■ Clinical commentary

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De novo status epilepticus possibly related to battery depletion of anterior thalamic brain stimulator

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ABSTRACT

Anterior thalamic deep brain stimulation is an effective therapeutic option for patients with drug-refractory focal epilepsy who are poor surgical candidates. Although the precise mechanism of action of thalamic neurostimulation is unknown, studies demonstrating increased efficacy over time have raised the possibility that therapeutic benefits are mediated by stimulation-related long-term neuroplastic changes. Adverse effects related to hardware malfunction have been previously described, and most commonly include local infection, sensory disturbances, and migration of leads. However, the withdrawal effect of sudden deep brain stimulation malfunction on seizure control is unclear. We present the case of a 21-year-old patient with intractable focal epilepsy who developed status epilepticus concurrently with unexpected deep brain stimulator battery failure, 21 months post implantation. This case demonstrates an unfamiliar possible adverse effect of anterior thalamic stimulation withdrawal and emphasizes the importance of stimulator hardware assessment in patients presenting with seizure worsening.

Key words: deep brain stimulation, status epilepticus, drug refractory epilepsy

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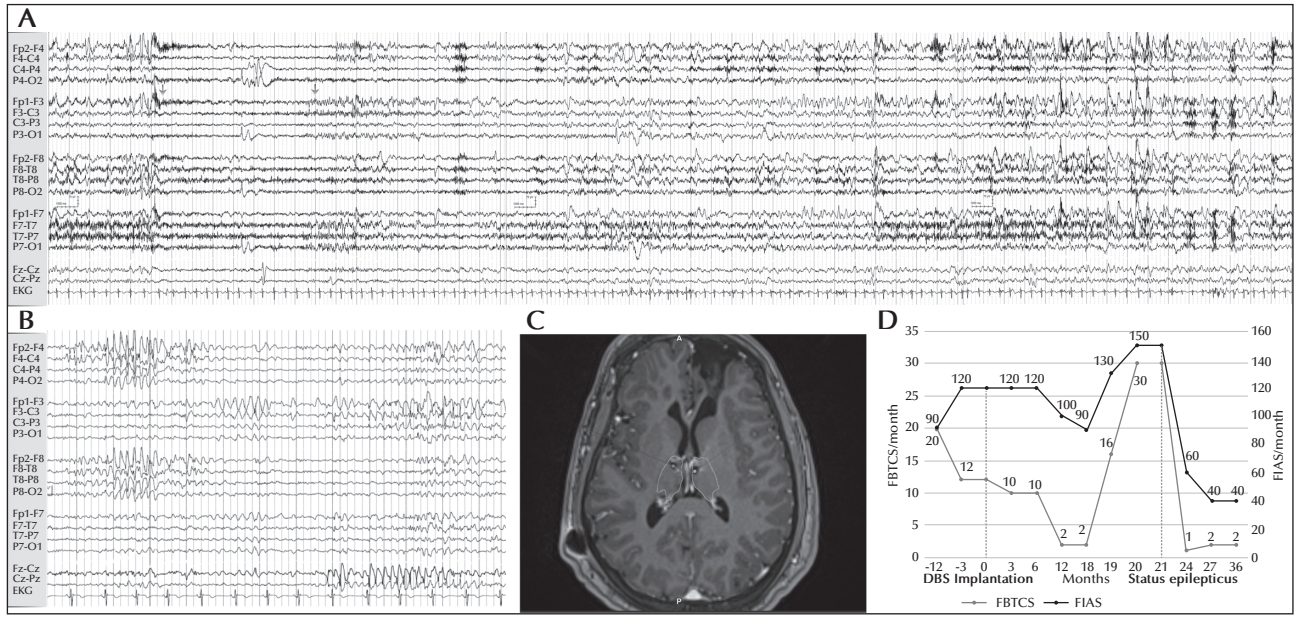
Thirty percent of patients with epilepsy do not reach adequate seizure control with anti-epileptic drugs (AEDs) or experience severe side effects, and suffer from drug-resistant epilepsy (DRE) [1]. Deep brain stimulation (DBS) of the anterior thalamic nuclei is a novel treatment that has been shown to reduce seizure burden in patients with focal DRE [2]. The beneficial neuromodulatory effects of DBS may take months to years [2, 3], probably reflecting the modulation of cortical and subcortical neural networks [4]. Yet, little is known about the clinical effects of abrupt cessation of chronic DBS treatment. We present a case report of a patient experiencing *de novo* status epilepticus (SE) due to DBS battery depletion.

