Clinical commentary

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Hippocampal deep brain stimulation: a therapeutic option in patients with extensive bilateral periventricular nodular heterotopia: a case report

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ABSTRACT – A female adult patient with extensive bilateral periventricular nodular heterotopia (PNH), who was referred for bilateral hippocampal deep brain stimulation (Hip-DBS), was investigated. She presented with daily focal aware and impaired-awareness seizures with automatism and weekly generalized tonic-clonic seizures. Her EEG showed bilateral independent ictal and interictal neocortical temporal lobe discharges and her MRI showed extensive, symmetric PNH. She was treated with bilateral Hip-DBS which led to a major decrease in her seizure frequency (one seizure per trimester). The outcome was stable over three years, and there was no additional neuropsychological deficits or device-related adverse effects. This is the first reported patient to be undergo long-term continuous Hip-DBS to treat bilateral PNH. DBS, a non-lesional, reversible, neuromodulatory technique, may prove to be a good therapeutic option in patients with extensive bilateral epileptogenic networks who present with temporal lobe epilepsy and who are usually considered poor candidates for resective surgery.

Key words: temporal lobe epilepsy, periventricular nodular heterotopia, DBS, outcome, epilepsy

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Bilateral periventricular nodular heterotopia (BiPNH) is often associated with refractory seizures. It may present as a unilateral or bilateral disease and prevail over the anterior or posterior quadrant, and is suggested to be more severe in males with bilateral disease (Dubeau *et al.,* 1995; Sisodiya *et al.,* 1999; Tassi *et al.,* 2005; Battaglia *et al.,* 2006). Multiple nodules and cortex may prove to be epileptogenic, however, there is no consensus on the pathophysiology regarding seizure generation, and a major role for the nodules or the cortex or an interaction between them has been discussed (Aghakhani *et al.,* 2005;

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Scherer, 2005; Battaglia *et al.,* 2005; Valton *et al.,* 2008). Different surgical approaches have been used to treat BiPNH, however, for most, the data are limited regarding seizure control with a high rate of long-term relapse. Focal resections are usually inadequate to control seizures due to the multifocal nature of this epileptic syndrome. The use of vagus nerve stimulation (VNS), radiosurgery and laser or radiofrequency has been described with variable and often transient outcome regarding seizures (Li *et al.,* 1997; Stefan *et al.,* 2007; Schmitt *et al.,* 2011; Agari *et al.,* 2012; Wu *et al.,* 2012; Esquenazi *et al.,* 2014). We describe the use of hippocampal deep brain stimulation (Hip-DBS) for treatment of refractory seizures in a patient with BiPNH.

Case study

A 34-year-old woman presented with refractory epilepsy that she had since the age of 23 years. She had daily autonomic focal aware seizures followed by focal impaired-awareness seizures with automatism; generalized tonic-clonic seizures occurred once a week. Ictal and interictal EEG showed bitemporal discharges; seizures were recorded from both temporal lobes independently (*figure 1*). MRI showed symmetric BiPNH (*figure 2*). She was taking lamotrigine at 600mg/day, oxcarbazepine at 1,200 mg/day and clobazam at 40 mg/day. Neuropsychological testing showed severe visual and verbal memory deficits (below 2 standard deviations) and an IQ of 83. She previously received VNS, which initially reduced seizure frequency by 60%; seizures relapsed to preimplantation frequency after two years under VNS. She remained with daily focal impaired-awareness seizures and weekly generalized tonic-clonic seizures. She was admitted for bilateral Hip-DBS under general anaesthesia, using Medtronic's quadripolar 3391 electrode. The leads were inserted through a posterior occipital burr hole. Direct imaging was performed using CT-MRI fused datasets. The most anterior contact was located at the level of the hippocampal head and the most posterior contact was located at the level of the posterior body of the hippocampus, both at the interface of the hippocampus and the periventricular nodules or in the lateral hippocampus (*figure 2*). Final stimulation parameters were: 2.5V, 300 µsec, 130 Hz, and continuous bipolar stimulation (cathode over the hippocampal head and anode over the posterior hippocampal body).

A marked reduction in seizure frequency was noted early after a month of full hippocampal stimulation. There was no progressive improvement over time. After three years of follow-up, she had one focal impaired-awareness seizure per trimester and no generalized tonic-clonic seizures. There was a marked improvement on her EEG; rare spiking could still be seen over both temporal lobes independently. After two years of follow-up, neuropsychological testing

