Original article

Epileptic Disord 2016; 18 (1): 34-43

Refractory status epilepticus and glutamic acid decarboxylase antibodies in adults: presentation, treatment and outcomes

Ayaz M. Khawaja [1], Brannon L. Vines [1], David W. Miller [2], Jerzy P. Szaflarski [1], Amy W. Amara [1]

[1] Department of Neurology
[2] Department of Anesthesiology and Perioperative Medicine, University of Alabama at Birmingham Hospital, Birmingham, AL, USA

Received May 12, 2015; Accepted December 07, 2015

ABSTRACT – *Aim.* Glutamic acid decarboxylase antibodies (GAD-Abs) have been implicated in refractory epilepsy. The association with refractory status epilepticus in adults has been rarely described. We discuss our experience in managing three adult patients who presented with refractory status epilepticus associated with GAD-Abs.
Methods. Case series with retrospective chart and literature review.
Results. Three patients without pre-existing epilepsy who presented to our institution with generalized seizures between 2013 and 2014 were identified. Seizures proved refractory to first and second-line therapies and persisted beyond 24 hours. Patient 1 was a 22-year-old female who had elevated serum GAD-Ab titres at 0.49 mmol/l (normal: <0.02) and was treated with multiple immuno- and chemotherapies, with eventual partial seizure control. Patient 2 was a 61-year-old black female whose serum GAD-Ab titre was 0.08 mmol/l. EEG showed persistent generalized periodic discharges despite maximized therapy with anticonvulsants but no immunotherapy, resulting in withdrawal of care and discharge to nursing home. Patient 3 was a 50-year-old black female whose serum GAD-Ab titre was 0.08 mmol/l, and was discovered to have pulmonary sarcoidosis. Treatment with steroids and intravenous immunoglobulin resulted in seizure resolution.
Conclusion. Due to the responsiveness to immunotherapy, there may be an association between GAD-Abs and refractory seizures, including refractory status epilepticus. Causation cannot be established since GAD-Abs may be elevated secondary to concurrent autoimmune diseases or formed *de novo* in response to GAD antigen exposure by neuronal injury. Based on this report and available literature, there may be a role for immuno- and chemotherapy in the management of refractory status epilepticus associated with GAD-Abs.

Key words: glutamic acid decarboxylase, status epilepticus, refractory seizures, NORSE, RSE, immunotherapy, chemotherapy, anti-GAD antibody

Correspondence:
Ayaz M. Khawaja
University of Alabama at Birmingham Hospital,
1720 7th Avenue South,
Birmingham,
AL, 35233, USA
<dr.ayazmk@gmail.com>

doi:10.1684/epd.2016.0797

There is an increased interest in the relationship between epilepsy, especially medication-refractory epilepsy, and autoimmunity (Toledano *et al*., 2014). In cases of known/documented autoimmune encephalitis, inflammation causes local or multifocal injury with subsequent development of frequently intractable epilepsy (Singh *et al*., 2015). Of the several recently described autoimmune aetiologies of epilepsies, the one caused by antibodies against the NMDA receptor is discussed most frequently (Rosenfeld and Dalmau, 2011). This is likely because of the dramatic presentation and potential for response to treatment (Rosenfeld and Dalmau, 2011). Other immune-mediated aetiologies have been reported in the literature including, but not limited to, antibodies against VGKC (voltage-gated potassium channel), mGluR5 (metabotropic glutamate receptor-5), LGI1 (leucine-rich glioma inactivated protein), and others (Armangue *et al*., 2014). A favourable response to immune-mediated therapies has been described in refractory epilepsies secondary to autoimmunity, although the evidence supporting this practice is poor (Gaspard *et al*., 2015; Khawaja *et al*., 2015). Other aetiologies need to be considered as well, especially in patients who present with refractory status epilepticus (RSE). Although the relationship between refractory epilepsies and glutamic acid decarboxylase antibodies (GAD-Abs) has been described, only limited cases of GAD-Ab-related RSE have been reported in the literature (Kanter *et al*., 2008; Cikrikcili *et al*., 2013; Kumar *et al*., 2013). The rarity of this syndrome is highlighted by the fact that even in the largest series of post-encephalitic epilepsies published to date, there are no cases of epilepsy related to GAD-Ab encephalitis (Singh *et al*., 2015). Because of scarcity of data, we report three cases of RSE in patients in whom extensive workup ultimately revealed elevated GAD-Ab titres in serum. Further, we discuss the response to immune-mediated therapies in these patients.