Case study

A 21-year-old, right-handed male suffered from perinatal asphyxia resulting in mild intellectual disability and mild left spastic hemiparesis. He experienced a first seizure at the age of one month, and an additional complicated hour-long febrile seizure occurred at the age of three years. The patient remained without additional seizures until the age of 12 years, at which time AED treatment was initiated. Since that age, the patient experienced different seizure types,

including focal seizures with impaired awareness (FIAS), focal to bilateral tonic-clonic seizures (FBTCS), and drop attacks. By the age of 16, the patient was experiencing 2-3 FIAS per day, and 4-5 FBTCS per month. He had been unresponsive to multiple AED regimens including phenobarbital, phenytoin, carbamazepine, valproate, topiramate, levetiracetam, sultiame, clobazam, rufinamide, zonisamide, lacosamide, and perampanel. Due to poor response to medical treatment, he underwent a pre-surgical evaluation. Video-EEG demonstrated focal seizures with left arm dystonic posturing, right manual automatism and altered consciousness. The ictal EEG showed a left frontal seizure onset with rapid bilateral synchronization (*figure 1A*). Interictal EEG demonstrated bilateral independent frontal epileptiform activity (*figure 1B*). Brain MRI demonstrated bilateral frontal encephalomalacias correlating to the vascular territories of the right anterior cerebral and left middle cerebral arteries. Interictal magnetoencephalography demonstrated bilateral frontal dipoles, more apparent over the right, and neuropsychological assessment disclosed bilateral frontal dysfunction. The patient was not found to be a good candidate for focal resection, and at the age of 17, he was implanted with a vagal nerve stimulator (VNS), with a minimal reduction in seizure frequency. At age 19, due to continued high seizure frequency, the patient underwent implantation of DBS (ActivaTM PC model 37601; Medtronic Inc.), targeting the anterior thalamic nuclei bilaterally; the procedure was performed according to accepted surgical protocols, as described elsewhere [2]. Post-implantation MRI demonstrated electrodes 1 and 9 within the anterior thalamic nucleus (*figure 1C*). The initial stimulation parameters were set to cycling on/off for 1/5 minutes, voltage of 5.0 V, pulse width of 90 microseconds, frequency of 145 Hz, , and contacts 1 and 9 were used for DBS stimulation. VNS and DBS were activated concomitantly. Seizure frequency at this time was, on average, 120 FIAS and 12 FBTCS per month. Notably, at this point, the patient had not previously experienced SE. Post DBS EEG at this time demonstrated right frontal interictal epileptiform activity.

Although initially no significant change in seizure rate was apparent, after 12 months of follow-up and while treated with AEDs (levetiracetam at 3,500 mg, clobazam at 20 mg, and valproate at 500 mg daily), VNS and DBS, the patient experienced improvement in seizure control with an 84% decrease in FBTCS to two FBTCS per month, and a 17% decrease in FIAS to 100 FIAS per month. At 18 months of follow-up, this improvement was preserved with two FBTCS and 90 FIAS per month (*figure 1D*). DBS routine check-up, at this time, showed a good battery level of 2.8 V, with impedance levels at normal values for both stimulating electrodes. Two months later, the patient experienced gradual clinical worsening with FBTCS frequency increasing up to one per day, and at 21 months following DBS implantation,



■ **Figure 1.** (A) Ictal EEG showing a left frontal seizure onset with rapid bilateral synchronization. (B) Interictal EEG demonstrating bilateral independent frontal epileptiform activity. (C) Post-implantation MRI showing electrode placement in the anterior thalamic nucleus. (D) Change in frequency of focal impaired awareness seizures (FIAS) and focal to bilateral tonic clonic seizures (FBTCS).

the patient presented to the emergency department with convulsive SE. Diagnostic investigations including laboratory and imaging tests ruled out metabolic, toxic, infectious, or structural triggers for seizure worsening. He was admitted to the neurological ICU, treated with 20 mg IV diazepam and 300 mg lacosamide. Initial medical treatment resulted in termination of convulsive SE, however, the patient still experienced multiple FIAS daily, thus initial medical therapy was followed by an addition of 300 mg lacosamide daily as well as increasing clobazam dosage from 20 to 30 mg daily. Investigation of the DBS demonstrated depletion of the DBS battery. VNS battery and impedance levels were normal. Due to depleted DBS battery level, the patient underwent urgent DBS battery replacement. Following battery replacement, therapeutic benefit was rapidly evident, and seizure frequencies, as recorded during post-operative hospitalization and continued close follow-up, returned to previous baseline rates at 18 months. Following this exacerbation, subsequent follow-up demonstrated no recurrence of seizure worsening.

Discussion

We describe the case of a 21-year-old patient with refractory focal epilepsy who experienced a first SE occurring concomitantly with unexpected DBS battery depletion and subsequent cessation of thalamic stimulation. SE is considered amongst the gravest neurological emergencies, and to the best of our knowledge, this severe complication has not been previously reported in relation to unexpected DBS hardware malfunction.