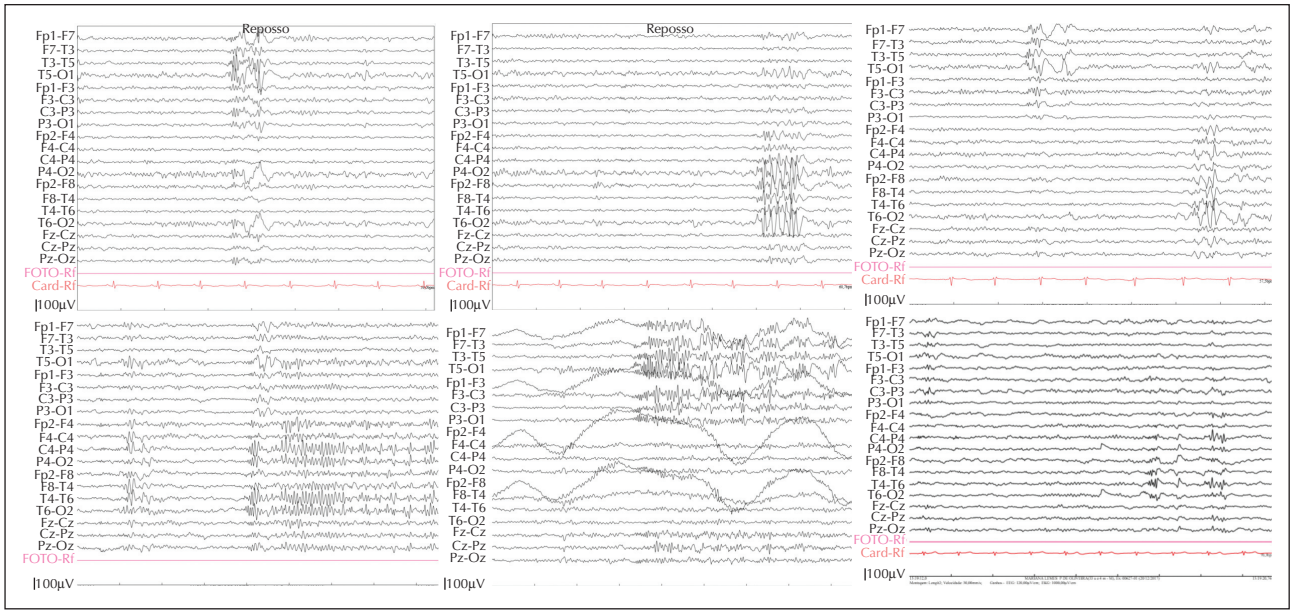

Figure 1. Upper panels: interictal activity prevailing over the left temporal lobe (left), over the right temporal lobe (middle) or seen bilaterally (right). Lower panels: a short electrographic seizure prevailing over the posterior right temporal lobe (left), a short electrographic seizure prevailing over the mid-posterior left temporal lobe (middle), and post-operative (two years) recording showing much less frequent spiking over both temporal lobes independently (right).

