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Patience can be a virtue with deep brain stimulation of the anterior thalami: another case report

To the Editor,

We read with great interest the case report by Grewal *et al*. (Grewal *et al*., 2016). A patient classified as a "non-responder" after seizure recurrence within the first month of responsive neurostimulation (RNS) treatment subsequently achieved more than four seizure-free years. The authors referred to the clinical observation that efficacy of neurostimulation has been shown to improve over time and recommended a one-year minimum observation period before considering RNS to be a "failure". We support their arguments for extending the observation period in neuromodulatory treatment, especially concerning deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT). Indeed, thorough unblinded long-term data from the SANTE study are available (Salanova *et al*., 2015); 74 of 110 patients, followed at each study visit, showed a median seizure reduction of 49% after one year and of 69% after two years of ANT-DBS treatment. However, changes in the AED drug regimen may have been a contributing co-factor.

We present an adolescent with pharmacoresistant, focal epilepsy, who became a responder after 18 months with unchanged DBS stimulation parameters and AEDs.

The 16-year-old female patient with low IQ developed pharmacoresistant frontal lobe epilepsy due to a post lymphomatoid granulomatosis with CNS and lung involvement at the age of six. Seizure frequency was up to 12 per day, averaging six per day. Clinically, three seizure types could be differentiated: (1) myoclonic seizures (short bilateral sudden asymmetric elevation of both arms with right predominance); (2) the same myoclonic seizures as in (1) but followed by a prolonged period of impaired awareness; and (3) complex motor seizures (body rocking and lip-smacking). The 1,5-Tesla MRI depicted small non-specific white matter lesions in the left and right frontal lobe, respectively. On video-EEG monitoring, (bi)frontal seizure onset without clear lateralization (high-amplitude theta wave, followed by general background suppression, then sometimes followed by bi-frontal mid-amplitude theta rhythm) was seen. After failure of six AEDs (sultiame, clobazam, valproate, levetiracetam, topiramate, and mesuximide) and VNS, DBS-ANT was initiated at the age of 11 years. Seizure frequency was reported to the physician monthly for 4.5 years by her parents, who were also questioned about their impression of seizure frequency and severity. The stimulation parameters were kept constant over the full-time period at 5.0 V; cycle: 1 min on/5 min off; pulse width: 90 μs; and frequency: 140 Hz. AEDs (valproate at 600 mg and mesuximide at 450 mg) were not changed for 3.5 years. The frequency of "disabling seizures", classified as myoclonic seizures with impairment of consciousness and complex motor seizures, had dropped below 50% from presurgical baseline after 18 months. The decrease in seizure frequency showed a linear correlation over time (Pearson r=0.864; p<0.001). Also, the overall monthly seizure rate showed progressive reduction, and after 24 months, values were lower than presurgical baseline (183±17 seizures per month) (*figure 1*). A 25% seizure reduction was reached after 36 months, and responder status after 48 months (linear correlation over time; Pearson r=0.866; p<0.001). The parents reported neither changes in overall seizure burden nor seizure severity during the whole observation period. AEDs remained unchanged for 43 weeks. The serum concentration of AEDs did not change considerably.

There are several arguments in favour of a neuromodulatory effect. Due to the patient's moderate intellectual disability, a significant placebo effect can be excluded. Interference by her parents seems unlikely, considering their overall negative attitude towards the DBS outcome, as well as their regularity and length of seizure documentation. Regarding the persistence of a lesional effect of electrode placement, different time spans have been previously reported; this usually persists for up to four months, and in rare cases it has been reported to last three years (Krishna *et al*., 2016). The initial absence of seizure reduction postsurgically and the slow gradual decrease in seizure frequency below the baseline makes a lesional effect unlikely, however. The observations by Grewal and colleagues and our own observations are in accordance with recent descriptions by other patients who have benefitted from a delayed stimulation effect for up to one year after

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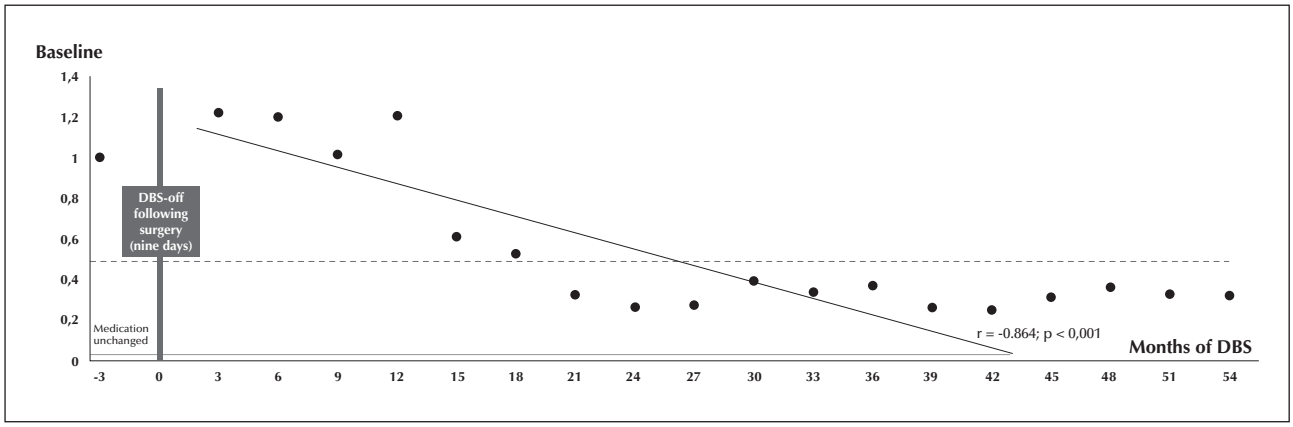

Figure 1. Monthly frequency of disabling seizures (black dots) during neurostimulation treatment. The reference is a three-month presurgical baseline. The red line marks the time span without change in medication, and the black line the linear correlation over time (Pearson r=0.864; p<0.001).

the onset of neurostimulation (Krishna *et al*., 2016). We concur with the authors that standard trial designs fail to address the possible impact of efficacy of the tested device. In general, long-term observation periods with stable AED medication are warranted and the lesional effect of neuromodulatory treatment should be further investigated with pooled, well controlled data. □

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

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TEST YOURSELF

(1) Are the first months of neurostimulation using ANT-DBS sufficient to determine the efficacy of treatment?

(2) What were the pros and cons for a long-term neuromodulatory effect using ANT-DBS in this particular case?

(3) Are there parameters that interfere with determining long-term effects in neuromodulatory treatment?

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".