Movement Disorders
CLINICAL PRACTICE
CASE REPORT

Response to GPi-DBS in a Case of *EIF2AK2*-Associated Early-Onset Generalized Dystonia

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The underlying cellular mechanisms implicated in the monogenic dystonias remain incompletely elucidated. Dysfunction of eukaryotic translation initiation factor, subunit 2 alpha (eIF2α) has been implicated in the pathophysiology of some monogenic dystonias.[1,2] Recently, *eukaryotic translation initiation factor 2 alpha kinase 2* (*EIF2AK2*) was identified as a causative gene for early-onset primary generalized dystonia.[3] We report a case of progressive *EIF2AK2*-associated generalized dystonia with onset of symptoms at 12-months of age which partially responded to bilateral deep brain stimulation (DBS) of the globus pallidus interna (GPi).

Case Report

The patient was born following an uncomplicated vaginal delivery and met early developmental milestones. At 12 months, he demonstrated toe walking but was able to walk flat-footed when instructed. Throughout early childhood, he demonstrated fine motor skill impairment, including difficulty tying shoes, buttoning clothes, cutting food, and holding/using a writing or eating utensil. Despite these motor difficulties, he actively participated in sports including basketball without major limitations save for running plantarflexed on his toes. He performed well academically without cognitive impairment and displayed no personality or mood disturbances.

At 13 years and 3 months of age, he developed relatively rapid-onset (over two months) worsening toe-walking, predominantly affecting his right more than left leg and right Achilles tendon tightness. He exhibited increasing difficulty with the toe-walking, developed posturing of his left arm while walking and playing basketball, and worsened right hand fine motor control, impacting handwriting. There were no preceding illnesses, fevers, or medication exposures associated with this abrupt deterioration.

The patient was enrolled in the Multicenter Pediatric Deep Brain Stimulation Registry (DBS-R) (ClinicalTrials.gov ID NCT06585618) and written consent was obtained (IRB-P00047069). His clinical examination at the age of 13 years and 4 months was notable for normal mental status, cranial nerves, strength, and sensory examination. His voice was slightly strained. He had plantarflexion contracture of the right Achilles that could not be overcome with passive or active movement. He exhibited intermittent left dystonic shoulder elevation and arm adduction, flexion at the elbow, and external rotation that worsened with voluntary movement. With the arms outstretched, the left arm exhibited dystonic postures with excessive external rotation and extension of the wrist. Fine motor movements of the hand were impaired; he could not dorsiflex the right foot due to Achilles contracture or the left due to excessive plantarflexion at rest. Gait was notable for excessive right foot plantar flexion and dystonic inversion that improved with walking backwards. In addition to dystonic posturing of the left arm while walking, right arm posturing manifested while walking characterized as flexion at the wrist and of the digits (Video 1).

Work-up included ceruloplasmin 17.2 mg/dl, negative slit lamp examination by ophthalmology, and normal MRI brain. A dystonia multigene panel by Invitae was negative. Trio exome sequencing revealed a de novo heterozygous missense variant in *EIF2AK2* NM_001135651.3:c.31A>T; p.(Met11Leu). The patient's dystonia exhibited minimal response to sequential trials of trihexyphenidyl, baclofen, clonazepam, and levodopa. Botulinum toxin injections in the arms and legs provided partial relief.