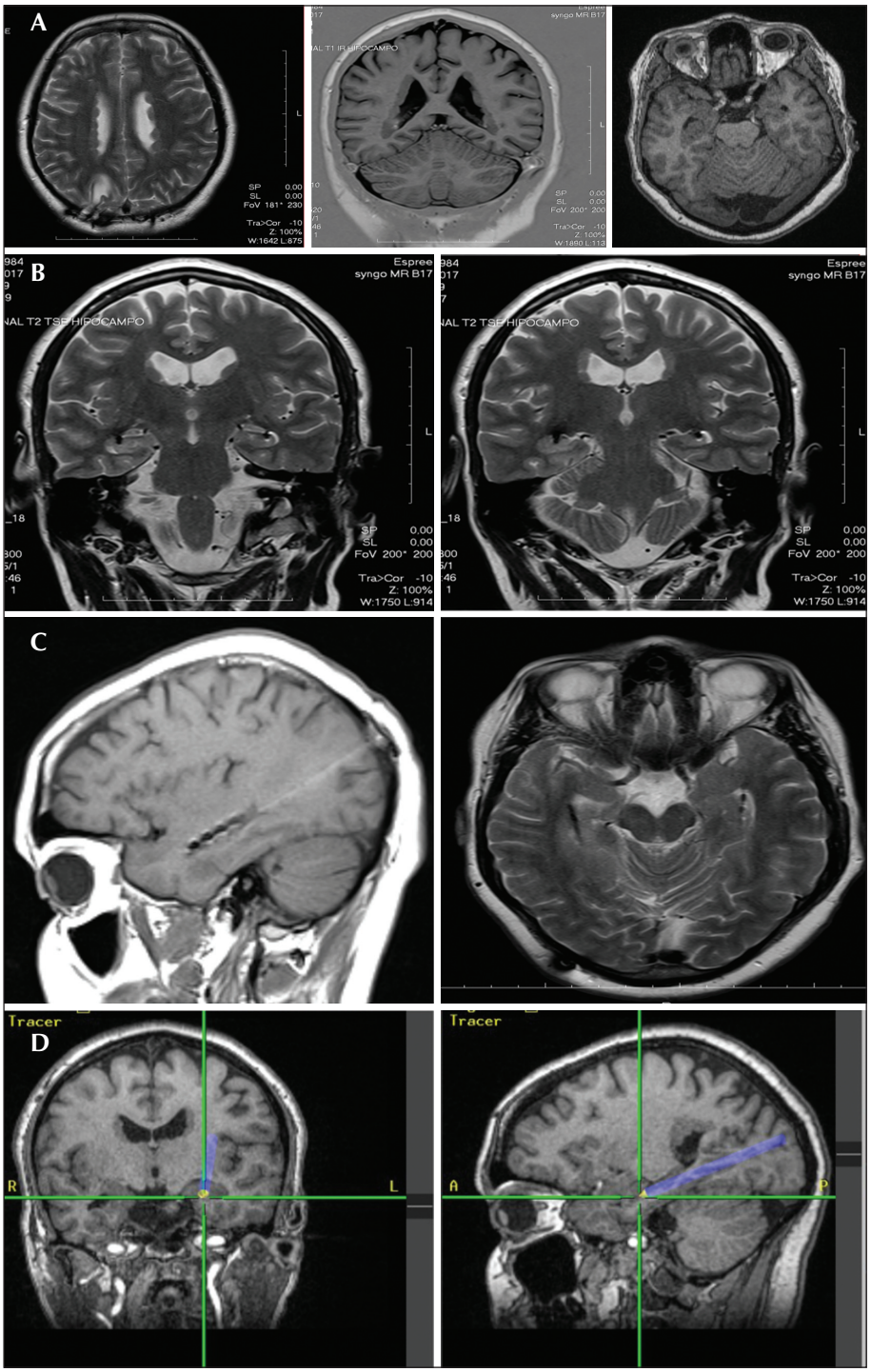

Figure 2. MRI investigation. (A) Extensive bilateral periventricular nodular heterotopia. (B) The location of DBS electrodes bilaterally; contacts are located in the lateral hippocampus proper (left hippocampus) or in the heterotopia/hippocampus interface (right mesial region). (C) Axial and sagittal MRI slices showing the position of the contacts postoperatively. (D) Intraoperative neuronavigational snapshot during electrode insertion.

showed no additional memory deficits; both visual and verbal memory deficits were still present but had improved (below 1 standard deviation) and her IQ was 85. There were no side effects related to Hip-DBS.

Discussion

This is the first reported patient in the literature in whom continuous bilateral Hip-DBS was used to treat refractory epilepsy related to BiPNH with a prolonged follow-up. Hip-DBS led to a dramatic seizure reduction in this patient with temporal lobe epilepsy and BiPNH. Reduction in seizure frequency started shortly after a month of full hippocampal stimulation. There was no progressive improvement, as seen with different methods of neuromodulation. This early and sustained response was also noted in our controlled Hip-DBS study (Cukiert *et al*., 2017). There was no cognitive or hardware-related adverse effects in this patient.

The hippocampus may be part of the epileptogenic area or a major relay for seizure spread in patients with bilateral PNH. Hippocampal DBS, a non-lesional procedure, might disrupt the epileptogenic network in such patients who are not candidates for resective procedures. Our observations suggest that, although limited to a single case report, Hip-DBS might prove to be a useful palliative procedure in this patient population.

The largest series of patients with PNH treated using brain neuromodulation was reported by Nune *et al*. (2019) using the RNS system. In this series, only one patient received bilateral hippocampal stimulation, and the outcome appeared to be good although direct data could not be extracted from the manuscript. A major difference between this patient and ours is that they used intermittent stimulation, and the present patient received continuous stimulation. Continuous stimulation has proven to be more efficacious than intermittent stimulation in patients with refractory temporal lobe epilepsy (Cukiert *et al*., 2017). There is ongoing discussion as to whether all patients would need to undergo invasive recordings before brain neuromodulatory techniques are used. In the study of Nune *et al*., 50% of the patients received RNS treatment without any invasive recording (as in the present case).

Hip-DBS is a novel, neuromodulatory, non-lesional, reversible treatment modality which may prove to be a good treatment option in this patient population, as is the case in other populations in which modulation of complex epileptic networks is needed. This modality may be particularly suited to patients with documented bilateral temporal lobe seizure onset or epileptogenesis, who are not considered to be good candidates for cortical-nodule resection. BiPNH is a rare disease, and larger series with longer follow-up periods are needed to further evaluate Hip-DBS efficacy in this setting. □

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) Periventricular nodular heterotopia:
A. is a bilateral genetic disease.
B. is mainly associated with generalized epileptogenicity and cognitive preservation.
C. presents with nodules that frequently locate to the cerebral surface or posterior fossa, although the nodules prevail in the periventricular regions.
D. is frequently associated with refractory focal seizures.
E. has been studied in large cohorts and its epileptogenicity is presently well understood.

(2) In the treatment of bilateral periventricular heterotopia:
A. seizure remission is usually seen after resection of the single most epileptogenic nodule.
B. gamma-knife is the preferred surgical option due to its early and sustained effect on seizures.
C. seizures are usually unilateral and easily treatable with antiepileptic drugs.
D. radiofrequency or laser-induced thermotherapy of lesions has no effect on seizure frequency.
E. neuromodulation could be offered as a non-lesional treatment option in such individuals.

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".