $GABA_BR$) rather than selective autoantibody testing is indicated, as such patients may have antibodies targeting heterogenous cell surface and synaptic targets, and their presentation may not be typical of the characteristic clinical phenotype thus far described for these individual syndromes. We recommend screening for an underlying malignancy with a whole body PET-CT scan, and in patients where there is a high index of suspicion of anti-NMDAR encephalitis, a pelvic MRI.

To our knowledge there are no definitive therapeutic guidelines for many of the neuronal surface antibody syndromes, with most of the literature focused on anti-NMDAR encephalitis as it has the longest follow-up in a large cohort to date [36]. We recommend initial treatment with 3 to 5 days of pulsed intravenous methylprednisolone (30 mg/kg/day up to 1 g/day) followed by high dose oral prednisone (1–2 mg/kg/day) and 2 g/kg of intravenous immunoglobulin administered over two to five doses [37]. A lack of response within 2 weeks should prompt consideration of three to five exchanges with plasmapheresis, or commencement of second line therapy such as rituximab or cyclophosphamide. Early recognition of these patients as having a potentially reversible condition, and initiation of immunotherapy, may reduce the chance of secondary neuronal injury and improve outcomes.

Conflicts of Interest/Disclosures

A.V. and the University of Oxford hold patents and receive royalties and payments for antibody assays. A.V. acts as a consultant to Athena Diagnostics and receives funding from Euroimmun AG (Luebeck) for antibody development. The other authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jocn.2013.09.024.

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