

Myoclonic status epilepticus as a presentation of caspr2 antibody-associated autoimmune encephalitis

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ABSTRACT – We present a case of autoimmune encephalitis associated with antibodies targeting contactin-associated protein-like 2. This case is notable because of the presentation with myoclonic status epilepticus and the prolonged clinical course of refractory seizures, which are demonstrated in the accompanying videos, and not previously associated with this condition. Treatment with prednisone, intravenous immunoglobulin, plasma exchange, rituximab, cyclophosphamide, and mycophenolate mofetil resulted in significant functional improvement. Historically, myoclonic status epilepticus is associated with a grave prognosis and minimal chance of meaningful recovery. This case demonstrates that autoimmune encephalitis remains an important differential diagnosis in patients with such a presentation, and that early recognition and the appropriate institution of immunotherapy can result in seizure control and functional recovery. [*Published with video sequences*]

Key words: autoimmune encephalitis, autoimmune epilepsy, VGKC complex associated encephalitis, caspr2 antibodies, myoclonic status epilepticus

Antibodies targeting the voltage-gated potassium channel (VGKC) complex and associated proteins have been identified as being relevant in both peripheral and central autoimmune neurological disorders, with autoimmune encephalitis now a recognised manifestation. We describe a patient with autoimmune encephalitis and antibodies targeting contactin-associated protein-like 2 (caspr2) who presented

with myoclonic status epilepticus. To our knowledge, myoclonic status epilepticus has not been previously described with autoimmune encephalitis associated with caspr2 antibodies. Refractory status epilepticus and myoclonic status epilepticus are frequently associated with a poor outcome including death or severe neurological disability (Jumao-as and Brenner, 1990; Ferlisi and Shorvon, 2012). This case demonstrates that autoimmune



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encephalitis is an important differential diagnosis in such patients, and that early diagnosis and targeted immunotherapy can improve prognosis and functional outcome.

Case study

A 35-year-old woman presented with a three-day history of a viral prodrome with lethargy, myalgia, vomiting, and a non-specific headache. She became hypersomnolent, and developed recurrent prolonged generalised convulsions prompting admission. She did not have any risk factors for epilepsy. There was a strong family history of autoimmunity and she had a brother diagnosed with idiopathic thrombocytopenic purpura, a mother with Graves disease, and a maternal uncle with systemic lupus erythematosus.

Initial observation revealed irregular bilateral myoclonus. She had prominent and asymmetric facial myoclonus, with eyelid, mouth, and tongue involvement, more notable on the left. She also had action myoclonus of the limbs. Progressive unresponsiveness prompted intubation for airway protection and a transfer to the intensive care unit. She continued to have refractory myoclonus (*video sequence 1*). Electroencephalograms (EEGs) revealed generalised periodic spike or polyspike-and-wave discharges at 2 Hz (*figure 1A*). Attempts at weaning sedation resulted in generalised myoclonic seizures without regaining consciousness (*figure 1B*).

Repeated cerebrospinal fluid (CSF) analyses demonstrated normal protein levels, a lymphocytic pleocytosis ($44 \times 10^6/l$ mononuclear cells), and intrathecal oligoclonal bands. CSF analysis was negative for herpes simplex virus (HSV), enterovirus, and Whipple's. A vasculitic screen, anti-phospholipid antibodies, and anti-thyroid antibody testing was negative. Serum and CSF antibodies against the N-methyl-D-aspartate receptor (NMDAR) and the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), and anti-neuronal antibodies against intracellular antigens, were negative. Magnetic resonance imaging of the brain demonstrated subtle bilateral hippocampal/parahippocampal high T2 fluid attenuated inversion recovery signal and mild diffusion restriction, without accompanying contrast enhancement (*figure 1C*). There was no malignancy on wholebody positron emission tomography, and no thymoma on imaging. Needle electromyography did not reveal neuromyotonia.

