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Deep Brain Stimulation For Medically-Refractory Status Dystonicus in *UBA5*-related Disorder

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Letter (New Observation):

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], though 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, Video 1), 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) [5] =3), refractory to treatment with increasing doses of clonazepam (Figure 1). Initial examination showed generalized dystonic posturing, associated with tachycardia, diaphoresis, and distress (Video 2, DSS=4), and elevated serum creatine kinase levels to 2436U/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 (5446U/L), necessitating escalation to treatment with intravenous infusions of dexmedetomidine and subsequently midazolam (Video 3). On day 7, the patient was intubated, and sedatives had to be escalated rapidly. Paralysis with vecuronium was initiated for 3 days due to 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 (Figure 1). Despite aggressive medical therapy (dexmedetomidine 2mcg/kg/hr, midazolam 0.4mg/kg/hr in addition to bolus doses), the dystonia remained refractory. Brain MR imaging showed cerebral and cerebellar volume reduction consistent with *UBA5*-related disorder. Continuous video-EEG 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: 2.2mA, 1a: 0.8mA, 1b: 0.8mA, 1c: 0.8mA; right GPi: contact 8: 2.2mA, 9a: 0.8mA, 9b: 0.8mA, 9c: 0.8mA; pulse width of 60μs, frequency of 145Hz), 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 (Video 4) on a stable medication regimen and DBS settings (left GPi: contact 0: 2.2mA, 1a: 0.6mA, 1b: 0.6mA, 1c: 0.6mA; right GPi: contact 8: 2.2mA, 9a: 0.7mA, 9b: 0.7mA, 9c: 0.7mA; pulse width of 60μs, frequency 135Hz). 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, Video 5).

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement:

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

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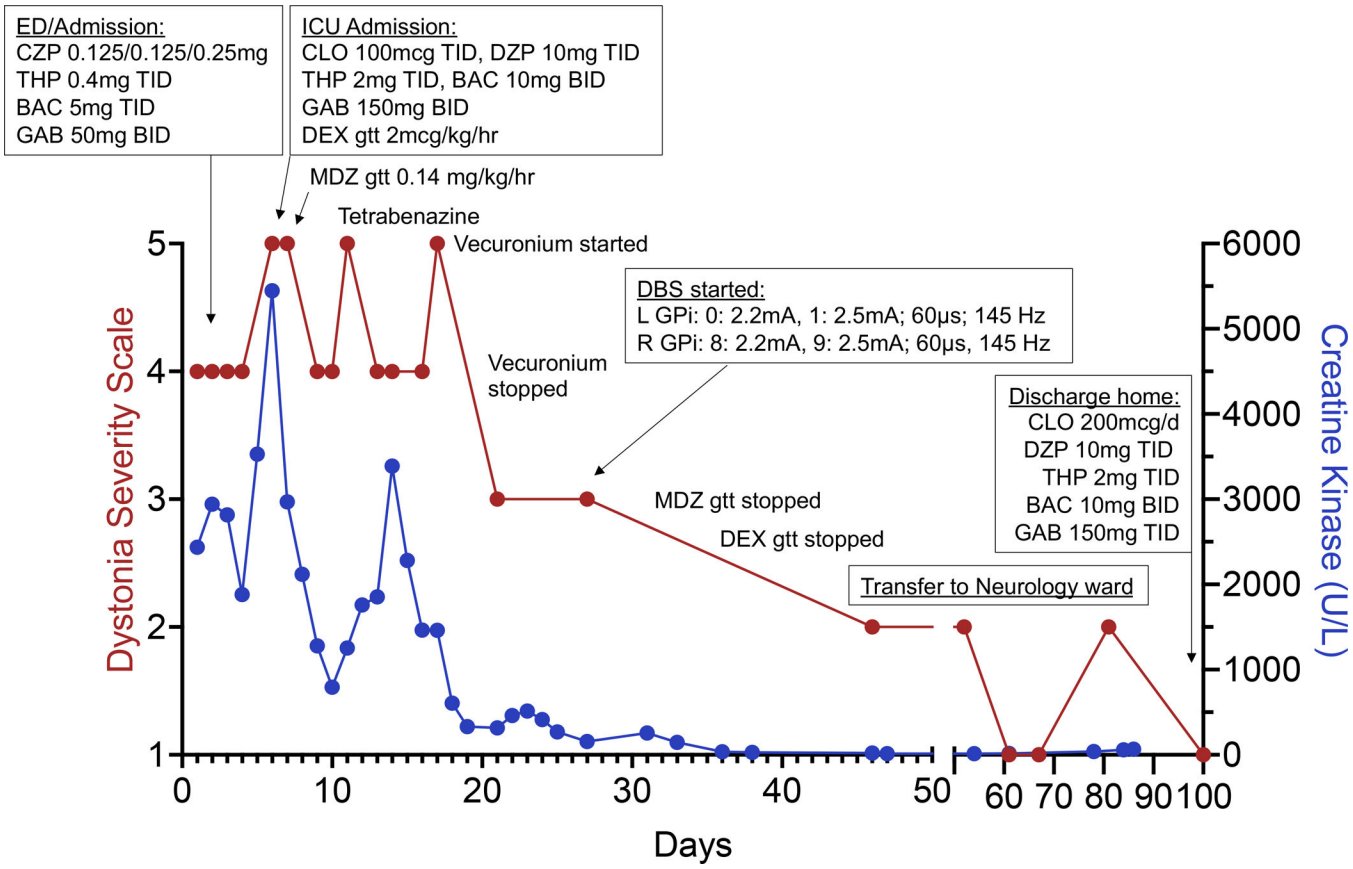

Figure 1.

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 22.1kg. 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).