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Letter to the Editor

Status dystonicus in pantothenate kinase-associated neurodegeneration due to internal pulse generator depletion: Case study and literature review

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Dear Editor

Status dystonicus (SD) is defined as a severe, life-threatening episode of a generalized or focal hyperkinetic movement disorder [1]. Many movement disorders may progress to SD either with or without a specific trigger. Unexpected interruption to deep brain stimulation (DBS) treatment due to battery depletion or other factors is increasingly recognized as a precipitant of SD [2,3] (Table 1). Here, we describe an adolescent female patient with kinase-associated neurodegeneration (PKAN) who was successfully treated with DBS of the subthalamic nuclei (STN) for dystonia until she suddenly deteriorated to SD. It turned out that battery depletion of the DBS internal pulse generator (IPG) was the probable cause of the SD, which resolved after implanting a new battery.

1. Case report

The case involved a 17-year-old patient with PKAN who had received DSB-STN treatment for generalized dystonia and spasticity over the duration of more than five years. At age 11, she initially presented with upper limb spasticity and was diagnosed with isolated dystonia, which was not made by the specialist of the movement disorders. Subsequently, she developed dystonia in head and neck, followed by lower limb dystonia and spasticity, which resulted in substantial functional impairment. At age 12, a comprehensive clinical assessment revealed the presence of generalized dystonia, involuntary movements of head and hands, and deterioration of memory and intelligence. Tests for muscle strength, coordination, and sensitivity were unremarkable. No symptoms of parkinsonism, chorea, or myoclonus were evident. Also, the neuro-ophthalmologic exam, including fundoscopy, was normal. A T2-weighted magnetic resonance imaging (MRI) scan revealed hypointense signals (pathologically, corresponding to abnormal iron deposition) of the bilateral globus pallidus along with central hyperintense signals (due to gliosis, vacuolisation, and increased water content), which represents a hallmark or “eye of the tiger” sign of PKAN (Fig. 1A). Sanger sequencing confirmed the clinically suspected PKAN by detecting the pathogenic mutation known as c.628 2T > G in the *PANK2* gene. Correspondingly, the patient received various treatments proposed for PKAN, including iron-chelation therapy, trihexyphenidyl, haloperidol, clonazepam, and carbamazepine, but none of these treatments sufficiently alleviated her clinical symptoms. Ultimately, she received bilateral implantation of DBS electrodes into the STN (Fig. 1B). Single channel non-rechargeable internal pulse generators (Medtronic, Minneapolis, MN, USA) were implanted subcutaneously in both sides of the infraclavicular area. Overall, she showed an excellent clinical response to the DBS-STN treatment. The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) score was 65/17 (motor/disability) preoperatively and dropped to 22/11 in the next week (see Supplementary Video 1, segment 1-A and B). Importantly, she was able to walk slowly without any aid. The patient's clinical status remained stable for a prolonged period after the DBS-STN surgery.

At age 17, however, after more than five years of continuous DBS-STN treatment, the patient's clinical status suddenly deteriorated. Within two months, she developed progressively severe episodes of generalized dystonia affecting the orofacial region, neck, trunk, and limbs, which made her unable to walk without using a wheelchair. Upon admission to a local hospital, it was found that the battery of the IPG at the left STN was nearly depleted. Three days later, the patient and her parents visited our hospital for battery replacement. At that time, however, she had developed a dystonic storm. She presented with a fever, sweating, and increasingly frequent episodes of dystonia involving neck, trunk, and limbs. Moreover, she suffered from painful muscle spasms and continuous orofacial dystonia, which compromised swallowing function. Laboratory tests confirmed the presence of leukocytosis and elevated serum creatine kinase. She scored 78/120 on the motor part and 26/30 on the disability part of the BFMDRS (see Video, segment 2). Following battery replacement surgery, her DBS-STN treatment was reestablished with the same parameters (left: 6–7- 90us/145 Hz/3. 45 V and right: 2–3- 90us/145 Hz/3. 50 V) that were used before the replacement surgery. The patient's condition did not improve until one week after the replacement operation. At one-month follow-up, however, the BFMDRS score had dropped to 46/17 (motor/disability) (see Video, segment 3). Furthermore, the patient regained the ability to sit independently, even though her sit-to-stand ability did not recover to a past level. No life-threatening complications occurred during her dystonic storm.

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Table 1
Clinical study reports of dystonic storm related to deep brain stimulation[a].

Reference	Number of patients	Diagnosis	Precipitating factor	Treatments	Outcome
Rohani et al. [8]	1	Tardive dystonia	Depletion of the IPG	Sedation(midazolam) and mechanical ventilation	The patient died due to bradyarrhythmia and asystole
Sobstyl et al. [5]	1	DYT1 dystonia	Depletion of the unilateral IPG	Sedation (propofol and fentanyl), mechanical ventilation, bicarbonate infusions, hyperventilation, dopamine infusion, hemodialysis and new IPG battery exchange	Patient's status improved within the next 2 weeks
Cheung et al. [6]	2	DYT1 dystonia	Sudden cessation of stimulation	Sedation and initiation of pallidal stimulation	The patients were recovered after up to 29 days
Bittar et al. [9]	1	Dystonia	Battery failure	New IPG battery exchange	The patient's neurological state improved within hours of reoperation
Nerrant et al. [3]	13	Dystonia	DBS interruption/ system dysfunction	Management in ICU and initiation of DBS	Most patients' status improved
Li et al	1	PKAN	Depletion of the left-sided IPG	New IPG battery exchange	Patient's status improved within the next week

PKAN: Pantothenate Kinase-Associated Neurodegeneration; ICU, intensive care unit.
[a] IPG: internal pulse generator.