Patient 1

Patient 1 is a 22-year-old previously healthy white female who developed headaches and fever a week prior to admission. Her symptoms were attributed to a urinary tract infection for which she was prescribed ciprofloxacin. She subsequently developed multiple generalized tonic-clonic (GTC) seizures prompting re-evaluation in the emergency department (ED). She was intubated for airway protection and treated with 0.1 mg/kg intravenous lorazepam, followed by 20 mg PE/kg fosphenytoin and then 20 mg/kg levetiracetam when seizures persisted. She was sedated on 50 mcg/kg/hr propofol. A routine EEG showed bifronto-temporal partial seizures with secondary generalization. Lumbar puncture showed elevated protein at 72 mg/dl, and white count of 21/mm^3. She was immediately started on antimicrobial therapy (*table 1*), admitted to the Neurosciences Intensive Care Unit (NICU), and placed on continuous EEG (cEEG). During cEEG, an increasing frequency of electrographic seizures were detected requiring escalation of treatment with addition of midazolam initially, then ketamine, and finally pentobarbital concurrent with discontinuation of propofol (*table 1*). Brain MRI obtained on Day 5 revealed subtle T2 signal hyperintensities, symmetrically in the hippocampi, pulvinar of thalami, amygdalae, and posterior left insular cortex (*figure 1A*). All microbiological investigations on cerebro-spinal fluid (CSF) were negative (*table 2*). Although burst suppression was achieved on pentobarbital and midazolam, any attempts to lower pentobarbital infusion rate resulted in emergence of generalized periodic discharges (GPDs). Despite the addition of several antiepileptic drugs (AEDs) (*table 1*) and administration of ketogenic diet for 40 days, she remained in refractory status epilepticus. Based on repeat MRI findings, a diagnosis of paraneoplastic limbic encephalitis could not be excluded and the patient was empirically started on intravenous methylprednisolone, followed by intravenous immunoglobulin (IVIg). A full-body CT scan was negative for neoplastic lesions. After IVIg was initiated, midazolam infusion was discontinued and pentobarbital infusion rate was maintained at 5 mg/kg/hr, achieving burst suppression. The only positive paraneoplastic finding was an elevated serum titre of GAD-Abs (0.49 mmol/l; normal: <0.02) in serum. The patient was then started on therapeutic plasmapheresis to complete five sessions. Due to failure to wean off pentobarbital, rituximab infusion was instituted, followed two weeks later by cyclophosphamide infusion, another course of IVIg therapy, and plasmapheresis. Finally, after a three-month NICU admission, the use of chemotherapy allowed pentobarbital to be weaned off without precipitating electrographic or clinical seizures. According to analysis of CSF conducted after completion of immunotherapy, a CSF GAD-Ab titre was not detectable (the serum GAD-Ab titre was not investigated). She was eventually transferred to the inpatient rehabilitation department for recovery. After one year of follow-up, the patient has occasional breakthrough seizures, is on maintenance intravenous rituximab infusion every six weeks, and has mild cognitive deficits with impaired recall of recent events, but is able to perform activities of daily living. She is currently treated with five AEDs (*table 1*).

Table 1. Treatments used (anticonvulsants, sedative infusions, antimicrobials, and immunotherapy) and status upon discharge or at follow-up, if available for all patients.

	Patient 1	**Patient 2**	**Patient 3**
Anticonvulsant medications (maximum dosage while inpatient)	Phenytoin 125mg QID Levetiracetam 4000mg BID Lacosamide 400mg BID Valproic acid 2000mg TID Topiramate 200mg BID Oxcarbazepine 2400mg daily (divided) Phenobarbital 97.2mg QID Vigabatrin 1000mg BID Clobazam 20mg BID Clonazepam 2mg TID	Phenytoin 400mg QHS Levetiracetam 4000mg BID Lacosamide 350mg BID Topiramate 250mg BID Phenobarbital 64.8mg TID Valproic Acid 1500mg QID	Levetiracetam 2000mg BID Phenytoin 150mg QID Lacosamide 250mg BID Clonazepam 1mg BID
Last known anticonvulsant medications (at discharge or follow-up)	Lacosamide 200mg BID Oxcarbazepine 600mg TID Topiramate 300mg BID Clonazepam 2mg QHS Perampenel 4mg QHS	Levetiracetam 4000mg BID Lacosamide 350mg BID Topiramate 250mg BID Phenobarbital 64.8mg TID	Levetiracetam 2000mg BID Phenytoin 200mg QHS Lacosamide 250mg BID
Maximum sedative infusion rate	Propofol 50mcg/kg/hr Midazolam 10mg/hr Ketamine 3mg/kg/hr Pentobarbital 5mg/kg/hr	Propofol 50mcg/kg/hr Midazolam 14mg/hr Ketamine 3mg/kg/hr Pentobarbital 3mg/kg/hr	Midazolam 5mg/hr Ketamine 3mg/kg/hr Fentanyl 100mcg/hr
Antimicrobial medications with doses at initial presentation	Acyclovir 1g TID Ceftriaxone 2g daily Moxifloxacin 400mg daily *(Vancomycin not administered due to a documented allergic reaction in past)*	Ceftriaxone 1g daily Vancomycin 1g BID	Acyclovir 550mg TID Ampicillin 2g QID Azithromycin 500mg daily Ceftriaxone 2g BID Vancomycin 1g daily
Immunotherapy	IVSM x1 IVIg x2 PLEX x2 Rituximab (on maintenance) Cyclophosphamide x1	None	IVSM x1 IVIg x1
Outcomes	Discharged home after a stay in the inpatient rehabilitation program. Mild cognitive deficits at clinic follow-up, and occasional breakthrough seizures.	Discharged to a skilled nursing facility. No follow-up data available.	Discharged to a subacute rehabilitation program in a nursing home. Was admitted a month later due to encephalopathy and abdominal abscess requiring surgical evacuation. At 2-month follow-up in pulmonary clinic for sarcoidosis, remains seizure-free.

IVSM – Intravenous steroids; IVIg – Intravenous Immunoglobulin; PLEX – Plasma Exchange; BID – two times a day; TID – three times a day; QID – four times a day; QHS – nightly.