Previous studies have examined the presence of SE during DBS treatment and the effects on seizure control of DBS withdrawal. In a long-term follow-up study of DBS treatment for epilepsy (SANTE trial), seven cases of SE occurred, however, none were reported to be related to hardware malfunction or battery depletion [3]. Two studies of patients with ANT DBS treatment have reported worsening of seizure control following battery depletion [5, 6]. Notably, in one study, although five of six patients experienced seizure aggravation following battery depletion, subsequent seizure frequency was lower than that of pre-DBS baseline [5]. Reports of DBS of the centromedian thalamic nuclei or the mesial temporal structures have also showed variable changes in seizure control following DBS battery depletion, with several reports of patients experiencing worsening of seizure control [7-9]. SE following cessation of DBS treatment has also been described. In one report, a patient that had undergone successful ANT DBS treatment for super-refractory SE two years prior, chose to explant electrodes and subsequently experienced SE leading to death -in this case, however, the SE was not *de novo* [10]. Likewise, in other cases in which DBS of the centromedian thalamic nucleus was used for treatment for super-refractory SE and febrile infection-related epilepsy syndrome, aggravation of seizure control or recurrent SE secondary to attempted withdrawal of stimulation were described [11, 12].

In patients with movement disorders treated with DBS, battery depletion is a well-known complication and may even cause a life-threatening akinetic hyperpyretic emergency [13]. In the SANTE trial follow-up, serious device-related adverse effects were not uncommon, occurring in 35% of patients, and most frequently included implant site infection and leads off-target, but also extension fracture, neurostimulator migration, and implant site sensory disturbances [3]. Notably, half of the subjects in this study needed battery replacement, after an average of 35 months, yet no battery depletion-related adverse effects were reported.

The battery life of DBS stimulators is affected by several factors, including stimulation intensity, tissue impedance, and battery self-drain and self-discharge [14]. Electric parameters affecting battery longevity include stimulation voltage, pulse width, frequency, and on/off cycling. According to a DBS battery online estimation tool, battery life for our patient (parameters: average amplitude of 6 V, pulse width of 90 microseconds, rate of 145 Hz, impedance of ≈1000 ς) was expected to be nearly five years [15]. The possible causes of early battery depletion in our patient could be due to an error in the parameter setting leading to a difference in cycling or no cycling, another hardware malfunction, or a significant increase in tissue impedance, yet this latter option is unlikely as imaging confirmed accurate and stable electrode positioning.

Little is known about the withdrawal effects of thalamic stimulation, whereas anti-epileptic medication withdrawal is a well-known and common cause of SE [16]. This contrast is possibly due to different mechanisms of action. While AEDs have transient pharmacodynamic effects on specific molecular targets in the nervous system, neurostimulation therapies exert a slower, long-term effect on multiple brain networks that are important for seizure generation [17]. Studies demonstrating long-term cumulative clinical efficacy of DBS treatment have raised the possibility of long-term DBS-related neuroplastic changes, and indeed, there are reports of improved seizure outcome even after DBS implantation [18]. In contrast, in our case, positive clinical neuromodulatory effects accrued over a period of 18 months, whereas, although the exact time of battery depletion was unknown, worse seizure control and SE was evident no more than two months following cessation of thalamic stimulation. Although

SE can occur spontaneously in a patient with refractory focal epilepsy, the temporal relationship with cessation of thalamic stimulation, the beneficial effect of restoring stimulation therapy, the absence of metabolic, infectious or other SE triggers, and the fact that this patient had not previously experienced SE suggest that positive neuromodulatory effects of stimulation on epileptic networks may have been reversed. Furthermore, in our patient, the long-term trend of improvement under DBS treatment was interrupted with a gradual, rather than sudden, worsening in seizure control prior to SE, possibly due to a carry-over effect of DBS treatment.

In conclusion, with the increasing use of DBS treatment in DRE patients, clinicians should keep in mind that in cases of exacerbation of seizure control or life-threatening SE, one must rule out unexpected DBS battery depletion as a possible trigger for worsening. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
None of the authors have any conflicts of interest to disclose.

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TEST YOURSELF

(1) Which of the following is *not* an important factor effecting battery life of a deep brain stimulator?

A. Seizure frequency
B. Self draining
C. Tissue impedance
D. Cycling on/off
E. Stimulation voltage

(2) Which mechanical complications associated with deep brain stimulation have been commonly reported in the SANTE trial long-term follow-up study?

A. Local infection
B. Sensory disturbances
C. Off-target electrode leads
D. Haemorrhagic stroke
E. A+B+C

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.