Clinical commentary

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GAD65 antibody-associated autoimmune epilepsy with unique independent bitemporal-onset ictal asystole

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ABSTRACT – Antibodies against the 65-kDa isoform of the intracellular enzyme, glutamate decarboxylase (GAD65), have been found in patients with limbic encephalitis and drug-resistant autoimmune epilepsy. We report a 22-year-old female who presented with new-onset seizures and neuropsychiatric symptoms. Video-EEG captured unique, independent bitemporal-onset focal seizures with impaired awareness and ictal asystole. An autoimmune epilepsy panel revealed elevated GAD65 antibodies in the serum (225 nmol/l) and CSF (2.78 nmol/l), while [^{18}F]-fluoro-deoxy-glucose positron emission tomography showed bitemporal hypometabolism (left > right). The patient was diagnosed with GAD65 antibody-associated autoimmune epilepsy. Our observation adds to the spectrum of neurocardiac syndromes associated with autoimmune epilepsy.

Key words: asystole, autoimmune epilepsy, GAD65, focal epilepsy, limbic encephalitis, neurocardiac syndromes

Ictal asystole (IA) is a rare, yet well-known, complication of focal epilepsy; particularly temporal lobe epilepsy (Guldiken *et al*., 2015; Van der Lende *et al*., 2016; Tényi *et al*., 2017; Strzelczyk *et al*., 2008). Most recent studies define IA as an RR interval longer than three seconds (Hampel *et al*., 2017). The epileptic lateralization of IA has been observed in both the right and left hemispheres (Tényi *et al*., 2017). The risk of sudden unexpected death in epilepsy (SUDEP) is a primary concern for neurologists and cardiologists when presented with a patient with epileptic-associated arrhythmia, however, no SUDEP cases have ever been described with ictal asystole (Van der Lende *et al*., 2016). Postictal asystole, in contrast, is most often preceded by generalized tonic-clonic seizures, is rarely seen following focal seizures, and has been repeatedly associated with SUDEP (Ryvlin *et al*., 2013). Although not associated with SUDEP, IA can cause traumatic falls due to syncope with sudden loss of muscle tone (Hampel *et al*., 2017).

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The relatively recent discovery of antibodies against intracellular and cell-surface neural antigens in patients with intractable seizures has led to the concept of autoimmune epilepsy (AE) (Brenner *et al.,* 2013). Studies suggest that autoimmune encephalitis may explain at least 20% of adult-onset epilepsies of unknown aetiology (Dubey *et al.,* 2017). Neurological antibodies have also been reported in 11-35% patients with chronic epilepsy, with antibodies to the voltage-gated potassium channel complex (VGKCc), 65-kilodalton isoform of glutamic acid decarboxylase (GAD65), and *N*-methyl-D-aspartate receptor (NMDAR) being the most common (Brenner *et al.,* 2013; Dubey *et al.,* 2017). GAD65 catalyses the synthesis of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system (Liimatainen *et al.,* 2010). GAD65 antibodies are found in immune-mediated neurological syndromes, such as stiff person syndrome, cerebellar ataxia, and epilepsy (Malter *et al.,* 2010). GAD65 antibody titres greater than 20 nmol/l are considered to be highly indicative of neurological autoimmunity, however, low titres (<20 nmol/l) may be seen in patients with diabetes or in the general population (Dubey *et al.,* 2017).

Case study

A 22-year-old, right-handed female developed medically refractory focal seizures with impaired awareness at the age of 20. Seizure semiology was characterized by variable aura, consisting of sensations of dizziness, the smell of metal, and *déjà vu*, followed by loss of awareness, right or left-hand flexion, and stiffening of the lower extremities lasting for up to two minutes, and postictal amnesia. Seizure frequency was approximately one per month. The patient's family reported memory impairment and symptoms of major depression. She continued having breakthrough seizures despite receiving brivaracetam and lamotrigine. Previous AEDs included levetiracetam, phenytoin, lacosamide, and eslicarbazepine acetate, which were discontinued due to lack of efficacy or side effects. Her neurological examination was normal. A standard 3T MRI seizure protocol with axial magnetization-prepared rapid gradient-echo (MPRGAE), coronal inversion recovery (IR) axial and coronal fluid attenuated recovery (FLAIR), coronal and sagittal T2, axial diffusion weighted imaging (DWI), apparent diffusion coefficient (ADC), and susceptibility weighted imaging (SWI) sequences was obtained approximately 22 months into her clinical course, which was normal.

