Clinical commentary

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Stimulation of the bilateral anterior nuclei of the thalamus in the treatment of refractory epilepsy: two cases of subcortical band heterotopia

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ABSTRACT – Subcortical band heterotopia is a neuronal migration disorder that may cause refractory epilepsy. In these patients, resective surgery has yielded inadequate results. Deep brain stimulation of the anterior nuclei of the thalamus has been used for the treatment of refractory epilepsy with good results. We describe the first two patients with subcortical band heterotopia who were submitted to deep brain stimulation of the anterior nuclei of the thalamus, with evaluation of seizure outcome after 12 and 18 months of follow-up. At these times, both showed a >50% decrease in seizure frequency and an increase in seizure freedom. Both patients had a depressive syndrome after surgery that responded fully to anti-depressive medication in one patient and partly in the other. In both, deep brain stimulation of the anterior nuclei of the thalamus was associated with good seizure outcome. This procedure can therefore be considered in the treatment of patients with subcortical band heterotopia and refractory epilepsy. Depression may be a transient adverse event of the surgery or stimulation, however, its aetiology is probably multifactorial.

Key words: epilepsy, deep brain stimulation, migration disorder, subcortical band heterotopia

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Subcortical band heterotopia (SBH) is a neuronal migration disorder characterised by bands of grey matter within the central white matter between the cortex and the ventricular surface. Together, SBH and lissencephaly comprise a spectrum of malformations associated with deficient neuronal migration. The majority of the cases are sporadic, but many of these and the familial ones are X-linked and related to *DCX* mutations. Mutations in *LIS1* and *TUBA1A* have also been described, more often related to some degree of lissencephaly (Bahi-Buisson *et al*., 2008; Guerrini and Dobyns, 2014).

Seizures are often the first manifestation of the disease, usually appear in the first decade of life, and frequently become refractory to pharmacological treatment. Neurological examination is normal in most cases (Barkovich *et al*., 1994; Bahi-Buisson *et al*., 2013). In patients with SBH, resective surgery has been mostly disappointing, even when the epileptic activity appears to be focal (Bernasconi *et al*., 2001).

The SANTE trial in 2010 was the first randomised and controlled trial establishing anterior nucleus of the thalamus-deep brain stimulation (ANT-DBS) as an effective palliative intervention for patients who are not candidates for resective surgery, with a 43% responder rate after one year (Fisher *et al*., 2010) and 69% after five years of follow-up (Salanova *et al*., 2015). In 2012, Medtronic® started a Registry for Epilepsy (MORE). The purpose of this observational registry is to evaluate the long-term effectiveness, safety, and health-related quality of life associated with ANT-DBS in the treatment of refractory epilepsy.

We herein present the clinical outcome of the first two reported patients with SBH and refractory epilepsy referred for DBS, included in this registry. The data were collected prospectively. Stereotactic coordinates of each electrode were confirmed by fusion of post-operative CT with pre-operative planning and MRI, as well as with published stereotactic thalamus atlases (Morel, 2007; Mai, 2008). The stimulation was started one month after the procedure and the parameters used were those described in the SANTE trial; 5 volts, 90 μsec, and 145 Hz (Fisher *et al*., 2010).

Case study

Patient 1 was a 51-year-old female with seizures since the age of 14 years, characterised by a visual aura, loss of contact, and manual and oroalimentary automatisms, sometimes with secondary generalization. She had already tried five antiepileptic drugs (AEDs) in different combinations and was taking valproate and levetiracetam, but maintained a mean of 4.6 (SD: 2.6) seizures a month in the previous year. Neurological examination was unremarkable. EEG showed slow and epileptiform activity in the right temporal and fronto-temporal areas, bilaterally. The patient was evaluated within the scope of our surgical epilepsy programme. Video-EEG showed right fronto-temporal and posterior temporal epileptiform activity and ictal onset. Brain MRI disclosed subcortical band heterotopia involving the parietal, temporal, and occipital lobes, bilaterally (*figure 1*). PET displayed bilateral temporal hypometabolism. Given that it was impossible to lateralize the epileptogenic zone, resective surgery was denied and ANT-DBS proposed. After 18 months of follow-up, there was a 61% decrease in the number of seizures (4.6 to 1.78 seizures/month) and an increase in seizure-free time from 20 to 70 days (*figure 2*). Valproate daily dose could be lowered by 25%. She experienced a new onset of a depressive syndrome which was easily controlled with anti-depressive medication (venlafaxine and amissulpride).

Patient 2 was a 48-year-old female, chronically depressed, with seizures since the age of 23 years, characterised by a disturbance of consciousness, oroalimentary automatisms, and blinking. Neurological examination was unremarkable. Six AED combinations had previously been tried and at the time of admission she was taking carbamazepine, valproate, and zonisamide, but maintained a mean of five seizures a month in the previous three months. Interictal EEG showed slow and epileptiform activity over the left posterior temporal, parietal, and central areas, as well as also slow and epileptiform bilateral independent activity in the anterior temporal area. Brain MRI showed bilateral subcortical band heterotopia in both frontal areas (*figure 1*). She was evaluated within our epilepsy surgery programme. Video-EEG showed ictal onset from the left parieto-occipital area. Neuropsychological evaluation revealed significant compromise in the following cognitive domains: attention (sustained and divided) and concentration, verbal memory (immediate, work-related, associative, and logic), visual memory, verbal fluency (low fluency), mental flexibility, and abstraction.

