Clinical commentary

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Effectiveness of multimodality treatment for autoimmune limbic epilepsy

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ABSTRACT – We evaluated the outcome of multimodality treatment in autoimmune limbic epilepsy in 3 consecutive patients (2 male and 1 female; age 33-55 years) presenting with a combination of focal non-convulsive status epilepticus, memory impairment, and psychosis. MRI showed right or bitemporal T2 or FLAIR hyperintensity. Video-EEG showed seizures of right temporo-occipital or bitemporal independent onset. Extensive workup failed to reveal infectious aetiology or an underlying tumour. However, the autoantibody panel was positive for one or more of these antibodies: anti-VGKC, anti-$GABA_B$, anti-VGCC (P/Q, N types), and anti-GAD65. All patients received: (1) conventional antiepileptic drugs including levetiracetam, lacosamide, phenobarbital, lamotrigine, and valproate; (2) immunomodulatory therapy including methylprednisolone, plasmapheresis, and intravenous immunoglobulin; and (3) rituximab. After a 4-6-week in-hospital course, the seizures resolved in all patients but 2 had persistent memory impairment. None had treatment-related complications. At the time of last follow-up, 2-3 months later, 2 patients remained seizure-free while 2 had residual memory impairment. Our findings suggest that multimodality treatment with a combination of conventional AEDs, immunomodulatory therapy, and rituximab is effective and safe in autoimmune limbic epilepsy.

Key words: limbic encephalitis, paraneoplastic syndrome, autoimmune epilepsy, status epilepticus, rituximab

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Limbic encephalitis (LE) is characterized by confusion, cognitive difficulty, memory impairment, and seizures caused by inflammation in the limbic structures. LE is generally felt to be a paraneoplastic condition attributed to an underlying malignancy, with antibodies directed against the intracellular antigens, such as Hu, Ma2, CRMP5[1], and amphiphysin. However, antibodies directed against the cell membrane or synaptic receptors (*e.g.* VGKC, NMDAR, LGI1, Caspr, $GABA_B$, GAD^2) have also been associated with LE, with or without an underlying malignancy (Davis and Dalmau, 2013). Although LE can present with various neuropsychiatric manifestations, seizures are

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common in this disorder, often leading to refractory autoimmune limbic epilepsy (ALE). Besides optimizing antiepileptic drugs (AEDs) and treating the underlying tumour (if identified), no clear guidelines exist for managing ALE (Ozkara and Vivegano, 2011). When seizures are intractable, immunomodulators (*e.g.* intravenous methylprednisolone [IVMP], intravenous immunoglobulin [IVIG], and plasmapheresis) have been used as first-line therapy with variable success. Immunosuppressants (*e.g.* cyclophosphamide) have been tried as second-line agents, but are not favoured because of serious adverse effects. In this article, we present a series of three consecutive patients (*table 1*) with refractory ALE who achieved successful outcome after receiving multimodality treatment with conventional AEDs, various immunomodulators, and an immunosuppressant (rituximab). Our aim is to add to the expanding literature on ALE, and to provide practical guidelines on prompt diagnosis and management of this potentially reversible illness.