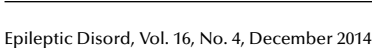
A thiopentone coma was commenced to achieve burst suppression as treatment of status epilepticus, and coma was maintained with propofol and midazolam. Treatment with combinations of multiple anticonvulsants including phenytoin, levetiracetam, sodium

valproate, topiramate, ethosuxamide, lacosamide, and clobazam failed to achieve seizure control without propofol and midazolam infusions. Repeated EEGs demonstrated diffuse cortical dysfunction, as well as bursts of maximal central discharges in synchrony with her clinical myoclonus (*figure 1D*). Frequently, clinical myoclonus was not accompanied by epileptiform discharges. Initial treatment included intravenous acyclovir and antibiotics on presentation until her HSV PCR and CSF cultures were proven to be negative. From the second day of admission, she received three doses of pulsed steroids (1 g/day) followed by oral prednisone (60 mg daily), and five doses of intravenous immunoglobulin to target a possible autoimmune encephalitis (*figure 1E*).

Serum antibodies against the VGKC complex were detected in pre-treatment admission blood tests. An initial sample tested at the Oxford laboratory demonstrated a VGKC antibody titre of 909 pmol/l (normal range 0-100). A cell-based assay demonstrated high titre antibodies targeting caspr2, with no antibodies present against leucine-rich glioma inactivated 1 (Lgl1). Glutamic acid decarboxylase (GAD) antibodies were also elevated at 148 U/ml (normal range: 0-5). Due to refractory myoclonic status epilepticus, a ketamine infusion was trialed based on previously reported success in status epilepticus (Pruss and Holtkamp, 2008). Two doses of 1 g rituximab over a fortnight were also administered. Serial samples of VGKC antibody titres throughout the patient's disease course were also tested at a national laboratory (*figure 1E*).

Ten days after commencement of rituximab and with ongoing reduction in sedation, her level of consciousness improved and she was able to follow one-step commands. She had marked weakness secondary to deconditioning, and persisting action induced facial and limb myoclonus. Despite clinical stability, anti-VGKC complex titres continued to rise, prompting further treatment with five plasma exchanges and commencement of mycophenolate mofetil. She was transferred to an inpatient rehabilitation unit after a four-month admission, and discharged home one month later. Anti-VGKC antibody titres progressively declined and eventually become undetectable (*figure 1E*). On discharge, there were no further clinical or EEG seizures, but there was persisting facial, bulbar, and tongue myoclonus, as well as speech dyspraxia and dysarthria. Maintenance immunosuppression with mycophenolate 1 g bd and conservatively weaned oral prednisone was continued. Anticonvulsant therapy was rationalized to levetiracetam at 1 g mane/2 g nocte, carbamazepine at 600 mg tds, and clonazepam at 6 mg qid.

She experienced five months of clinical stability. However, persistent myoclonus, despite the absence of



clinical seizures, and a rebound of VGKC levels, despite ongoing B cell depletion, prompted cessation of mycophenolate and institution of five further plasma exchanges and monthly pulses of cyclophosphamide over 12 months (500 mg/month). Twenty months post disease onset, she was seronegative for VGKC complex antibodies, with improved swallowing function, and no spontaneous myoclonus, although she had residual action-induced facial myoclonus and speech impairment (*video sequence 2*). Her functional improvement allowed a return to employment, with neuropsychiatric assessment demonstrating no significant residual cognitive deficits. Maintenance immunotherapy included 10 mg of prednisone and 75 mg of azathioprine daily.

Discussion

The VGKC complex is a diverse group of signalling proteins with multiple transmembrane subunits as well as auxiliary proteins that play a vital role in neuronal excitability (Vincent *et al.*, 2004). Antibodies targeting the VGKC complex have been identified as being relevant in both peripheral and central autoimmune neurological disorders. Limbic encephalitis (LE) refers to the subacute onset of amnesia and behavioural changes often associated with sleep disturbance, seizures, and hallucinations, accompanied by medial temporal lobe signal change on MRI (Vincent *et al.*, 2004). A number of patients with LE who have antibodies targeting cell surface receptors such as the VGKC complex, do not always have an associated malignancy, and are potentially treatment-responsive with immunotherapy, such as steroids, intravenous immunoglobulin, and plasma exchange (Vincent *et al.*, 2004; Lancaster *et al.*, 2011).