Table 2. The pertinent serum and cerebrospinal fluid investigations completed for all patients (positive testing is highlighted in bold; tests that were not performed are underlined and italicized).

	Patient 1	**Patient 2**	**Patient 3**
Serum investigations	*ACE*	*ACE*	ACE 41 units/L (N=9-67)
	Paraneoplastic antibodies (Ma2, NMDA, Yo, **GAD65**, amphiphysin, VGKC, VGCC, ANNA-1 /2/3, AGNA-1, PCA-1/2, CRMP-5, striated muscle)	Paraneoplastic antibodies (Ma2, NMDA, Yo, **GAD65**, amphiphysin, VGKC, VGCC, ANNA-1 /2/3, AGNA-1, PCA-1/2, CRMP-5, striated muscle)	Paraneoplastic antibodies (Ma2, NMDA, Yo, **GAD65**, amphiphysin, VGKC, VGCC, ANNA-1 /2/3, AGNA-1, PCA-1/2, CRMP-5, striated muscle)
	RPR	RPR	RPR
	Immunoglobulins - **EBV IgG**, Toxoplasmosis, VZV, WNV, HSV, CMV, QF TB, HBsAg, HCV, HHV-6, Arbovirus, HIV	Immunoglobulins WNV, HBsAg, HCV, HIV, Arbovirus ANA, Anti-DNA, ANCA-C, ANCA-P, IgG	Heavy metal screen Serum and urine **(24 hour urinary Cadmium 1.7 mcg/spec – N=0.0-1.3)**
	Protein electrophoresis		HIV
			ANA, Anti-TPO
	ANA, ANCA-C, ANCA-P, SSA/B, C3, C4, CH50, Anti-TPO		**Thiamine <7 nmol/l (N=8-30)**
Serum GAD-Ab titres	0.49 mmol/l	0.08 mmol/l	0.08 mmol/l
CSF investigations	Glucose: 51 mg/dl Protein: 72 mg/dl White count: 21/mm^3	Glucose 71 mg/dl Protein 55 mg/dl White count: 3/mm^3	Glucose: 68 mg/dk Protein: 27 mg/dl White count: 3/mm^3
	Bacterial and fungal cultures	Bacterial and fungal cultures	Bacterial and fungal cultures
	Viral tests (HSV, VZV, CMV, EBV, WNV, Arbovirus, Enterovirus, JCV)	Viral tests (HSV, Arbovirus, JCV)	Toxoplasmosis Viral tests(HSV, VZV, CMV, WNV)
	ACE	Oligoclonal bands, IgG index and synthesis rate	Cytology ACE: 5 units/L
	GAD65: 0.0 after immunotherapy	ACE 2 units/L	**GAD65: 0.0 after immunotherapy**

ACE – Angiotensin Converting Enzyme; RPR – Rapid plasma regain; ANA – Anti-nuclear antibodies; ANCA – Anti-neutrophil Cytoplasmic Antibody; SSA/B – Sjögren-Syndrome related antigen; TPO – Thyroid peroxidase; HSV – Herpes Simplex Virus; VZV – Varicella Zoster Virus; WNV – West Nile Virus; CMV – Cytomegalovirus; JCV – John Cunningham Virus; HBsAg – Hepatitic B surface Antigen; HCV – Hepatitis C Virus; HHV6 – Human Herpes Virus 6; QF TB – Quantiferon Tuberculosis; HIV – Human Immunodeficiency Virus; AGNA – Anti-glial Nuclear Antibody; CRMP – Collapsin Response Mediator Protein; NMDA – N-methyl D-Aspartate; VGKC – Voltage-gated Potassium Channel; VGCC – Voltage-gated Calcium Channel; ANNA – Antineuronal Nuclear Antibody; PCA – Purkinje Cell Cytoplasmic Antibody.

Patient 2

Patient 2 is a 61-year-old African/American female with diabetes and hypertension who developed encephalopathy leading to GTCs. She was brought to the ED where seizures continued, requiring lorazepam administration, and ultimately intubation. She was admitted to the NICU and sedated on propofol.