She was admitted for continuous video-EEG monitoring for seizure quantification and medication optimization. For the first day of monitoring, brivaracetam was reduced from 50 mg to 25 mg, twice daily, and lamotrigine was reduced from 300 mg to 150 mg, twice daily. After 24 hours, AEDs were discontinued. Interictal EEG showed a mild degree of slowing in the bitemporal head regions and infrequent left temporal spikes and sharp waves. One seizure with left temporal and another with right temporal onset was captured on the second day of admission. Her first seizure began as a sentinel sharp wave within the left temporal region, followed by rhythmic left temporal delta activity. Twenty-five seconds into the ictal EEG onset, asystole ensued which lasted for 28 seconds. Ten seconds into ictal asystole, the EEG showed generalized suppression of the background activity lasting for 28 seconds, admixed with diffuse electrode artefact. Approximately 25 seconds into ictal EEG onset and 11 seconds into ictal asystole, the patient arose out of sleep and exhibited syncopal myoclonic jerking (*figure 1A*). The second seizure began as right temporal rhythmic delta-to-theta discharges, which spread to the right anterior and midline regions. Thirty seconds after ictal EEG onset, asystole, lasting for nine seconds, occurred. This was followed by spontaneous return of normal sinus rhythm for about four seconds before asystole recurred for seven seconds (*figure 1B*). The latter coincided with 15 seconds of generalized suppression of the background activity. Clinically, the patient complained of dizziness and a *déjà vu* sensation prior to EEG changes. She became lethargic during asystole.

Cardiology was consulted for possible pacemaker placement due to concern for risk of SUDEP, however, the patient opted for prolonged cardiac monitoring with loop recorder placement. Given the multifocal nature of seizure onset, neuropsychiatric symptoms, and refractoriness of seizures from the onset, AE was suspected. An autoimmune epilepsy panel revealed a serum GAD65 antibody level of 225 nm/l and a CSF level of 2.78 nm/l. The CSF examination was otherwise unremarkable. [^{18}F]-fluoro-deoxy-glucose positron emission tomography (FDG-PET) demonstrated bitemporal hypometabolism, greater on the left than the right (*figure 2*). Neuropsychiatric testing documented relative variability in domains of attention, processing speed and mathematics, and moderate clinical depression. The patient was diagnosed with AE, however, a decision was made to hold immunotherapy due to the patient's reasonable seizure control with current AED regimen as well as the historically limited response of GAD65-related encephalitis to immune therapy (Feyissa *et al.,* 2017). Upon six months of follow-up, she reported five seizures in the interim, occurring monthly. There were two brief aura/focal aware seizures characterized by dizziness and *déjà vu*, as well as three focal seizures with impaired awareness, one of which

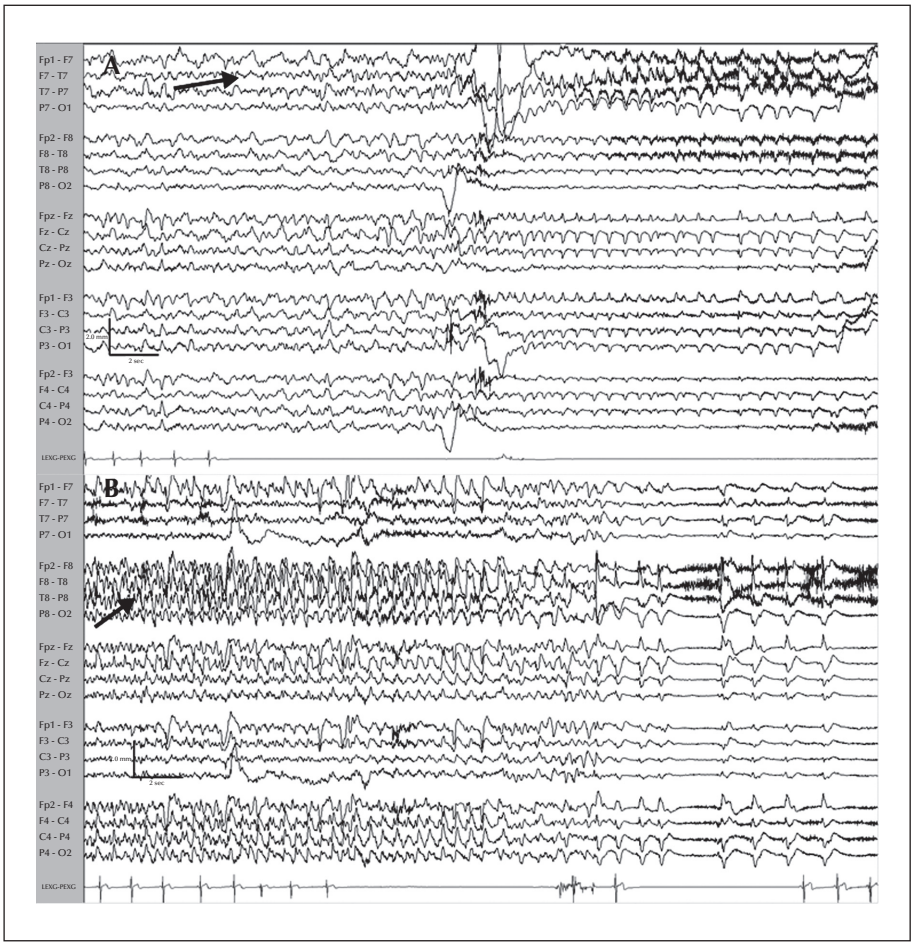

Figure 1. EEG-ECG tracings from a patient with GAD65 antibody-associated autoimmune epilepsy with unique independent bitemporal-onset ictal asystole, showing a left temporal-onset focal seizure discharge with a sentinel sharp wave (not shown), followed by rhythmic left temporal delta activity associated with ictal asystole (A; arrow) and a right temporal-onset focal seizure with ictal asystole (B; arrow).

resulted in a fall. The cardiac monitor documented a five-second period of ictal asystole during the latter. Subsequently, the dose of lamotrigine was increased due to continued breakthrough seizures and ictal asystole. Despite these recurrent seizures and asystole, the patient preferred to continue with AEDs and declined immunotherapy.

Pacemaker placement was a strong consideration given the prolonged periods of asystole she experienced. However, the patient was very hesitant to have the pacemaker after discussion with the cardiology department due to the somewhat invasive nature of the implantation, and preferred conservative management in the form of cardiac monitoring and treatment with AEDs. Given that there are no reports of SUDEP associated with ictal asystole, but rather postictal asystole, our patient and the cardiology department were comfortable with conservative management rather than cardiac pacemaker placement.

Discussion

Ictal Asystole has been predominately documented in idiopathic epilepsy and focal symptomatic seizures. Recently, neurocardiac syndromes including episodic bradycardia (with anti-LGI1 encephalitis AE) and ictal asystole (with anti-NMDR encephalitis) have been reported in AE (Lee *et al.,* 2011; Naasan *et al.,* 2014). To the best of our knowledge, we report the first case of GAD65-associated AE with independent bitemporal-onset ictal asystole.

The study of an autoimmune basis for drug-resistant epilepsy is receiving increasing interest, including patients without the typical phenotype of limbic encephalitis (Brenner *et al.,* 2013). Among other features, it has been suggested that seizures occur as an early and prominent feature in AE, and these are characteristically refractory to conventional AED therapy. Seizures and epilepsy may be the primary presentation of GAD65 antibody-associated

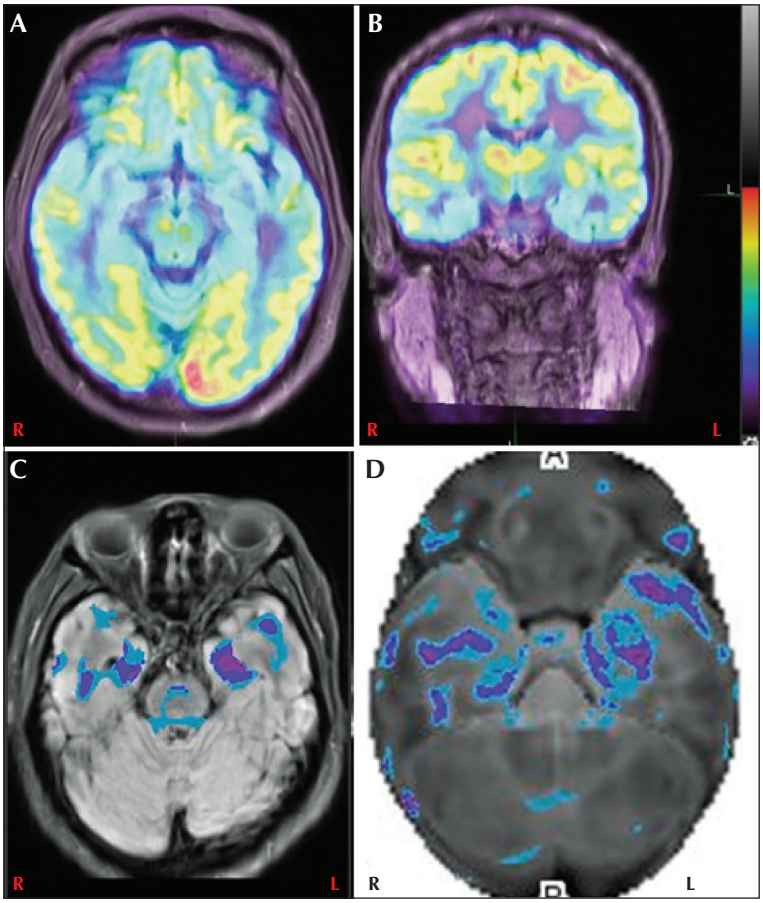

Figure 2. Axial (A) and coronal (B) fused PET MRI showing bitemporal (left>right) hypometabolism. Axial fused PET MRI (C) and surface rendering (D) in the same patient shows significant clustering in the bitemporal lobes (left>right). L: left; R: right.

encephalitis, with patients typically experiencing temporal lobe seizures (Liimatainen *et al.,* 2010; Malter *et al.,* 2010). Neurocognitive impairment is commonly seen in limbic encephalitis, as in our patient. It is unknown whether GAD65 antibodies are pathogenic or represent a biomarker of immune-mediated neuronal injury (Malter *et al.,* 2010). In general, GAD65 antibody-mediated encephalitis tends to have a more limited response to immunotherapies compared to other antibody-mediated epilepsies, such as anti-leucine-rich glioma inactivated subunit 1 antibody (LGI1)-mediated AE (Malter *et al.,* 2010).

The neuroanatomical localization of IA most likely relates to insular and temporal lobe involvement (Tényi *et al.,* 2017). IA is typically seen in temporal, left-sided-onset, long-standing, drug-resistant epilepsy (van der Lende *et al.,* 2016; Tényi *et al.,* 2017). However, these elements, particularly lateralization, have been reported inconsistently (Benditt *et al.,* 2015). Independent, bilateral temporal onset of seizures with IA in our patient also argues against a specific lateralization. The precise pathogenesis of IA is largely speculative, but may be due to involvement of the central autonomic network, which controls the parasympathetic and sympathetic output, or alternatively involvement of vasovagal reflex pathways (Palma and Benarroch, 2014). The relationship between AE and cardiac arrhythmias is also largely unknown and should be further investigated. In addition, it is unknown whether patients with AE, in particular, have a higher incidence of IA.

The duration of asystole in temporal lobe seizures has been reported to consistently last <30 seconds, in contrast to extratemporal seizures being more prolonged (Tényi *et al.,* 2017). In one study, IA resulting in clinical syncope only occurred with asystole duration of ≥six seconds, and left temporal lateralization tended to result in clinical syncope more commonly (Bestawros *et al.,* 2015). Based on a recent systematic review, no cases of SUDEP were identified in 157 cases of IA. The usefulness of pacemakers in ictal asystole has been long debated (Strzelczyk *et al.* 2008, 2011; Benditt *et al.,* 2015). In the setting of an acute and potentially reversible CNS insult, such as encephalitis and gliomas, treatment of the encephalitis or tumour resection, along with AEDs, may be sufficient to reduce the risk of further episodes of ictal asystole (Hampel *et al.,*

2017). In cases in which seizures cannot be fully controlled by AEDs or alternative treatments (*e.g.* epilepsy surgery), implantation of a cardiac pacemaker seems advisable to prevent syncope-related injuries (Benditt *et al.*, 2015).

This case further supports that multifocal onset of seizures, early drug resistance, and neuropsychiatric dysfunction are features suggestive of AE, and a high index of suspicion must be present to identify these patients. Further study is needed to determine whether recognition of IA and earlier institution of immunosuppression in AE can prevent the development of neuropsychiatric symptoms. The role of pacemakers in immunotherapy-responsive AE with IA also deserves further investigation. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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TEST YOURSELF

(1) When should autoimmune epilepsy be suspected?

(2) What is the lateralization value of ictal asystole (right or left hemisphere)?

(3) Should patients with ictal asystole receive pacemaker placement?

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".