Unlike the other assays used to detect neuronal surface antibodies, the VGKC complex assay does not involve direct transfection of the antigen into a cell line. Instead, a complex of VGKC, which includes closely associated proteins, is bound using dendrotoxin. Antibody binding is detected using immunoprecipitation methods (Ramanathan *et al.*, 2014). While it was initially thought that the antibodies targeted components of the VGKC itself such as various Kv1 subunits, it is

now known that the majority of antibodies actually target proteins such as leucine-rich glioma inactivated 1 (LGI1) and contactin-associated protein 2 (caspr2), which are closely associated with the VGKC complex (Irani *et al.*, 2010). For assays to detect caspr2 and LGI1 specifically, transfected cell lines are often used as a method to detect antibodies bound to these expressed proteins. While some overlap exists, LGI1 antibodies have been more frequently associated with patients presenting with LE and epilepsy without underlying malignancies, while antibodies targeting caspr2 have been associated with Morvan's syndrome, peripheral nerve hyperexcitability, and associated thymomas (Irani *et al.*, 2010).

This case describes a presentation with myoclonic status epilepticus, which has not previously been associated with caspr2 antibodies. While the elevated level of GAD antibodies in this patient is noted, it is known whether this phenomenon is relatively common in autoimmune neurological disease and whether it may occur concurrently with other neuronal antibodies (Graus *et al.*, 2010). Myoclonic status epilepticus in adults is classically associated with anoxic brain injury, and less commonly with metabolic encephalopathies and poorly controlled generalised epilepsy syndromes (Jumao-as and Brenner, 1990). Myoclonic status epilepticus, particularly in the case of anoxic brain injury, usually confers an extremely poor prognosis (Jumao-as and Brenner, 1990; Ferlisi and Shorvon, 2012). Our patient had a clinical presentation of new-onset encephalopathy and seizures, with CSF lymphocytic pleocytosis and unmatched intrathecal oligoclonal bands, supportive of a diagnosis of autoimmune encephalitis, and further substantiated by the detection of serum caspr2 autoantibodies. The improvement of her clinical course with immunosuppressive therapy mirrored by a reduction in the levels of serum antibodies, suggests, but does not confirm, a causative association. A case of opercular myoclonic-anarthric status epilepticus in association with GAD antibodies was recently reported (Monnerat *et al.*, 2013), and highlights the notion that some cases of myoclonic status epilepticus may have an autoimmune aetiology amenable to immunotherapy.

This case demonstrates the essential role of immunosuppressive therapy in seizure control in patients with

Figure 1. (*Continued*) (C) Coronal and axial sections of T2 fluid attenuated inversion recovery (FLAIR) sequences on MRI demonstrating subtle bilateral hippocampal hyperintensity compatible with limbic encephalitis (indicated by arrows). (D) This EEG performed on week 2 of presentation demonstrates evidence of induced burst suppression. With attempts to wean off sedation, generalised spike discharges which were maximal centrally can be noted, with clinical accompaniment of myoclonus. (E) Graphical representation of anti-VGKC complex antibody titres (tested in Australia) over time and with treatment.