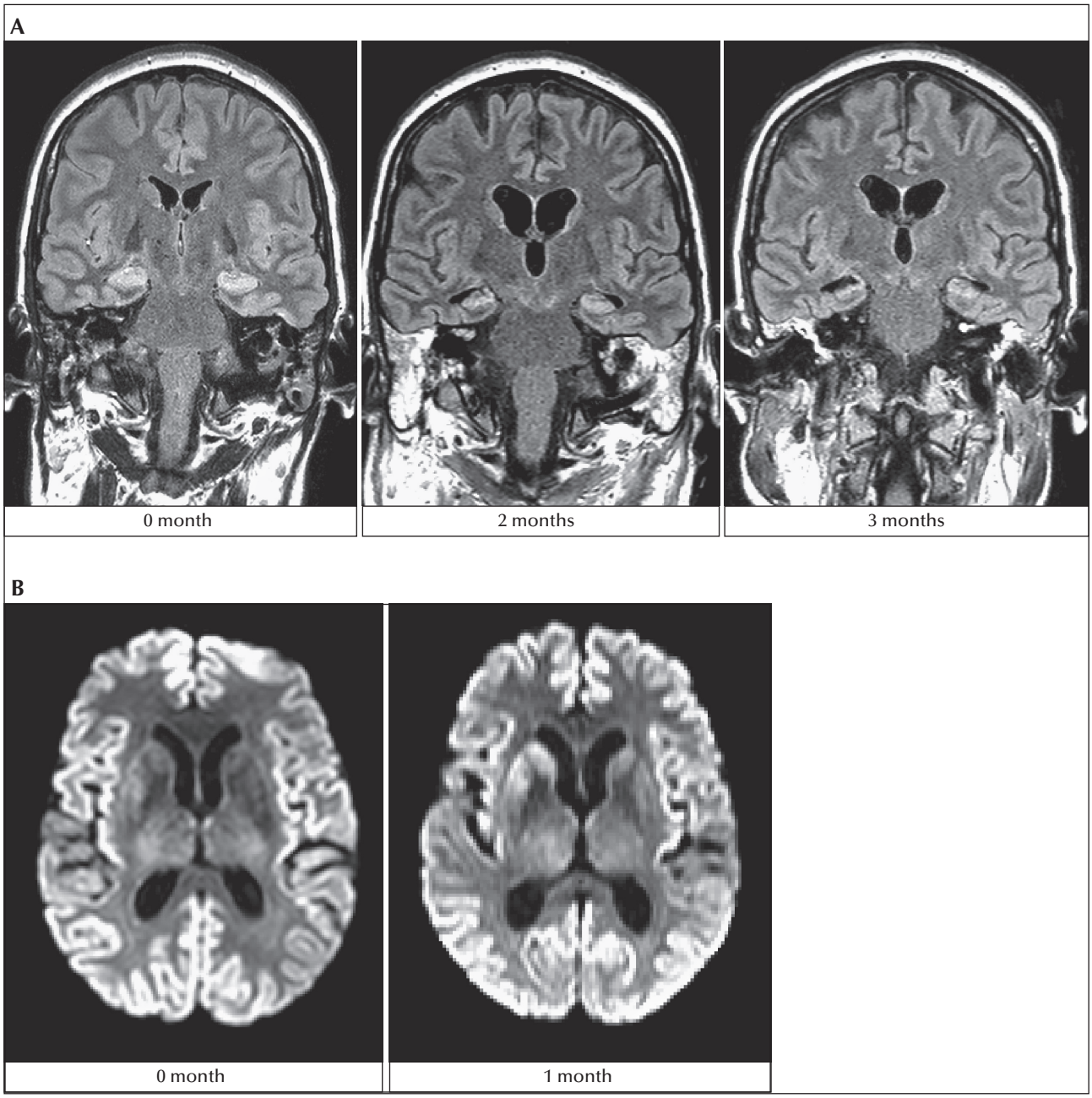
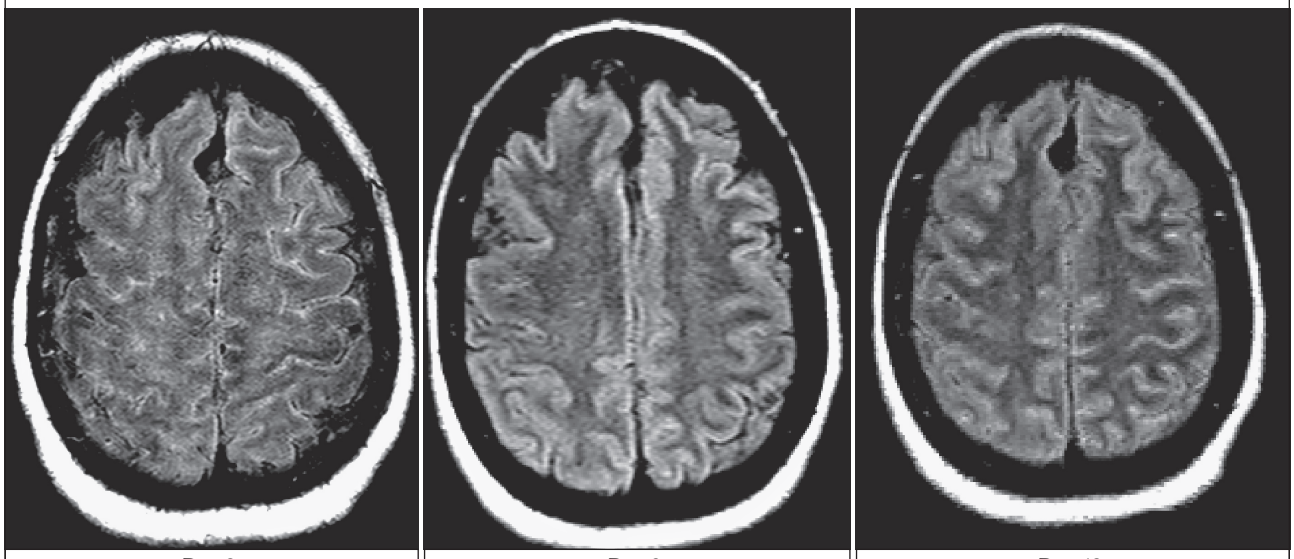


Figure 1. (A) Brain MRI with coronal T2-FLAIR sequence in Patient 1 at times zero, two and three months, respectively, showing FLAIR hyperintensities in bilateral hippocampi and insular cortices that eventually resolved. Generalized brain and hippocampal atrophy with ventriculomegaly was also evident at two and three months.
(B) Brain MRI with axial diffusion-weighted sequence in Patient 2 at times zero and one month, respectively, showing diffuse cortical diffusion restriction. In the second image, there is new diffusion restriction demonstrated in subcortical structures, right > left.
(C, see next page) Brain MRI in Patient 3 on Day 2 showed diffuse increased T2-FLAIR signal within the sulci, which may have improved on repeat MRI on Day 9, but was visualized again on another MRI on Day 12. The MRI on Day 9 was performed with intravenous gadolinium contrast, whereas the first and last MRI were performed without contrast.