Resective surgery was considered not to be suitable for this patient and ANT-DBS was accepted by the patient. After 12 months of follow-up, there was a 75% decrease in the number of seizures (5 to 1.25 seizures/month) and an increase in seizure-free time from 14 to 176 days (*figure 2*). Valproate and zonisamide daily doses could be slightly lowered. She experienced a worsening in her depressive symptoms which were only partially controlled with medication (nortriptyline and trazodone).

Discussion

In both patients, ictal onset zones could not be clearly established, which prevented resective surgery, and

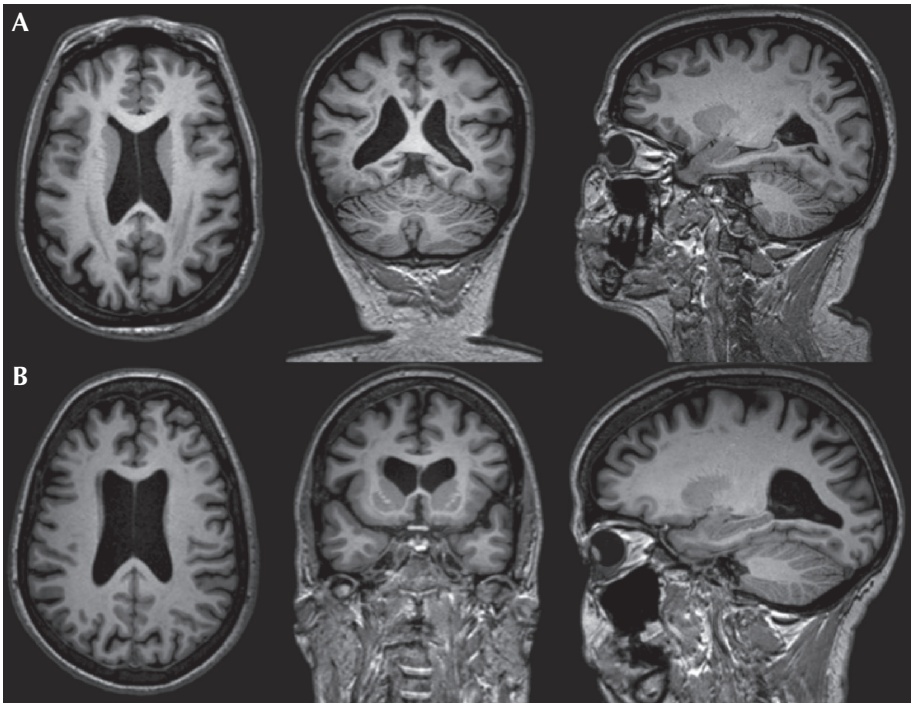

Figure 1. (A) Patient 1 brain MRI (T1 MPR 3D) shows SBH of the temporal, occipital and parietal lobes.
(B) Patient 2 brain MRI (T1 MPR 3D) shows subtle SBH of the frontal lobes bilaterally.