Case studies

Patient 1 was a 53-year-old Caucasian male with a history of hypertension, hyperlipidaemia, and coronary artery disease, who presented with new-onset seizures of eight weeks duration. His seizures were characterized by staring, left head deviation, left facial twitching, and generalized tonic-clonic activity. Seizures remained intractable to multiple AEDs, and he developed anterograde memory loss, agitation, visual and auditory hallucinations, and worsening confusion leading to persistently altered mental status. Upon transfer to our facility, the patient was severely disoriented and confused without focal neurological deficits. Video-EEG monitoring (VEM) showed focal non-convulsive status epilepticus (FNCSE) with clinical and electrographic seizures originating from the right temporo-parietal region (*figure 1A*). Interictal EEG showed periodic lateralized epileptiform discharges (PLEDs) in the right temporo-parieto-occipital region. Brain MRI showed FLAIR hyperintensity in the medial right temporal lobe (*figure 2A*). CSF studies showed normal glucose, mildly elevated protein (55 mg/dL), normal nucleated cell count, negative HSV PCR, and negative West Nile virus (WNV) antibodies. Although FNCSE eventually resolved on a combination of levetiracetam, lacosamide, and phenobarbital, he remained amnestic and confused, with subsequent VEM showing electrographic seizures of left temporal onset. He was treated empirically with 5 g IVMP over 5 days. Because of only minimal improvement in mental status, he received five cycles of plasmapheresis. Paraneoplastic panel showed anti-VGCC[3] (P/Q and N type) and anti-$GABA_B$ antibodies. CT of chest and abdomen was negative for tumour. Cervical lymph node biopsy showed no evidence of malignancy. Despite improvement in the mental state, he continued to have short-term memory impairment and developed visual hallucinations. This prompted a course of 2 g/kg IVIG over 5 days, followed by 1 g IV rituximab to achieve long-term immunosuppression. At the time of discharge from the acute care setting to a rehabilitation facility, the seizures were controlled but mild disorientation and short-term memory impairment persisted. At the last follow-up visit, 91 days after inpatient discharge, the patient had one witnessed complex partial seizure; he had residual memory impairment and behavioural problems, despite significant improvement.

Patient 2 was a 33-year-old African-American female with a history of glutamic acid decarboxylase 65 (GAD65) antibody-positive stiff person syndrome and seizures, who presented with progressively worsening memory impairment and intractable seizures. She also reported a one-year history of fatigue, gait ataxia, rigidity, and myoclonus triggered by loud noise (hyperekplexia). Upon admission, she was noted to have dysconjugate gaze, increased tone, bilateral dysmetria, and wide-based ataxic gait. VEM showed brief but frequent electrographic seizures of independent right and left temporal onset (*figure 1B*). Interictal EEG showed frequent right temporal sharp waves. Brain MRI showed bilateral FLAIR hyperintensities involving the parahippocampal gyri (*figure 2B*), raising the possibility of ALE as a new diagnosis despite prior history of epilepsy. CSF studies were unremarkable. Seizures improved with IV fosphenytoin, lacosamide, and lamotrigine. Given the history of GAD65-positive syndrome, she was empirically treated with IVIG, at 2 g/kg over five days. Serum paraneoplastic panel showed anti-GAD65 (4,531 nmol/L) and anti-VGKC (0.04 nmol/L) antibodies. CT chest and abdomen did not show underlying malignancy. Because of persistent left posterior temporal electrographic seizures, she was treated with 500 mg IV rituximab without complications. Subsequent monitoring showed resolution of electrographic seizures. Two months later, she was readmitted with increased frequency of clinical and electrographic seizures of bitemporal independent onset (left greater than right), prompting an increase in baseline AEDs and a second dose of 500 mg IV rituximab. At the time of discharge, CD19

[1] CRMP: collapsin response mediator protein.

[2] Caspr: contactin-associated proteinlike; $GABA_B$: gamma aminobutyric acid type B; GAD: glutamic acid decarboxylase; LGI: leucine-rich glioma inactivated; NMDAR: N-methyl D-aspartate receptor; VGKC: voltage-gated potassium channel.

[3] VGCC: voltage-gated calcium channel.

Table 1. Clinical characteristics of three patients.