C



Day 2 | Day 9 | Day 12

The patient had urosepsis with coagulase negative Staphylococcus species, and was treated with vancomycin for 14 days. At admission, therapy with phenytoin was initiated, with subsequent additions of levetiracetam and lacosamide (*table 1*). Initial long-term EEG monitoring showed non-convulsive status epilepticus (NCSE) requiring addition of midazolam and ketamine infusions with concurrent discontinuation of propofol. Pertinent CSF findings included elevated protein at 55 mg/dl, white count of 3/mm^3, and negative microbiological testing. Brain MRI obtained on Day 7 showed diffuse cortical diffusion restriction (*figure 1B*). There was no history of hypotensive episodes or hypoxic ischaemic injury, and, therefore, the MRI changes were attributed to status epilepticus. Due to failure to control GPDs, pentobarbital was eventually started at 2 mg/kg/hr, which achieved burst suppression, and other infusions were discontinued. GPDs re-emerged with any attempts to lower pentobarbital infusion rate. A full-body CT scan was negative. Serum GAD-Ab titre was elevated at 0.08 mmol/l. Although immunotherapy was considered, inability to contact next of kin prompted preparation for withdrawal of care after consultation with the ethics team. After tracheostomy and gastrostomy tube placement, the patient was weaned off pentobarbital infusion and mechanical ventilation, and discharged to a nursing home on levetiracetam, lacosamide, topiramate, and phenobarbital for treatment of seizures.

Patient 3

Patient 3 is a 50-year-old African/American female who presented to the ED after she was found to be unresponsive by the family, with witnessed GTCs. She was intubated, sedated on midazolam infusion, treated with levetiracetam, and placed on cEEG demonstrating triphasic waves and right hemispheric epileptiform discharges. These evolved into NCSE. Consequently, phenytoin and lacosamide were added due to persistence of NCSE. Brain MRI on Day 2 showed diffuse increased T2-FLAIR signal within the sulci, which improved on repeat MRI on Day 9, but was visualized again on Day 12 (*figure 1C*). These findings were attributed to hyperoxygenation, secondary to mechanical ventilation. Other pertinent findings included a high serum titre of GAD-Abs (0.08 mmol/l), low serum thiamine, elevated cadmium in a urinary specimen collected over 24 hours, and evidence of sarcoidosis on chest CT confirmed by biopsy after endobronchial ultrasonography (*table 2*). Prednisone was started for treatment of sarcoidosis, and a five-day course of IVIg infusion was finished. She improved initially, but had recurrence of periodic lateralized epileptiform discharges, and therefore ketamine infusion was started (*table 1*). After treatment with IVIg, GAD-Ab titre in CSF was found to be normal (<0.02 mmol/l). Subsequently, high-dose IV methylprednisolone was given for five days, and improvement on cEEG was noted. No further seizures were recorded, and

encephalopathy improved over the course of a month. She was eventually discharged to a subacute rehabilitation programme in a nursing home on levetiracetam, phenytoin and lacosamide. After two months of follow-up at a pulmonary clinic, she remained seizure-free.

Discussion

The role of GAD antigens

GAD exists in two isoforms; GAD_{67} and GAD_{65} (Erlander *et al*., 1991). GAD_{65} localizes to axon terminals where it produces GABA from glutamate that mediates neurotransmission (Lynex *et al*., 2004). GAD_{67} has a more widespread brain distribution and it produces GABA that mediates non-synaptic functions such as trophic activity, synaptogenesis and neuronal protection (Pinal and Tobin, 1998). Mice lacking the GAD_{67} gene have developmental abnormalities at birth, whereas mice lacking the GAD_{65} gene are normal at birth and subsequently develop spontaneous seizures (Kash *et al*., 1997). This animal model provides support for implicating GAD_{65} in human epileptogenesis. GAD-Ab is purported to inhibit release of GABA from GABA-ergic neurons allowing unopposed glutamate release. GAD-Ab can be associated with Type 1 diabetes mellitus (DM), cerebellar ataxia (CA), stiff person syndrome (SPS), and refractory complex partial seizures (CPS) (Giometto *et al*., 1996; Saiz *et al*., 1997).