2. Discussion

Our patient with PKAN developed a dystonic storm after her DBS-STN treatment was unexpectedly interrupted due to battery depletion of the implanted IPG. We resolved the SD by restoring the IPG battery. Furthermore, the clinical benefits of DBS-STN in relation to the patient's dystonia and spasticity steadily re-emerged after battery replacement. These observations may indicate that the stabilization of the abnormal motor system activations underlying her SD was a necessary first step in regaining the therapeutic benefits of DBS-STN [4]. The present finding that SD emerged after IPG battery depletion, along with its reversal after battery replacement, substantiates previous reports of DBS-related SD in PKAN and other disorders [3,5,6] (Table 1).

This case report serves to underline that the integrity of the IPG requires careful and persistent consideration in DBS treatment of patients with dystonia. It is noteworthy that, in our patient, the IPG targeting the left side of the STN was compromised, while the battery of the IPG targeting the opposite side of the STN still functioned normally. In any case, it was difficult to estimate the battery duration of the IPG in advance. The battery life is a function of not only the life cycle of the IPG and the total electrical energy consumed, but also the stimulation parameters used [7], which are typically not fixed but variable, being adjusted over the treatment course according to the patient's symptom severity.

The use of rechargeable batteries may be preferred over non-rechargeable devices to monitor the IPG functional status. Rechargeable batteries may also be particularly useful when treating pediatric patients. However, it should be realized that periodic battery recharging could become in itself a trigger for SD. Accordingly, for DBS treatment of pediatric patients, non-rechargeable batteries should be the first choice. Moreover, regardless of the battery type used, it remains crucial to schedule timely follow-up evaluations of the status of the IPG battery. In fact, the periodical assessment of the patient, DBS system, and DBS settings is a basic requirement that must be met in DBS treatment in general and, specifically, in DBS treatment of dystonia related to PKAN. The latter remains a challenging clinical condition to treat and, despite DBS therapy, still foreshadows progressive brain and clinical deterioration for too many patients.

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Informed consent

The patient and her legal guardian gave their written informed consent before DBS treatment and study participation.

Financial disclosure

None.

Relevant conflicts of interest

The authors report no conflict of interest.

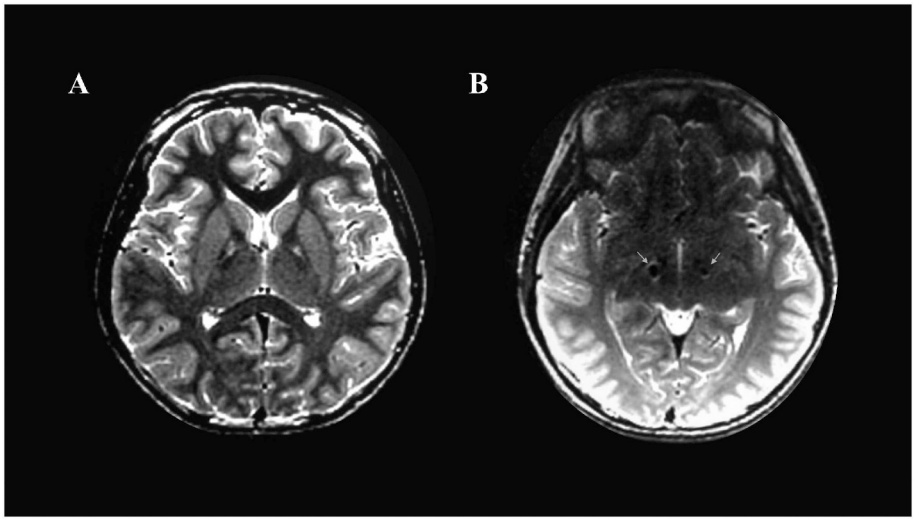

Fig. 1. Patient's magnetic resonance image (T2-weighted sequence) at age 17. [A] Central hyperintense signals and hypointense signals of globus pallidus, known as the “eye of the tiger” sign of PKAN. [B] Electrode positions (orange arrows) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

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Hongxia Li[a,1], Chencheng Zhang[b,1], Yixin Pan[b], Bomin Sun[b], Dianyou Li[b,*,2], Yiwen Wu[a,c,**,3]

[a] *Department of Neurology, Institute of Neurology, RuiJin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China*
[b] *Department of Functional Neurosurgery, RuiJin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China*
[c] *Laboratory of Neurodegenerative Diseases & Key Laboratory of Stem Cell Biology, Institute of Health Science, Shanghai Institutes for Biological Sciences (SIBS), Chinese Academy of Sciences (CAS), Shanghai Jiao Tong University School of Medicine, Shanghai, China*
E-mail addresses: ldy11483@rjh.com.cn (D. Li), wyw11380@rjh.com.cn (Y. Wu).

* Corresponding author at: Department of Functional Neurosurgery, RuiJin Hospital, Shanghai Jiao Tong University School of Medicine, 197 Ruijin Er Road, Shanghai, China.
** Corresponding author at: Department of Neurology, Institute of Neurology, Shanghai Jiao Tong University School of Medicine, Ruijin Hospital, 197 Ruijin Er Road, Shanghai 200025, China.
[1] These authors contributed equally to this work.
[2] Dr. Dianyou Li is co-corresponding author.
[3] Dr. Yiwen Wu is corresponding author.