	Patient 1	**Patient 2**	**Patient 3**
Age (years)	53	33	55
Gender	M	F	M
Race	Caucasian	African-American	Caucasian
Time from symptom onset to duration	8 weeks	4 weeks	12 weeks
Prodromal syndrome	Yes	Yes	Yes
Presenting symptom	Behavioural changes	Memory loss	Seizure
Seizures	Clinical and electrographic	Clinical and electrographic	Clinical
Behavioural changes	Yes	No	Yes
Memory impairment	Yes	Yes	Yes
Autonomic dysfunction	Yes	Yes	Yes
CSF pleocytosis	No	No	No
Elevated CSF Protein	Yes	No	Yes
Autoantibodies	Anti-$GABA_B$, anti-VGCC (P/Q and N type)	Anti-GAD65, anti-VGKC	Anti-VGKC
EEG findings	Right temporo-parietal focal non-convulsive status epilepticus	Bitemporal independent focal non-convulsive status epilepticus	Right temporal focal non-convulsive status epilepticus
MRI Findings	FLAIR hyperintensity involving right medial temporal lobe	FLAIR hyperintensity involving bilateral hippocampii and fornices (right greater than left)	FLAIR hyperintensity involving right hippocampus and uncus
Malignancy workup	Negative	Negative	Negative
Antiepileptic drugs	Levetiracetam, lacosamide, phenobarbital	Fosphenytoin, lacosamide, lamotrigine	Levetiracetam, valproate, lamotrigine, phenobarbital
IV steroids	Yes	Yes	Yes
Plasmapheresis	Yes	No	Yes
IV immunoglobulins	Yes	Yes	Yes
Rituximab	Yes	Yes	Yes
Last follow-up visit	91 days; rare seizure; residual memory and behavioural problems	63 days; seizure free; intermittent muscle spasm and back pain	68 days; seizure free; residual memory problem