Relationship of GAD-Ab with refractory epilepsies

One study reported increased GAD-Ab IgG levels with an oligoclonal pattern in CSF and serum from a patient with SPS, epilepsy, and diabetes (Solimena *et al*., 1988). Other case reports include elevated serum GAD-Ab in patients with epilepsy and palatal myoclonus (Nemni *et al*., 1994); refractory temporal lobe epilepsy (Giometto *et al*., 1998); concurrent cryptogenic epilepsy, cerebellar ataxia and upbeat nystagmus (Vulliemoz *et al*., 2007); refractory epilepsy and diabetes (Yoshimoto *et al*., 2005); and refractory generalized seizures and cerebellar ataxia (Nociti *et al*., 2010). In another study, GAD-Ab was reported in 8/51 patients with treatment-resistant CPS compared to 0/49 patients with controlled primary generalized epilepsy syndromes (Peltola *et al*., 2000). These findings were echoed in another report where GAD-Ab titres were found elevated in 4/74 patients with uncontrolled epilepsy (juvenile myoclonic and CPS) compared to 0/31 patients with controlled epilepsy (Kwan *et al*., 2000). Higher GAD-Ab titres may not necessarily be related to higher seizure frequency or duration, as other sources (such as pancreatic islet cell antibodies and greater prevalence of concomitant autoimmune diseases) may account for GAD-Ab generation (Kwan *et al*., 2000; Peltola *et al*., 2000). However, relatively higher GAD-Ab titres have been reported in children with status epilepticus compared to children with refractory epilepsy (Lin *et al*., 2012). The significance of different titres and the connection with severity of epilepsy remains unknown as it is not clear whether GAD-Ab is epileptogenic or an epiphenomenon.

Relationship of GAD-Ab with RSE

The three cases described in this report provide insight into the presentation of the GAD-Ab encephalitis-related RSE and elaborate on the complexities of treatment and outcomes in this patient population. While the association between GAD-Ab and refractory epilepsies has been reported multiple times, the association with RSE is less well established and to date, only three adult cases have been reported (Kanter *et al*., 2008; Cikrikcili *et al*., 2013; Kumar *et al*., 2013). The first provides description of a patient with high intrathecal GAD-Ab titres who showed minimal improvement with IVIg and plasmapheresis. Eventually, pulse-dose cyclophosphamide therapy was initiated with remarkable control of seizures, and decreased intrathecal GAD-Ab. An unexpected termination of immunotherapy resulted in recurrent CPS that immediately resolved with re-initiation of cyclophosphamide. The second report discusses an older patient with NCSE whose overall condition improved with corticosteroids and IVIg alone; this was associated with a decrease in GAD-Ab titres. The third report discusses the case of a 30-year-old female with new-onset refractory seizures, who was treated initially for presumed autoimmune encephalitis with steroids and IVIg. This was followed by a single-stage palliative surgery to resect the epileptogenic focus, which included a large prerolandic left frontal and anterior temporal resection (Kumar *et al*., 2013). Serum GAD-Ab was found elevated at >250 units/ml (normal: <5 U/ml). Since seizures persisted, a second IVIg infusion was administered and followed by plasmapheresis, and ultimately cyclophosphamide, with resultant disappearance of seizures. Additionally, status epilepticus has been reported in four out of eight children less than 13 years of age with suspected autoimmune epilepsy, two of whom had positive serum GAD-Ab; all patients demonstrated response to IVIG or corticosteroids alone (Specchio *et al*., 2010). Finally, GAD-Ab titres may be elevated in the presence of other medical comorbidities including diabetes mellitus, which was present only in the second of the three patients

reported here (Tuomilehto *et al*., 1994; Lundgren *et al*., 2010).

Presentation of patients with GAD-Ab-related RSE appears to be similar. All patients in our series presented with encephalopathy and generalized convulsions, which was also the feature in cases reported by Kanter *et al*. (2008) and Kumar *et al*. (2013). Patient 1 additionally presented with headaches and fever, similar to the case reported by Kanter *et al*. The patient described by Cikrikcili *et al*. (2013) was most unique in presentation, with non-convulsive seizures. However, the clinical presentation shares features with RSE secondary to other autoimmune aetiologies and therefore it is not possible to distinguish between these syndromes based on presenting features alone (Gaspard *et al*., 2015; Khawaja *et al*., 2015).

The characteristic feature of all GAD-Ab-related RSE syndromes reported thus far, including ours, is the response to immunotherapy, including intravenous corticosteroids, IVIg, plasmapheresis, and chemotherapeutic agents. Efficacy of the immunomodulatory therapeutic approach extends to SPS and cerebellar ataxia (Vulliemoz *et al*., 2007; Nociti *et al*., 2010), as well as other suspected autoimmune epilepsies without detectable antibodies, as demonstrated by a positive response in two out of four children in one report (Suleiman *et al*., 2013). In Patient 1, the combination of rituximab and cyclophosphamide was eventually successful in controlling the status epilepticus, although the benefit was not immediate, and required aggressive adjunctive therapy. While immunotherapy may improve refractory seizures, chemotherapy may be required to achieve adequate seizure suppression. AEDs alone may be insufficient to control seizures as demonstrated by Patient 2, whose last EEG recording still demonstrated GPDs on multiple maximally dosed AEDs. GABA-ergic therapy may also be attempted although it failed in Patient 1 (vigabatrin) and all GAD-Ab-positive patients reported by Kwan *et al*. (2000). Consideration should be given to early administration of immunotherapy since the antibody panel including GAD-Abs may take a few weeks to report. Even in cases where the antibody panel is negative and no discernible cause for RSE could be elucidated, there may be a role for immunotherapy as demonstrated in other seronegative autoimmune syndromes such as limbic encephalitis (Modoni *et al*., 2009; Gaspard *et al*., 2015; Khawaja *et al*., 2015).