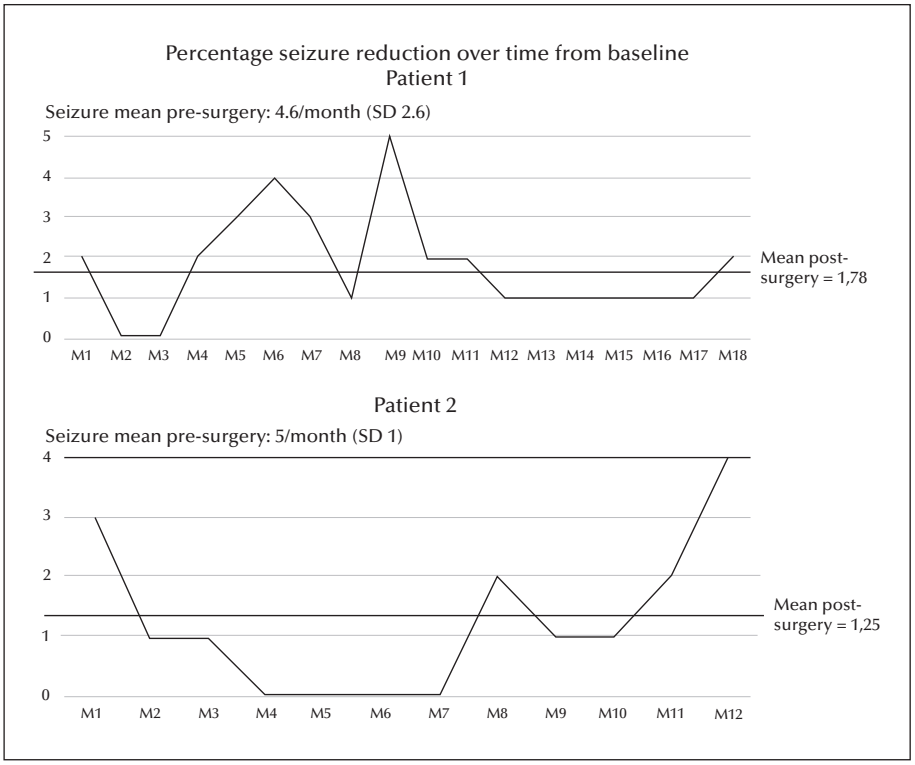

Figure 2. Percentage of seizure reduction over time from baseline mean (standard deviation) M1 corresponds to the first month after surgery when the stimulation was OFF.
The horizontal line represents the mean of the entire 18 months (Patient 1) and 12 months (Patient 2).

therefore we chose DBS. The seizure outcome at one and one and a half years of follow-up corroborated the SANTE trial data (Fisher *et al*., 2010; Salanova *et al*., 2015) with a >50% decrease in seizure frequency in both patients. The characteristics of seizures did not change.

Both patients also experienced either *de novo* or worsening of depressive symptoms. Both patients were evaluated and treated by the psychiatrist in our epilepsy surgery group. None of them had suicidal tendencies. Both patients improved after a few months but they are still on antidepressants. These symptoms did not necessitate the stimulation to be halted.

This occurrence is in accordance with the SANTE trial, in which depression was the most common and statistical significant adverse event at five years of follow-up. A recent systematic review and meta-analysis of the literature showed a positive association between epilepsy and depression (Fiest *et al*., 2013), although no mention was made about surgical patients. Further studies, including the MORE registry, will help to clarify the relationship between DBS and depression.

The mechanisms of action of DBS in epilepsy, particularly those involved in the progressive improvement of patients over time, are still unclear. In temporal lobe epilepsy, the Papez circuit might play a role. Corticothalamic projections to the frontal and temporal lobes are probably also involved (Laxpati *et al*., 2014; Toprani and Durand, 2014). The several proposed mechanisms might account for the effectiveness of DBS in different types and locations of epilepsy.

However, this study has some limitations. Besides the uncontrolled nature of single case reports, these patients were not blinded to the procedure and could have had surgery during a period of higher seizure frequency. To minimise this possibility, the mean seizure frequency after surgery was compared to the mean seizure frequency during the previous year for Patient 1 and during the previous three months for Patient 2; seizure diaries were kept and frequent follow-up visits scheduled.

These patients had focal epilepsy which is an indication for this procedure, however, which patient characteristics predict a good response to ANT-DBS is not entirely clear.

To our knowledge, these are the first two reported cases of SBH referred for ANT-DBS who were followed for 12 and 18 months, respectively. Although the interpretation of the data is limited, the results appear to be promising. This neuromodulation technique could therefore be considered as an option for patients with SBH and refractory epilepsy, given the fact that resective surgery is frequently either inappropriate or ineffective.

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

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References

Bahi-Buisson N, Poirier K, Boddaert N, *et al*. Refinement of cortical dysgeneses spectrum associated with *TUBA1A* mutations. *J Med Genet* 2008; 45: 647-53.

Guerrini R, Dobyns W. Malformations of cortical development: clinical features and genetic causes. *Lancet Neurol* 2014; 13: 710-26.

Bahi-Buisson N, Souville I, Fourniol FJ, *et al*. New insights into genotype-phenotype correlations for the doublecortin-related lissencephaly spectrum. *Brain* 2013; 136: 223-44.

Barkovich AJ, Guerrini R, Battaglia G, *et al*. Band heterotopia: correlation of outcomes with magnetic resonance imaging parameteres. *Ann Neurol* 1994; 36: 609-17.

Bernasconi A, Martinez V, Rosa-Neto P, *et al*. Surgical resection for intractable epilepsy in "double cortex" syndrome yields inadequate results. *Epilepsia* 2001; 42: 1124-9.

Fisher R, Salanova V, Witt T, *et al*. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 2010; 51: 899-908.

Salanova V, Witt T, Worth R, *et al*. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology* 2015; 84: 1017-25.

Morel A. *Stereotatic Atlas of the Human Thalamus and Basal Ganglia*. CRC Press, 2007.

Mai JK. *Atlas of the Human Brain 3rd edition*. Academic Press, 2008.

Fiest K, Dykeman J, Patten SB, *et al*. Depression in epilepsy. A systematic review and meta-analysis. *Neurology* 2013; 80: 590-9.

Laxpati N, Kasoff W, Gross R. Deep brain stimulation for the treatment of epilepsy: circuits, targets, and trials. *Neurotherapeutics* 2014; 11: 508-26.

Toprani S, Durand DM. Deep brain stimulation in the dish: focus on mechanisms. *Epilepsy Curr* 2014; 14: 201-2.

TEST YOURSELF

(1) What was the most common adverse event in the SANTE trial?

(2) Did the outcome following ANT-DBS in the SANTE trial improve, stabilise or worsen over time, after implantation?

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".