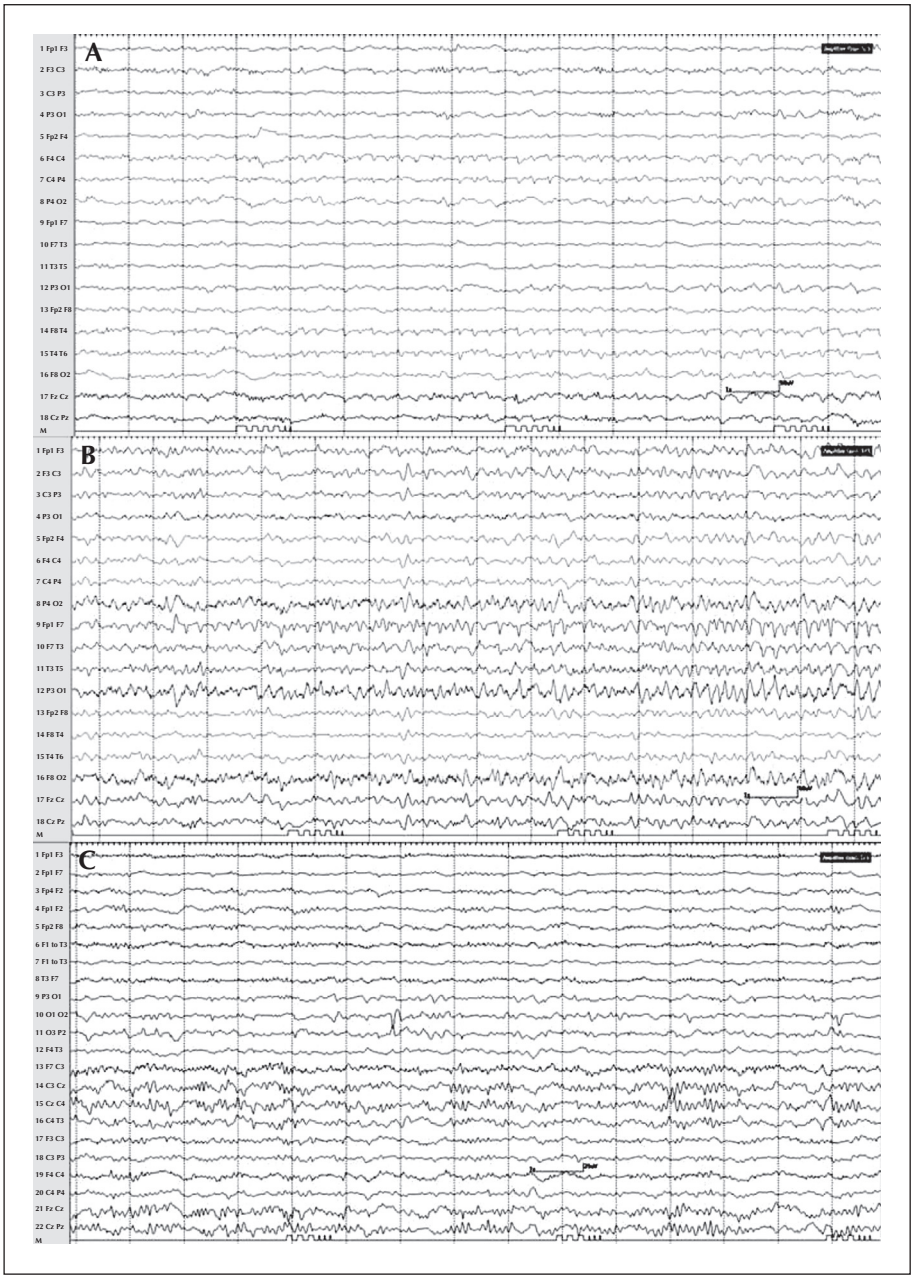

Figure 1. EEG findings: (A) right temporo-parietal ictal discharge in Patient 1; (B) left temporal ictal discharge in Patient 2; and (C) right posterior temporal-occipital interictal epileptiform discharges in Patient 3.

count was 0.1%, and the electrographic seizures had resolved, but she continued to have spasms that were non-epileptic, felt to be related to the underlying stiff-person syndrome. At the last follow-up visit, 63 days after inpatient discharge, she had remained seizure-free, however, she continued to have intermittent muscle spasm and back pain.

Patient 3 was a healthy 55-year-old Caucasian male who presented to the outside facility with worsening memory impairment, behavioural problems, agitation, and FNCSE with clinical seizures of right temporal onset. Brain MRI showed T2 hyperintensity involving the right medial temporal lobe (*figure 2C*). CSF studies showed elevated protein (77 mg/dL), normal glucose, and normal cell count. Studies for infectious aetiology were unremarkable. Biopsy of the right temporal lobe was non-diagnostic, consistent with non-specific inflammation. Upon transfer to our facility, the seizures were controlled by a combination of levetiracetam, valproate, lamotrigine, and phenobarbital, but he remained confused and agitated without focal neurological deficits. VEM showed no clinical or

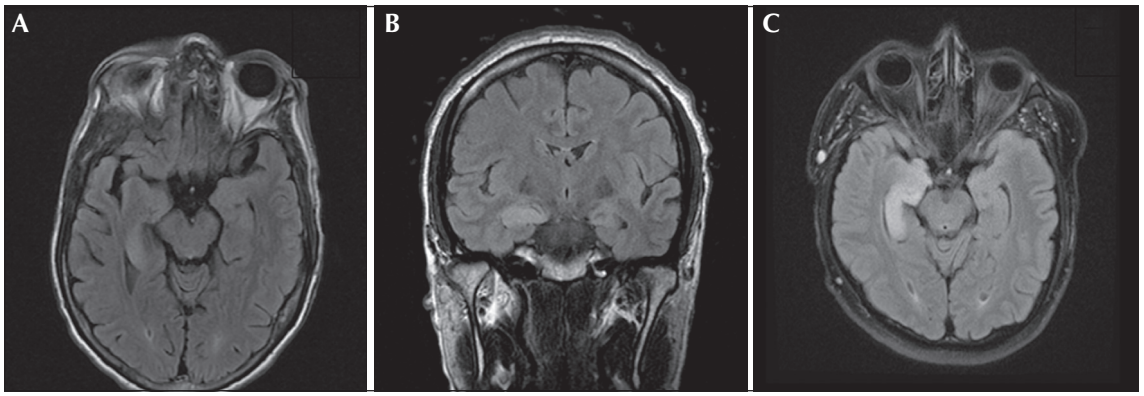

Figure 2. MRI findings: (A) FLAIR hyperintensity in the medial right temporal lobe in Patient 1; (B) bilateral FLAIR hyperintensities in the parahippocampal gyri in Patient 2; and (C) T2 hyperintensity in the right medial temporal lobe in Patient 3.