Due to the scarcity of data on GAD-Ab-related RSE, lack of response to immunotherapy has not been reported. Poor response has been previously reported in RSE unrelated to GAD-Ab by Van-Lierde *et al*., where the majority of patients who received intravenous corticosteroids and/or plasmapheresis either developed severe mental and physical disability, or died (Van Lierde *et al*., 2003). The only study showing no response to immunotherapy was a case series of six children aged 1.5-13.5 years with GAD-Ab-related status epilepticus (Lin *et al*., 2012). IVIg and methylprednisolone were used in all patients, with one patient dying due to sepsis, three patients with poor outcomes (Glasgow Outcomes Scale [GOS]$\leq$3), and two with better outcome (GOS$\geq$4). For refractory autoimmune temporal lobe epilepsy secondary to serum and intrathecal GAD-Ab in an adult patient, only transient remission occurred for two weeks following intravenous methylprednisolone (IVSM), as reported by Giometto *et al*. (1998). Unsatisfactory seizure control after IVSM and azathioprine was documented by Vulliemoz *et al*. in a patient with epilepsy and cerebellar ataxia related to GAD-Ab, although ataxia subsequently improved (Vulliemoz *et al*., 2007). In the largest retrospective case series of new-onset RSE published to date, the overall outcomes were poor with a 22% mortality rate (Gaspard *et al*., 2015). While the effects of immunotherapy were not specifically studied, it was noted that immunotherapy was used less frequently in cryptogenic cases compared to those with an identified aetiology.

In conclusion, we recommend testing all serum antibodies including GAD-Ab in all patients, early during the course of RSE. In the setting of elevated GAD-Ab titres, an autoimmune aetiology may be suspected. This is based on case reports of responses to immunotherapy in GAD-Ab-related RSE, refractory epilepsies alongside GAD-related syndromes, and autoimmune-encephalitis due to other antibodies targeting intraneuronal or synaptic proteins. It is unclear whether presence of GAD-Ab indicates exposure to GAD antigen from neurons after injury sustained by status epilepticus, or increased *de novo* production due to other existing autoimmune-mediated comorbidities. The significance of high compared to low GAD-Ab titres, and whether these are epileptogenic or an epiphenomenon, is also unknown. Based on anecdotal evidence, there may be a benefit from immunotherapy such as steroids, IVIg and plasmapheresis. Additionally, the use of chemotherapy agents such as rituximab and/or cyclophosphamide should be contemplated in cases where no immediate benefit is observed. In our opinion, consideration for empiric administration of immunotherapy should also be given in cases where a cause for RSE is not immediately determined by initial laboratory and radiographic evaluation, as the antibody panel can take a few weeks to report, and the window of early intervention could potentially be missed. □

Disclosures.

The authors have no conflicts of interest to disclose.

Data included in this article were presented, in part, at the 2014 Annual meeting of the American Academy of Neurology (Khawaja

et al., *2014). The three patients included in the current study were previously described as part of a larger cohort included in another report (Khawaja* et al., *2015).*

References

Armangue T, Leypoldt F, Dalmau J. Autoimmune encephalitis as differential diagnosis of infectious encephalitis. *Curr Opin Neurol* 2014; 27: 361-8.

Cikrikcili U, Ulusoy C, Turan S, *et al*. Non-convulsive status epilepticus associated with glutamic acid decarboxylase antibody. *Clin EEG Neurosci* 2013; 44: 232-6.

Erlander MG, Tillakaratne NJ, Feldblum S, Patel N, Tobin AJ. Two genes encode distinct glutamate decarboxylases. *Neuron* 1991; 7: 91-100.

Gaspard N, Foreman BP, Alvarez V, *et al*. New-onset refractory status epilepticus: etiology, clinical features, and outcome. *Neurology* 2015; 85(18): 1604-13.

Giometto B, Miotto D, Faresin F, Argentiero V, Scaravilli T, Tavolato B. Anti-gabaergic neuron autoantibodies in a patient with stiff-man syndrome and ataxia. *J Neurol Sci* 1996; 143: 57-9.

Giometto B, Nicolao P, Macucci M, Tavolato B, Foxon R, Bottazzo GF. Temporal lobe epilepsy associated with glutamic acid decarboxylase autoantibodies. *Lancet* 1998; 352: 457.

Kanter IC, Huttner HB, Staykov D, *et al*. Cyclophosphamide for anti-GAD antibody-positive refractory status epilepticus. *Epilepsia* 2008; 49: 914-20.

Kash SF, Johnson RS, Tecott LH, *et al*. Epilepsy in mice deficient in the 65-kda isoform of glutamic acid decarboxylase. *PNAS* 1997; 94: 14060-5.

Khawaja AM, Amara A. Refractory Status Epilepticus: A report of two cases to illustrate the significance of GAD Antibody. *Neurology* 2014; 82 (Meeting Abstracts): P6.341.

Khawaja AM, Dewolfe JL, Miller DW, Szaflarski JP. New-onset refractory status epilepticus (NORSE)-the potential role for immunotherapy. *Epilepsy Behav* 2015; 47: 17-23.

Kumar G, Mittal S, Moudgil SS, Kupsky WJ, Shah AK. Histopathological evidence that hippocampal atrophy following status epilepticus is a result of neuronal necrosis. *J Neurol Sci* 2013; 334: 186-91.

