Movement Disorders
CLINICAL PRACTICE
LETTERS: GENOTYPE AND PHENOTYPE

Good Response to Deep Brain Stimulation in Two Forms of Inherited Chorea Related to GNAO1 and Neuroacanthocystosis with Illustrative Videos

Erin A. Yamamoto, MD,[1] Megan Berry, DO,[2] William Harris, MD,[3] Maryam N. Shahin, MD,[1] Jenny L. Wilson, MD,[4] Delaram Safarpour, MD,[5] and Ahmed M. Raslan, MD,[1,]*

Chorea is a hyperkinetic movement disorder characterized by involuntary brief, random, and irregular muscle contractions conveying a feeling of restlessness.[1] Inherited choreas constitute a significant portion of choreas, including neuroacanthocytosis (NA), *GNAO1*-associated movement disorder (GNAO1), Huntington's disease, dentatorubral-pallidoluysian atrophy, Wilson's disease, familial paroxysmal kinesigenic choreoathetosis, and intracerebral calcifications. We report two cases of inherited chorea due to NA and GNAO1 treated by deep brain stimulation (DBS), with marked improvement. Currently, chorea is not an approved indication for DBS; however, reports of off-label globus pallidus interna (GPi) DBS for genetic choreas demonstrate generally satisfactory outcomes. Electronic medical records were reviewed and medical histories were documented for each case report. Written informed consent was obtained.

A 9-year-old female (Case 1) diagnosed with cerebral palsy developed episodes of severe, generalized chorea, each lasting several weeks under sedation in a pediatric intensive care unit. All pharmacologic treatments for chorea had failed and high doses of diazepam, clonidine and narcotics could not abort the episodes. Complications included developmental regression, fractures, rhabdomyolysis, skin breakdown, and weight loss. Genetic testing revealed a *GNAO1* variant (c.611G > T;p.Gly204Asp) which was previously reported in another child with GNAO1.[2]

At age 17, she was admitted for another refractory chorea episode (Video 1). After interdisciplinary team discussions the patient's parents decided to proceed with DBS (over pallidotomy due to bilateral symptoms). Bilateral GPI DBS electrode (Medtronic model 3387, Minneapolis, MN, USA) trajectories were planned using a pre-operative high-resolution MRI merged with an intraoperative CT scan with fiducials. Leads were connected to an implantable neurostimulator Activa™ RC (Medtronic) pulse generator in a single stage procedure under general anesthesia. A second intraoperative CT scan confirmed lead placement. The DBS was activated immediately to bipolar mode, and adjusted post-operatively to address gagging/discomfort and movement control (using monopolar configuration and second distal contact as cathode, pulse width of 60 ms, frequency of 120 Hz and amplitude of 1.3 mA bilaterally). Limb dyskinesias were controlled almost immediately (Video 2), orolingual dyskinesias ceased after a few weeks. She was discharged to home on post-operative day (POD) 13.

At 6 weeks, the generator was explanted and antibiotics initiated due to an infection. Severe chorea returned and persisted until a generator was re-implanted on the contralateral side. Eight months after re-implantation, in the setting of malnutrition, DBS wires eroded through her scalp. Her parents contemplated DBS explant with antibiotics and future reimplantation, but given her improved quality of life with stimulation, they opted for hospice care with the exposed DBS system. The patient died 1 year after initial DBS placement.

A 41-year-old male (Case 2) with a history of attention deficit hyperactivity disorder, seizure, and anxiety presented with progressive abnormal movements including truncal spasms, choreiform and dystonic movements. He developed tics, obsessive–compulsive and severe self-harming behaviors. Two heterozygous *VPS13A* variants were identified, confirming a diagnosis of NA. Severe orolingual dyskinesias (Video 3) impaired eating, resulting in significant weight loss and a need for gastrostomy tube

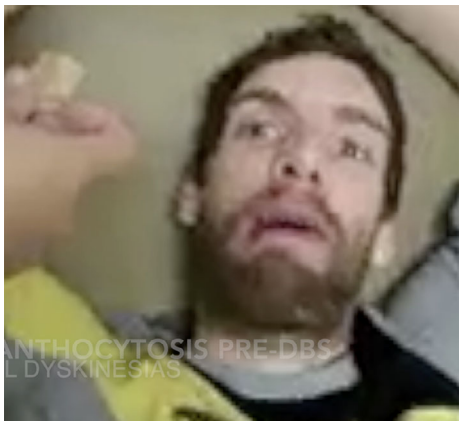
[1]*Neurological Surgery, Oregon Health & Sciences University, Portland, Oregon, USA;* [2]*Pediatrics, University of Wisconsin, Madison, Wisconsin, USA;* [3]*Department of Neurosurgery, University of Colorado School of Medicine, Aurora, Colorado, USA;* [4]*Pediatric Neurology, Oregon Health & Sciences University, Portland, Oregon, USA;* [5]*Neurology, Oregon Health & Sciences University, Portland, Oregon, USA*

***Correspondence to:** