Clinical commentary

Refractory epilepsy secondary to anti-GAD encephalitis treated with DBS post SEEG evaluation: a novel case report based on stimulation findings

Lisa Gillinder [1,2], Alexander Lehn [2,3], Jason Papacostas [1], Sarah Olson [2], Stefan Blum [2,3], Sasha Dionisio [1,2]

[1] Mater Advanced Epilepsy Unit, Mater Hospital, South Brisbane, Queensland
[2] Department of Neurology and Neurosurgery, Princess Alexandra Hospital, Woolloongabba, Queensland
[3] Mater Centre for Neurosciences, Mater Hospital, South Brisbane, Queensland, Australia

ABSTRACT – We report a case of medically refractory anti-GAD encephalitis which was treated with deep brain stimulation (DBS) after seizure termination was achieved using cortical stimulation during stereo-electroencephalography (SEEG) evaluation. The patient underwent bilateral SEEG implantation and cortical stimulation. Upon stimulation, mimicking the intrinsic seizures (at 1 Hz), it was possible to induce seizures with typical semiology, on multiple attempts. Stimulation during these seizures with high frequency (50 Hz) resulted in complete termination of the seizure. DBS was inserted after the SEEG evaluation, targeting the bilateral anterior nucleus of the thalamus. There was a sustained reduction in seizure frequency and severity 12 months post insertion. There were also improvements in quality of life. To the best of our knowledge, this is the only case reported in which DBS was successfully used to treat refractory epilepsy in a patient with seizures that were proven to be responsive to electrical stimulation during SEEG recording.

Key words: anti-GAD antibody encephalitis, refractory epilepsy, deep brain stimulation

Correspondence:
Lisa Gillinder
Advanced Epilepsy Unit,
Centre for neurosciences,
Mater Adults Hospital,
South Brisbane,
4101 Qld, Australia
<lisa.gillinder@mater.org.au>

Anti-glutamic acid decarboxylase (GAD) antibody (Ab)-associated limbic encephalitis is an increasingly recognised entity characterised by temporal lobe seizures, amnesia, and encephalopathy (Malter *et al.*, 2010). Affected patients often respond poorly to immunotherapy, especially if treatment is delayed, and anti-GAD titres frequently remain elevated after treatment. Treatment for refractory temporal lobe epilepsy, despite immunotherapy, appears to be related to post-inflammatory astrogliosis causing secondary hippocampal

sclerosis, as opposed to an ongoing uncontrolled autoimmune-driven inflammatory process (Bien *et al.*, 2007). In these cases, treatment should focus on seizure control and other treatment avenues need to be explored.

An emerging option for the treatment of refractory focal epilepsy that is not amenable to surgical resection is the use of deep brain stimulation (DBS). This is a novel therapy which has been shown to reduce seizure frequency (Fisher *et al.*, 2010). It involves insertion of neurostimulating electrodes into targeted regions of the thalamus, to influence and modulate intrinsic inhibitory networks to desired cortical regions.

In this article, we report a case of anti-GAD Ab encephalitis presenting with severe refractory epilepsy and discuss how the performed evaluation culminated in insertion of DBS resulting in benefit to the patient.

Case study

A 29-year-old male initially presented in 2007 (aged 23) with status epilepticus and was diagnosed with anti-GAD Ab limbic encephalitis based on Ab detection in cerebrospinal fluid (CSF) and serum by immunofluorescence. Serum and CSF inflammatory markers were elevated, and anti-GAD titre was >1,000. There was an initial response to immunotherapy with IVIg, steroids, and mycophenolate with stabilisation of the seizures (frequency of one per month). His initial clinical history is reported in the literature (Saidha *et al.*, 2010). Anti-GAD titre remained unchanged post therapy and there were no cognitive deficits.

More than five years later, the patient presented with poorly controlled seizures and an average seizure count of 300 per month. Antiepileptic medications were optimised and the modified Atkins diet was commenced, however, seizure count was only reduced to 150 per month. Serum and CSF inflammatory markers were normal. As the anti-GAD titre was persistently high, additional immunotherapy with two cycles of rituximab and two further induction courses of IVIg were given, with no seizure reduction.

Pre-SEEG work-up

Seizure type and frequency were recorded by the patient daily and tabulated on a monthly basis. Assessment of patient quality of life was measured using QoLIE31. All factors were recorded pre-procedure and each month post-procedure.

MRI was acquired using a Philips Ingenia 3.0T (Amsterdam, Netherlands) as well as a Siemens Magnetom Avanto 1.5T (Erlangen, Germany) system. Volume loss was reported in the left hippocampus with T2 signal

abnormality, in keeping with left hippocampal sclerosis. FDG-PET was also acquired using a GE Discovery 690 CT-PET scanner (Chicago, Illinois) and revealed hypometabolism, seen in the mesial left temporal lobe. Neuropsychological assessment revealed bilateral temporal lobe abnormalities.

The patient was admitted for five-day video-EEG monitoring using 10-20 electrode configuration with bilateral sphenoidal electrodes. This showed bitemporal interictal discharges and continuous slowing in the left temporal region and intermittent slowing in the right temporal region. There were frequent seizures (>100 during the recording), originating independently from both temporal regions, but rapidly affecting the contralateral temporal region. Many of the seizures produced no clinical signs. There were also others which were heralded by a musical or experiential aura of either *déjà vu* or *jamais vu*. The seizures arising from the left would then sometimes progress to dialeptic symptoms. Given that the MRI showed unilateral hippocampal sclerosis, the seizure semiology was unchanged since onset and associated with the left-sided seizures. A decision was made to proceed with a stereo-electroncephalogram (SEEG) to determine whether this was a unilateral temporal lobe epilepsy with rapid contralateral propagation and false lateralization, in order to establish whether a surgical solution could be provided (Sammaritano *et al.*, 1987).

SEEG results

The patient had a bilateral implantation targeting the hippocampus, amygdala, temporal pole, Heschl's gyrus/posterior insula, anterior insula, precuneus, and orbitofrontal area. SEEG was performed using Dixi electrodes. The patient was admitted for five days of recording with medication reduction, during which typical seizures were recorded.

The interictal recording revealed very frequent discharges occurring independently in a localized limbic network (in the hippocampi, amygdala, and temporal pole). Notably, there was no involvement outside the mesial temporal structures, suggesting the absence of significant involvement of the extended temporal network.

The ictal recording identified focal and independent EEG seizures arising from left and right hippocampi, occurring every 3-5 minutes. Many of these were associated with no clinical signs. Both hippocampi produced seizures with experiential symptoms (*déjà vu* and *jamais vu*). Seizures with musical aura or dialepsis were only recorded from the left hippocampus. These seizures propagated locally to the ipsilateral amygdala and temporal pole without extended network recruitment. An important observation was that every

seizure onset began with repetitive spiking (1 Hz), which evolved during a prolonged period (typically 60-90 seconds) and only resulted in clinical symptoms during synchronization with the ipsilateral temporal pole and amygdala. This suggested that the epilepsy was highly localised and confined within the hippocampus itself.

Cortical stimulation was also performed as part of the routine SEEG evaluation. Stimulation at 1 Hz, 5 mA to each hippocampus, mimicking intrinsic seizure generation, induced seizures with typical semiology on multiple attempts.

Of particular interest was the finding that both the low-frequency stimulation-induced seizures and the habitual seizures could be affected by high-frequency stimulation. When 25 Hz, 3 mA was used, this resulted in modulation of the seizure propagation. When 50 Hz, 3 mA was utilised, complete termination of the electrographic seizure was seen. This was repeated on five attempts and after a six-hour period of resting to ensure that the effect was not due to network saturation. All attempts successfully terminated seizures. An example can be seen in *figure 1*.

This phenomena of neuromodulation has previously been reported and forms the basis of the rationale of the Repetitive Nerve Stimulation (Sun and Morrell, 2014). The patient was discussed at the epilepsy multidisciplinary team meeting in conjunction with the movement disorder team. The idea to insert a deep brain stimulator was derived from three observations:
– the epileptogenic zone was highly localized to both hippocampi;
– the natural seizures arose from low-frequency repetitive discharges that achieved synchronization and recruitment of localised structures only;
– high-frequency stimulation was able to modulate and terminate seizures arising with and without cortical stimulation.

This was used instead of responsive neurostimulation as this technology is not currently available in Australia. Given that there are direct connections between the hippocampi and the anterior nucleus of the thalamus, we hypothesised that high-frequency stimulation of these directly connected regions would modify the seizures (Krishna and Lozano, 2014). This was discussed with the patient and full informed consent was obtained for this novel approach.

DBS insertion

Surgical DBS insertion was performed targeting the anterior nucleus of the thalamus bilaterally using a transventricular approach. A rechargeable neurostimulator system was used ('Brio', St. Jude Medical) and the stimulation parameters were based on those used

in the SANTE trial as well as findings from cortical stimulation during SEEG recording (Fisher *et al.*, 2010). Over a period of three months, the stimulation amplitude was incrementally increased to a target of 4 mA with a pulse width of 100 μs and a frequency of 110 Hz. The DBS system was set in a cycling mode of 1-min ON and 5-min OFF cycles.

Outcome

Seizure frequency ranged from 90-160 events per month with dialepsis during the six months pre-procedure. In the 12 months following implantation, the seizure frequency has been 30-70 seizures per month (*figure 2*). However, these are only auras (musical and *déjà vu*) with no loss of awareness. This result is consistent with Engel Class 1B. QoLIE31 T-score improved from 37 to 51 post-procedure with particular improvement in the social function domain and stable cognitive scores. From a subjective point of view, the patient has returned to work and has started a family. He remains on the same AEDs.

Discussion

This case represents a novel approach to the management of patients with refractory epilepsy post limbic encephalitis. Anti-GAD encephalitis is a well-recognised cause of drug-resistant epilepsy, especially in patients presenting with status epilepticus (Pillai *et al.*, 2016). It is also more common than previously thought (Falip *et al.*, 2012). Furthermore, it is not only resistant to antiepileptic therapy, but also increasingly recognised as being poorly responsive to immunosuppression, with limited or no effect on seizure control (Peltola *et al.*, 2000, Malter *et al.*, 2015).

This was evident in our case, and despite escalation of immunosuppression, the epilepsy remained refractory. Further to this, at initial presentation, the patient exhibited biomarkers consistent with active inflammation in the form of serological and CSF abnormalities, however, on representation, these markers had normalised. Additionally, FDG-PET scanning revealed no hypermetabolic areas, which is now known to be an almost universal finding in active encephalitis caused by autoantibodies against intracellular antigens, such as GAD (Baumgartner *et al.*, 2013). Malter *et al.* published, in 2015, the first summary of therapeutic options in such cases, showing that seizure response to all treatment modalities was poor. Interestingly, they report a patient undergoing temporal lobe resection 10 years after diagnosis for refractory seizures. At histopathological evaluation, no inflammation was found. These findings suggest that active inflammation may not be the primary factor driving the
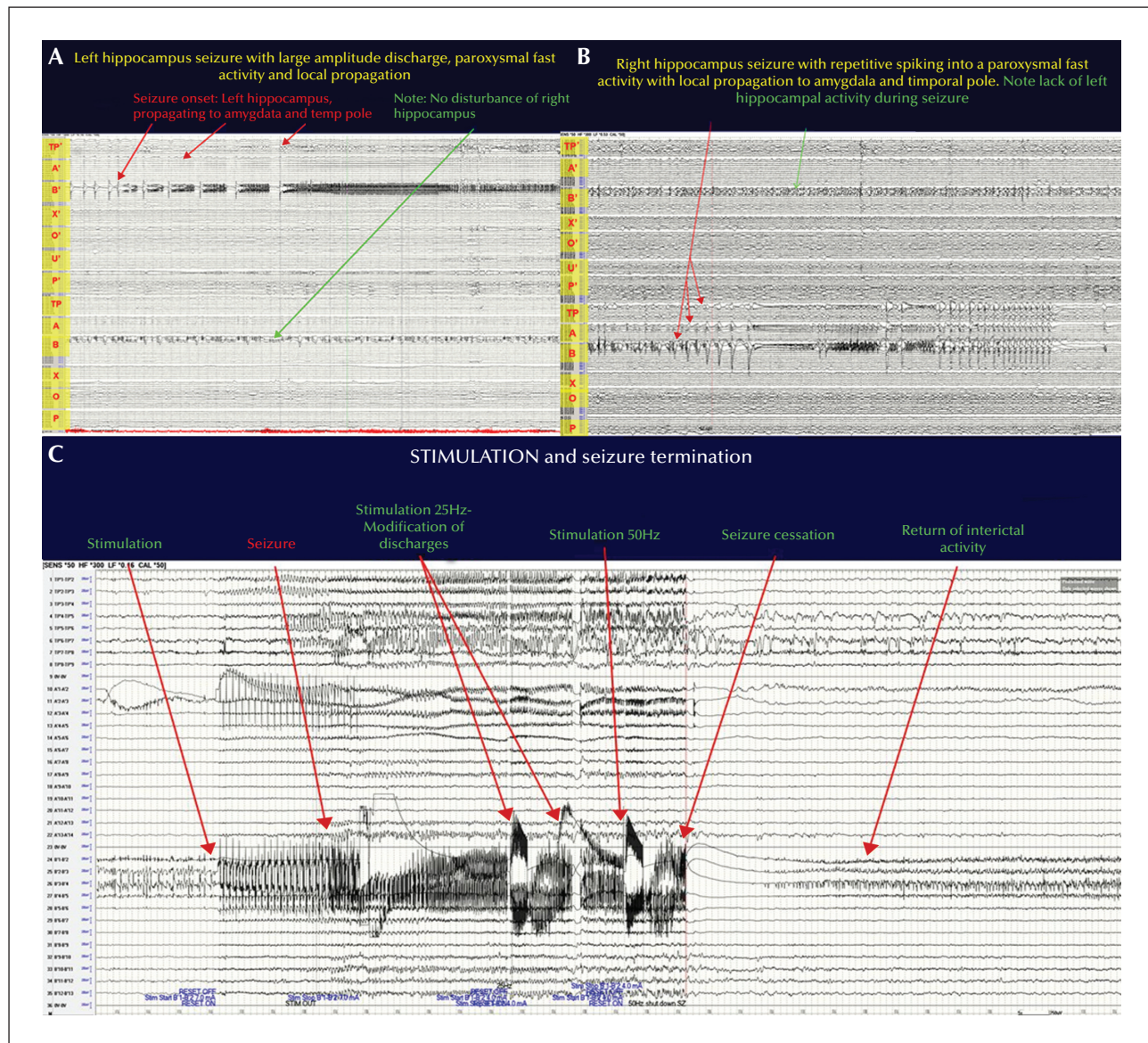
Figure 1. (A) Left hippocampus seizure with large-amplitude discharge, paroxysmal fast activity, and local propagation. (B) Right hippocampus seizure with repetitive spiking into a paroxysmal fast activity with local propagation to the amygdala and temporal lobe; note the lack of left hippocampal activity during the seizure. (C) Stimulation and seizure termination.

refractory nature of the epilepsy. If this is the case, the decision to pursue escalation of immunosuppressive options becomes heavily weighted by risk.

DBS is a novel therapy which has been investigated revealing promising results for the treatment of drug-resistant epilepsy in several studies, however, it has never been performed post-SEEG assessment (Lim *et al.*, 2007; Fisher *et al.*, 2010; Lee *et al.*, 2012; Piacentino *et al.*, 2015). The largest of these trials was the Sante trial in which 110 participants with refractory focal epilepsy, who were not candidates for surgical resection, underwent electrical stimulation of the anterior nucleus of

the thalamus. The authors demonstrated persistent significant improvements in all groups, however, this was most pronounced in patients with temporal lobe seizures, similar to our case. The effects of electrical stimulation on the anterior nucleus of the thalamus has been demonstrated to cause desynchronisation of cortical networks, thus the improvement of the epilepsy is likely related to modification of electrical activity in the affected areas (Kim *et al.*, 2017). We have demonstrated, with the use of cortical stimulation, the direct effects of this modification, with repeated successful seizure termination.
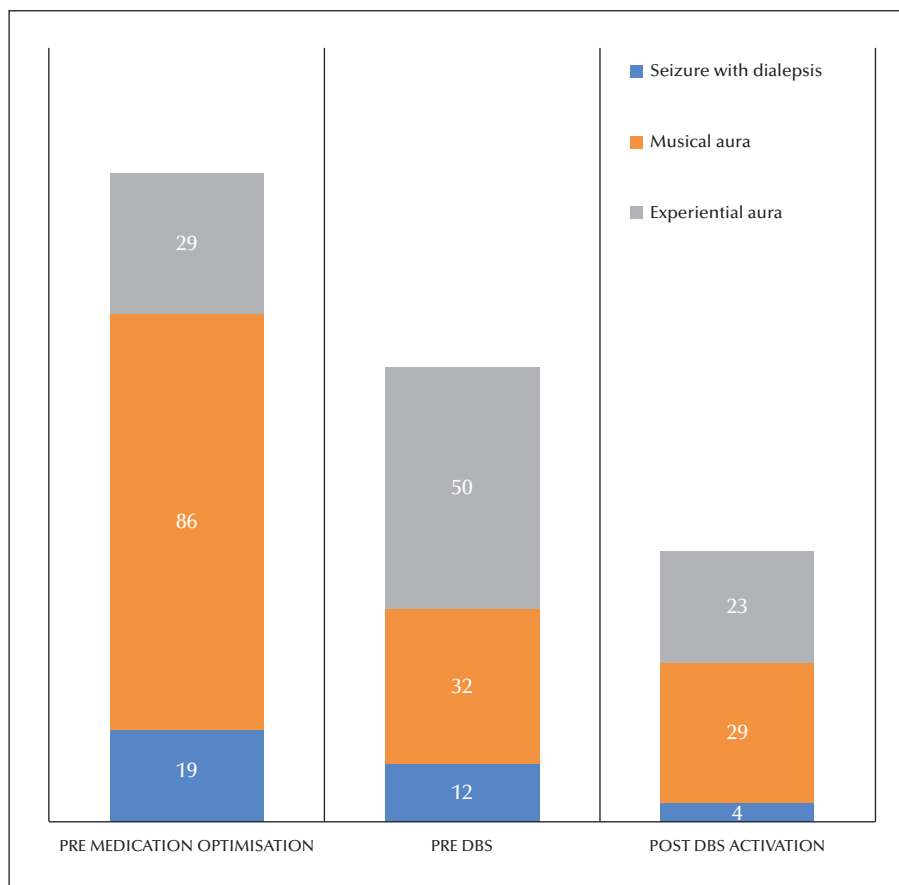
Figure 2. Reduction in number of seizures per month with escalation of therapy: prior to medical optimisation with anti-epileptics and further immunosuppression, one month prior to DBS insertion, and one month post-DBS activation.

Conclusion

To the best of our knowledge, this is the only case reported in which DBS was successfully used to treat refractory epilepsy in a patient with seizures that were proven responsive to electrical stimulation during SEEG recording. After more than 12 months post-surgery, there are sustained improvements in seizure frequency which is in line with most recent data. There has also been a significant improvement in quality of life. □

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

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

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TEST YOURSELF

(1) What was the largest trial to demonstrate the benefits of DBS insertion in refractory epilepsy?

(2) What are the treatment options for independent bilateral epilepsy when surgical resection is not an option?

(3) Where is the primary auditory cortex located?

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".