Deep brain stimulation for medically refractory status dystonicus in *UBA5*-related disorder

Bilateral globus pallidus internus deep brain stimulation (GPi-DBS) is increasingly used in the treatment of medically refractory dystonia in children, including for status dystonicus. GPi-DBS has proven effective for DYT-*TOR1A*, DYT-*KMT2B*, DYT/CHOR-*GNAO1*, DYT-*THAP1*, DYT-*SGCE* and MxMD-*ADCY5*,[1] although the full spectrum of monogenic hyperkinetic disorders with a favorable response to DBS remains to be established. Here, we report the case of a 7-year-old male with *UBA5*-related epilepsy-dyskinesia syndrome (NM_024818.6: c.1111G > A, (p.Ala371Thr); c.110C > T (p.Thr37Ile)) who presented with medically refractory status dystonicus and showed a rapid and sustained response to GPi-DBS.

In line with the phenotypic spectrum of *UBA5*-related disorder,[2-4] the patient presented with a developmental epileptic encephalopathy with intellectual disability (non-verbal), axial hypotonia, spastic tetraparesis (GMFCS 5), and mild generalized dystonia, as well as dysphagia with G-tube dependence. Seizures were controlled on valproic acid and his dystonia was managed with trihexyphenidyl, with no prior history of status dystonicus. In the setting of weaning trihexyphenidyl for anticholinergic side-effects, the patient presented with a 4-week prodrome of increased dyskinesia (mostly chorea of the upper limbs, Supplementary Video S1), followed by rapid deterioration to status dystonicus with prominent generalized dystonic posturing, inability to tolerate a seated position, and fragmented sleep (dystonia severity scale [DSS] = 3),[5] refractory to treatment with increasing doses of clonazepam (Fig. 1). Initial examination showed generalized dystonic posturing, associated with tachycardia, diaphoresis, and distress (Supplementary Video S2) (DSS = 4), and elevated serum creatine kinase (CK) levels to 2436 U/L. Treatment with increasing doses of clonidine and diazepam was initiated. On day 5 of the admission, the patient's dystonia worsened to a DSS of 5 with respiratory distress and increased CK-emia (5446 U/L), necessitating escalation to treatment with intravenous infusions of dexmedetomidine and subsequently midazolam (Supplementary Video S3). On day 7, the patient was intubated and sedatives had to be escalated rapidly. Paralysis with vecuronium was initiated for 3 days because of refractory dystonic posturing and persistent CK-emia. Dystonia-targeted therapy was intensified with increasing doses of trihexyphenidyl (eventually limited by urinary retention), diazepam, tetrabenazine, clonidine, and gabapentin (Fig. 1). Despite aggressive medical therapy (dexmedetomidine 2mcg/kg/h, midazolam 0.4 mg/kg/h in addition to bolus doses), the dystonia remained refractory. Brain magnetic resonance imaging showed cerebral and cerebellar volume reduction consistent with *UBA5*-related disorder. Continuous video-electroencephalography identified no seizures. GPi-DBS (Medtronic Percept PC) was placed on day 29 and stimulation was initiated the next day. Parameters were gradually increased. Under DBS (double unipolar configuration, left GPi: contact 0: 2.2 mA, 1a: 0.8 mA, 1b: 0.8 mA, 1c: 0.8 mA; right GPi: contact 8: 2.2 mA, 9a: 0.8 mA, 9b: 0.8 mA, 9c: 0.8 mA; pulse width of 60 μs, frequency of 145 Hz), rapid and sustained control of the patient's dystonia was achieved, allowing de-escalation of treatment with stepwise discontinuation of intravenous infusions, tetrabenazine, and a significant reduction in medication doses. At the time of discharge, the patient had no significant dystonia and only mild dyskinesia (Supplementary Video S4) on a stable medication regimen and DBS settings (left GPi: contact 0: 2.2 mA, 1a: 0.6 mA, 1b: 0.6 mA, 1c: 0.6 mA; right GPi: contact 8: 2.2 mA, 9a: 0.7 mA, 9b: 0.7 mA, 9c: 0.7 mA; pulse width of 60 μs, frequency 135 Hz). He continued to gradually improve, was able to participate in physical and occupational therapy, tolerated seated positions, recovered sleep, and eventually fully returned to his previous baseline (DSS = 1) (Supplementary Video S5).