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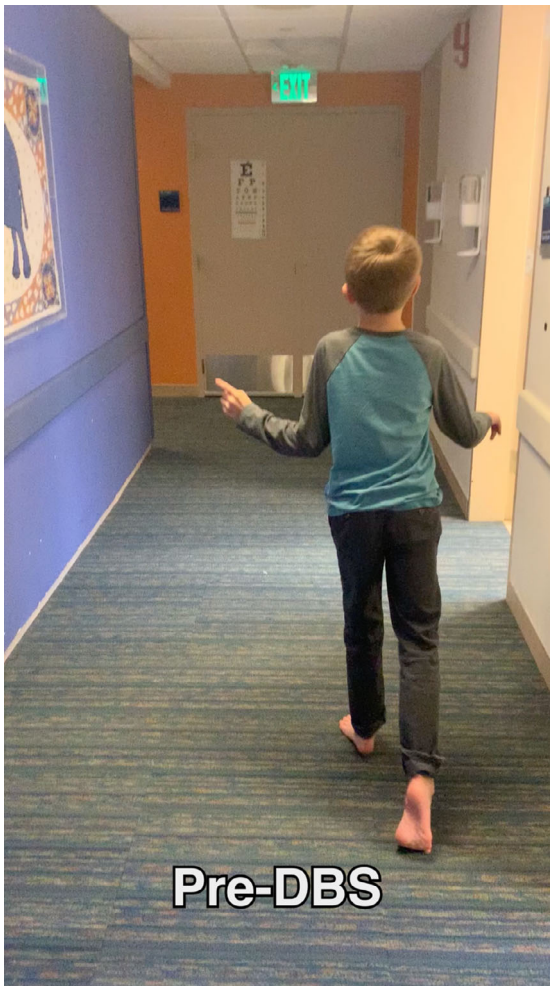
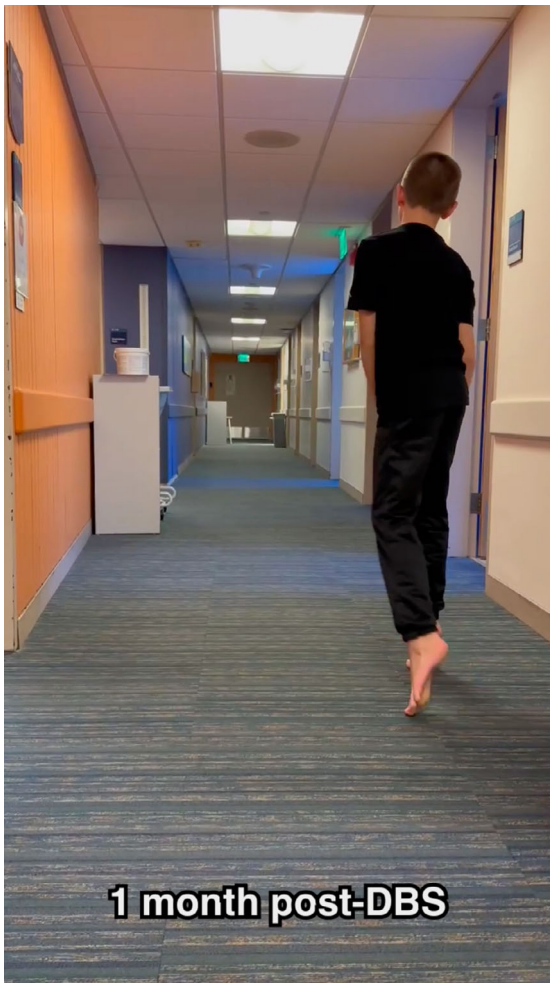


Video 1. Initial patient examination prior to DBS demonstrating generalized dystonia characterized by dystonic posturing of the left arm and excessive right foot plantar flexion and dystonic inversion. In addition to dystonic posturing of the left arm while walking, right arm posturing manifested while walking characterized as flexion at the wrist and of the digits.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.70395



Video 2. Patient examination 1 month after bilateral GPi DBS implantation showing improvement of generalized dystonia, most notably marked reduction in dystonic posturing of his upper limbs while walking. Examination occurred right after stimulation was turned on.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.70395

Doses of all oral medications and injections were adequate enough to evaluate for a response. The patient's dystonia progressed slowly leading to further gait impairment with worsening action-induced upper limb dystonia and fine motor tasks. At age 14 years and 7 months (16 months after symptom worsening), he underwent bilateral GPi DBS implantation with Medtronic Percept™ PC directional leads with BrainSense™ technology. The device was activated 1 month following implantation (Video 2) at which time early clinical improvements were observed, likely attributable to a lesional effect. Fahn-Marsden Dystonia Rating Scale: Movement Scale improved from 47 prior to DBS to 15, 1 year after programming, a response that remained largely stable at 13 months post implantation (Video 3) with the following settings: left GPi: Case +; contacts 1- and 2-; 1.5, 2.0 mA/60 microseconds/165 Hz; right GPi: Case +; contacts 9- and 10-; 1.3, 1.7 mA/90 microseconds/165 Hz. For each side, the whole ring was activated. Specifically, after DBS implantation there was improvement in adductor laryngeal dystonia, bilateral upper limb dystonia with resolution of dystonia at rest and most actions, and bilateral lower limb dystonia with resolution of dystonia at rest. He continued to have more lower limb dystonia when walking and intermittent upper limb dystonia with some actions.