Values above the dotted line (80 pM) are elevated above the normal range. Arrows indicate the timing of institution and duration of therapy. Anti-VGKC titre: anti-voltage-gated potassium channel complex antibody titre; AZT: azathioprine; Cyclo: cyclophosphamide (monthly pulses over twelve months); IVIg: intravenous immunoglobulin (five doses); PE: plasma exchange (five exchanges); MMF: mycophenolate mofetil.

autoimmune encephalitis. Autoantibodies targeting cell surface receptors and transmembrane domains have been recognised as an aetiological cause of new-onset seizures in “autoimmune epilepsies” (Bien, 2013). Such patients have a reasonable chance of seizure freedom with the commencement of appropriate immunotherapy, but frequently fail to achieve seizure control on anticonvulsants alone (Bien, 2013). While there are no definitive therapeutic guidelines for the treatment of autoimmune encephalitis or epilepsy, recommended treatment often includes early therapy with intravenous immunoglobulin and/or pulsed intravenous methylprednisolone followed by oral prednisone, with failure to respond within a few weeks prompting consideration of plasmapheresis, or second-line therapy with broader immunosuppressive agents including cyclophosphamide or rituximab (Quek *et al.*, 2012; Lancaster *et al.*, 2011; Ramanathan *et al.*, 2014). This case highlights the fact that new-onset status epilepticus and myoclonic status epilepticus may not be universally poor predictors of outcome, and that autoimmune encephalitis needs to be considered as an early differential diagnosis in patients who present in this manner. Recognition is important as early diagnosis and targeted immunotherapy can improve seizure control, neurological recovery, and cognitive outcome.

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Legends for video sequences

Video sequence 1

Florid multifocal myoclonus is observed, most prominent in the face with eyelid, mouth, and tongue involvement. The facial myoclonus appears asymmetric, with more involvement of the left side. Truncal and limb myoclonus is also present.

Video sequence 2

The patient is now twenty months post presentation. She is able to mobilise independently, with mild residual midline ataxia. While there is no spontaneous myoclonus, action-induced myoclonus, particularly involving her face and vocal cords, is evident with attempts to speak.

Key words for video research on www.epilepticdisorders.com

Phenomenology: myoclonic seizures, myoclonus (non-epileptic), reflex seizures, status epilepticus (convulsive)

Localization: central motor, multifocal

Epilepsy syndrome: epileptic encephalopathy not otherwise classified, not applicable

Aetiology: encephalitis

References

- Bien CG. Value of autoantibodies for prediction of treatment response in patients with autoimmune epilepsy: Review of the literature and suggestions for clinical management. *Epilepsia* 2013; 54(2): 48-55.
- Ferlisi M, Shorvon S. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. *Brain* 2012; 135: 2314-28.
- Graus F, Saiz A, Dalmau J. Antibodies and neuronal autoimmune disorders of the CNS. *J Neurol* 2010; 257: 509-17.
- Irani SR, Alexander S, Waters P, *et al.* Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. *Brain* 2010; 133: 2734-48.
- Jumao-as A, Brenner RP. Myoclonic status epilepticus: A clinical and electroencephalographic study. *Neurology* 1990; 40: 1199-202.
- Lancaster E, Martinez-Hernandez E, Dalmau J. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. *Neurology* 2011; 77: 179-89.
- Monnerat BZ, Velasco TR, Nakano FN, Junior AV, Martins APP, Sakamoto AC. Opercular myoclonic-anarthric status epilepticus due to glutamate decarboxylase antibody-associated encephalitis. *Epileptic Disord* 2013; 15(3): 342-6.
- Pruss H, Holtkamp M. Ketamine successfully terminates malignant status epilepticus. *Epilepsy Res* 2008; 82: 219-22.
- Quek AM, Britton JW, McKeon A, *et al.* Autoimmune epilepsy: Clinical characteristics and response to immunotherapy. *Arch Neurol* 2012; 69(5): 582-93.
- Ramanathan S, Mohammed S, Brilot F, Dale RC. Autoimmune encephalitis: Recent updates and emerging challenges. *J Clin Neurosci* 2014; 21(5): 722-30.
- Vincent A, Buckley C, Schott JM, *et al.* Potassium channel antibody-associated encephalopathy: A potentially immunotherapy-responsive form of limbic encephalitis. *Brain* 2004; 127: 701-12.