Key Words: Dystonia, status dystonicus, deep brain stimulation, UBA5, epilepsy-dyskinesia syndrome

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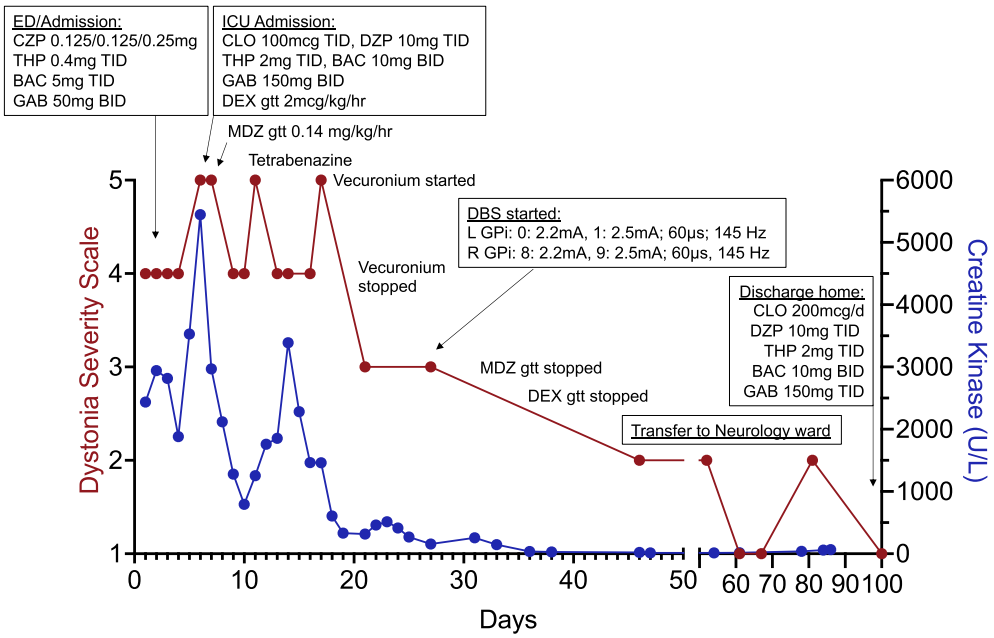

FIG. 1. Clinical course shown as a timeline of medications, interventions, and level of care relative to dystonia severity scale (DSS) scores (left y-axis) and serum creatine kinase levels (right y-axis). The patient's weight is 22.1 kg. Abbreviations: BAC, baclofen; CLO, clonidine; CZP, clonazepam; DBS, deep brain stimulation; DEX, dexmedetomidine; GAB, gabapentin; GPi, globus pallidus internus; L, left; MDZ, midazolam; R, right; THP, trihexyphenidyl. [Color figure can be viewed at wileyonlinelibrary.com]

This case illustrates the challenges of managing status dystonicus in rare movement disorders and provides first evidence that status dystonicus in *UBA5*-related disorder may be responsive to GPi-DBS. Our report has limitations, including the relatively short follow up (4 months after DBS implantation) and unknown natural history of this ultra-rare disease. Although there is no general agreement on the optimal timing of DBS placement in the treatment of pediatric status dystonicus, our experience calls for early genetic testing and early consideration of DBS in the management of status dystonicus, particularly in the setting of monogenic hyperkinetic movement disorders.

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Data Availability Statement

The full data set is available from the corresponding author upon request.

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Supporting Data

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

Z.Z.: Acquisition of data, clinical examination, analysis and interpretation of data, drafting and revision of manuscript for critical intellectual content.

N.S.: Clinical examination, analysis and interpretation of data, and revision of manuscript for critical intellectual content.

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