Discussion

Heterozygous variants in *EIF2AK2* have been associated with early-onset isolated generalized dystonia presenting in toddler to preschool-aged children[3,4] in addition to neurodevelopmental

Video 3. Patient examination six months and 13 months after DBS implantation showing sustained partial response to bilateral GPi DBS therapy with an improved ability to maintain plantigrade foot posture during ambulation.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.70395

and complex movement disorder phenotypes.[5,6] Our case contributes to the growing literature on *EIF2AK2*-associated dystonia, reaffirming its presentation as an early-onset dystonia. Additionally, we highlight that *EIF2AK2*-associated dystonia may demonstrate partially responsiveness to GPi DBS, as noted in one other case report of isolated adolescent-onset dystonia.[7] Magrinelli et al reported DBS therapy improved dystonia involving speech, upper limbs, and trunk with less effect on dystonic tremor and lower limb dystonia.[7] Conversely, DBS improved lower limb dystonia in our patient's case.

Given the rarity of conditions such as EIF2AK2-associated dystonia, collaboration among clinicians is critical to refining patient selection for DBS and optimizing programming strategies. Platforms like DBSMatchMaker (www.dbsmatchmaker.com), a web-based tool designed to connect clinicians treating rare movement disorder cases, provide a valuable means for physicians worldwide to share insights and improve patient outcomes.[8]

Overall, in individuals with isolated early-onset and progressive dystonia, exome sequencing with attention to variants in *EIF2AK2* should be considered. Further studies with larger cohorts are necessary to 1) better characterize the clinical spectrum of *EIF2AK2*-associated dystonia and 2) define the natural history of this rare disease, and 3) evaluate the full scope of DBS responsiveness in this population.

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.

S.R.: 1A, 1B, 1C, 3A, 3B
K.Y.: 1A, 1B, 1C, 3A, 3B
D.E.-F.: 1A, 1B, 1C, 3B

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Ethical Compliance Statement: Informed patient consent was obtained. IRB approval was obtained through Boston Children's Hospital, Harvard Medical School (IRB-P00047069). We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. ■

References

1. Rittiner JE, Caffall ZF, Hernández-Martinez R, et al. Functional genomic analyses of mendelian and sporadic disease identify impaired eIF2α signaling as a generalizable mechanism for dystonia. *Neuron* 2016;92(6):1238–1251.
2. Beauvais G, Rodriguez-Losada N, Ying L, et al. Exploring the interaction between eIF2α dysregulation, acute endoplasmic reticulum stress and DYT1 dystonia in the mammalian brain. *Neuroscience* 2018;371:455–468.
3. Kuipers DJS, Mandemakers W, Lu CS, et al. EIF2AK2 missense variants associated with early onset generalized dystonia. *Ann Neurol* 2021;89(3):485–497.
4. Waller SE, Morales-Briceño H, Williams L, et al. Possible EIF2AK2-associated stress-related neurological decompensation with combined dystonia and striatal lesions. *Mov Disord Clin Pract* 2021;9(2):240–244.
5. Mao D, Reuter CM, Ruzhnikov MRZ, et al. De novo EIF2AK1 and EIF2AK2 variants are associated with developmental delay, leukoencephalopathy, and neurologic decompensation. *Am J Hum Genet* 2020;106(4):570–583.
6. Calame DG, Hainlen M, Takacs D, Ferrante L, Pence K, Emrick LT, Chao HT. EIF2AK2-related neurodevelopmental disorder with leukoencephalopathy, developmental delay, and episodic neurologic regression mimics Pelizaeus-Merzbacher disease. *Neurol Genet* 2021;7(1):e539.
7. Magrinelli F, Moualek D, Tazir M, et al. Heterozygous EIF2AK2 variant causes adolescence-onset generalized dystonia partially responsive to DBS. *Mov Disord Clin Pract* 2021;9(2):268–271.
8. Zubair U, Agianda HAP, Yang K, et al. DBSMatchMaker: connecting clinicians globally for deep brain stimulation in rare diseases. *Mov Disord* 2025;40:765–767.