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Clinical Study

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

Sudarshini Ramanathan [a,b], Andrew Bleasel [a,b], John Parratt [c,d], Carolyn Orr [e], Russell C. Dale [f], Angela Vincent [g], Victor S.C. Fung [a,b,*]

[a] Department of Neurology, Westmead Hospital, Westmead, NSW 2145, Australia
[b] Westmead Clinical School, University of Sydney, Sydney, NSW, Australia
[c] Department of Neurology, Royal North Shore Hospital, St Leonards, NSW, Australia
[d] Northern Clinical School, University of Sydney, Sydney, NSW, Australia
[e] Macquarie Neurology, Macquarie University Hospital, Macquarie University, NSW, Australia
[f] Neuroimmunology Group, Institute for Neuroscience and Muscle Research, The Kids Research Institute at the Children's Hospital at Westmead, University of Sydney, Westmead, NSW, Australia
[g] Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

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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);

* Corresponding author. Tel.: +61 2 9845 6793; fax: +61 2 9635 6684.
E-mail address: vfung@usyd.edu.au (V.S.C. Fung).

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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