electrographic seizure activity, but showed frequent right posterior temporal-occipital interictal epileptiform discharges (*figure 1C*). He received 5 g IVMP over 5 days. Levetiracetam was discontinued due to concern of behavioural problems, but the other AEDs were continued. Quetiapine was started for agitation and visual hallucinations. Lack of improvement in mental status prompted five cycles of plasmapheresis followed by IVIG, at 2 g/kg over 5 days. Quetiapine was stopped and haloperidol was started. Paraneoplastic panel was positive for anti-VGKC antibodies (0.13 nmol/L). CT chest and abdomen did not show underlying malignancy. Because of persistently altered mental status, he was treated with rituximab 500 mg IV. At the time of discharge to an inpatient rehabilitation facility, CD19 count was 0.2%, and the seizures were completely controlled and the agitation was markedly improved. At last follow-up visit, 68 days after inpatient discharge, the patient had remained seizure-free, and had no more behavioural outbursts or agitation, however, he continued to have residual memory impairment.

Discussion

For patients with new-onset seizures in the setting of acute or subacute neurocognitive manifestations, a diagnosis of autoimmune limbic epilepsy (ALE) should be entertained. However, no definitive guidelines exist for treating ALE (Ozkara and Vivegano, 2011). Our study demonstrates that if seizures remain refractory to conventional AEDs, immunomodulation can be beneficial while the diagnostic workup is pursued. If an underlying malignancy is discovered, the treatment of the tumour seems to be most effective. However, when the malignancy workup is negative, rituximab appears to be an effective and safe option as our study demonstrates. Our series is along the lines of a recent study which reported success with various combinations of IVMP, IVIG, plasmapheresis, and cyclophosphamide in 12 patients with autoimmune epilepsy (Quek *et al.,* 2012). Our series expands the literature and highlights the effectiveness of rituximab in a heterogeneous group of ALE patients with different types of antibodies.

The rationale for immunotherapy in ALE is based on multiple lines of evidence. It has been shown that the antibodies from patients bind to the $GABA_B$ receptors in rat neurons, and disruptions of the rodent $GABA_B$ receptors result in clinical phenotypes similar to limbic encephalitis and epilepsy (Lancaster *et al.,* 2010). Immunoglobulins from patients with anti-NMDAR antibodies have been shown to cause neuronal dysfunction in cultured hippocampal neurons, while infusion of CSF from these patients resulted in a reduction of hippocampal NMDAR immunostaining in rats (Hughes *et al.,* 2010). Brain biopsies of patients with LE have revealed inflammatory changes, such as extensive neuronal loss, gliosis, microglial nodules, perivascular lymphocytic cuffing, and leptomeningeal mononuclear cell infiltrates (Graus *et al.,* 2008). Thus, these findings point towards immune-mediated neuronal damage which can be curbed by immunosuppressants.

Besides the conventional AEDs to control the seizures, we hypothesize that multimodality immunotherapy is effective in ALE because of different mechanisms of action on the immune system. First, glucocorticoids reduce inflammation by modulating chemokine and cytokine production, adhesion molecule expression, and white blood cell production (Rhen and Cidlowski, 2005). Second, plasmapheresis, an extracorporeal blood purification technique, removes large molecular-weight molecules, such as immunoglobulins, and filters out plasma membrane proteins such as VGKC complexes from the blood (Winters, 2012). Third, IVIG, a sterile, purified IgG product from pooled human plasma, helps modulate complement activation, suppress idiotypic antibodies, saturate Fc

receptors on macrophages, and suppress cytokines, chemokines, and metalloproteinases (Boros *et al*., 2005). Finally, rituximab, a humanized monoclonal IgG, targets CD20, the surface antigen of B lymphocytes, thereby eliminating the latter prior to their differentiation into plasma cells (Dropcho, 2013).

None of our patients underwent PET, thus there remained a small possibility that an underlying malignancy could still exist. We could also not determine which therapy may have provided the greatest impact on outcome, since all of the therapies were administered over a short period of time. Nevertheless, our series demonstrates successful treatment of intractable non-paraneoplastic ALE using conventional AEDs, empiric immunomodulation, and rituximab, the latter being a potentially less toxic alternative to cyclophosphamide. Further studies are needed to support our findings and determine the optimum duration of immunotherapy to prevent relapse. □

Disclosures.
None of the authors have any conflict of interest to disclose.

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