Kwan P, Sills GJ, Kelly K, Butler E, Brodie MJ. Glutamic acid decarboxylase autoantibodies in controlled and uncontrolled epilepsy: a pilot study. *Epilepsy Res* 2000; 42: 191-5.

Lin JJ, Lin KL, Hsia SH, *et al*. Antiglutamic acid decarboxylase antibodies in children with encephalitis and status epilepticus. *Pediatr Neurol* 2012; 47: 252-8.

Lundgren VM, Isomaa B, Lyssenko V, *et al*. GAD antibody positivity predicts type 2 diabetes in an adult population. *Diabetes* 2010; 59: 416-22.

Lynex CN, Carr IM, Leek JP, *et al*. Homozygosity for a missense mutation in the 67 kda isoform of glutamate decarboxylase in a family with autosomal recessive spastic cerebral palsy: parallels with stiff-person syndrome and other movement disorders. *BMC Neurol* 2004; 4: 20.

Modoni A, Masciullo M, Spinelli P, *et al*. Successful treatment of acute autoimmune limbic encephalitis with negative VGKC and NMDAR antibodies. *Cogn Behav Neurol* 2009; 22: 63-6.

Nemni R, Braghi S, Natali-Sora MG, *et al*. Autoantibodies to glutamic acid decarboxylase in palatal myoclonus and epilepsy. *Ann Neurol* 1994; 36: 665-7.

Nociti V, Frisullo G, Tartaglione T, *et al*. Refractory generalized seizures and cerebellar ataxia associated with anti-GAD antibodies responsive to immunosuppressive treatment. *Eur J Neurol* 2010; 17: E5.

Peltola J, Kulmala P, Isojarvi J, *et al*. Autoantibodies to glutamic acid decarboxylase in patients with therapy-resistant epilepsy. *Neurology* 2000; 55: 46-50.

Pinal CS, Tobin AJ. Uniqueness and redundancy in GABA production. *Perspect Dev Neurobiol* 1998; 5(2-3): 109-18.

Rosenfeld MR, Dalmau J. Anti-NMDA-receptor encephalitis and other synaptic autoimmune disorders. *Curr Treat Options Neurol* 2011; 13: 324-32.

Saiz A, Arpa J, Sagasta A, *et al*. Autoantibodies to glutamic acid decarboxylase in three patients with cerebellar ataxia, late-onset insulin-dependent diabetes mellitus, and polyendocrine autoimmunity. *Neurology* 1997; 49: 1026-30.

Singh TD, Fugate JE, Hocker SE, Rabinstein AA. Postencephalitic epilepsy: clinical characteristics and predictors. *Epilepsia* 2015; 56: 133-8.

Solimena M, Folli F, Denis-Donini S, *et al*. Autoantibodies to glutamic acid decarboxylase in a patient with stiff-man syndrome, epilepsy, and type I diabetes mellitus. *N Engl J Med* 1988; 318: 1012-20.

Specchio N, Fusco L, Claps D, Vigevano F. Epileptic encephalopathy in children possibly related to immune-mediated pathogenesis. *Brain Dev* 2010; 32: 51-6.

Suleiman J, Brilot F, Lang B, Vincent A, Dale RC. Autoimmune epilepsy in children: case series and proposed guidelines for identification. *Epilepsia* 2013; 54: 1036-45.

Toledano M, Britton JW, Mckeon A, *et al*. Utility of an immunotherapy trial in evaluating patients with presumed autoimmune epilepsy. *Neurology* 2014; 82: 1578-86.

Tuomilehto J, Zimmet P, Mackay IR, *et al*. Antibodies to glutamic acid decarboxylase as predictors of insulin-dependent diabetes mellitus before clinical onset of disease. *Lancet* 1994; 343: 1383-5.

Van Lierde I, Van Paesschen W, Dupont P, Maes A, Sciot R. *De novo* cryptogenic refractory multifocal febrile status epilepticus in the young adult: a review of six cases. *Acta Neurol Belg* 2003; 103: 88-94.

Vulliemoz S, Vanini G, Truffert A, Chizzolini C, Seeck M. Epilepsy and cerebellar ataxia associated with anti-glutamic acid decarboxylase antibodies. *J Neurol Neurosurg Psychiatry* 2007; 78: 187-9.

Yoshimoto T, Doi M, Fukai N, *et al*. Type 1 diabetes mellitus and drug-resistant epilepsy: presence of high titer of anti-glutamic acid decarboxylase autoantibodies in serum and cerebrospinal fluid. *Intern Med* 2005; 44: 1174-7.

TEST YOURSELF

(1) Which of the following syndromes is anti-GAD antibody NOT associated with?
A. Type 1 diabetes mellitus
B. Ovarian teratoma
C. Stiff-person syndrome
D. Cerebellar ataxia
E. Refractory epilepsy

(2) Which of the following is TRUE regarding anti-GAD antibodies?
A. Higher serum titres result in a higher incidence of drug-resistant epilepsy
B. Anti-GAD antibodies are commonly isolated from the sera of patients with drug-resistant complex partial epilepsy
C. Anti-GAD antibodies inhibit glutamate release from axon terminals
D. Anti-GAD antibodies may be an epiphenomenon if isolated from the sera of patients with refractory status epilepticus
E. There is strong evidence to support the use of immunomodulatory therapy in the treatment of anti-GAD antibody-related refractory seizures

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".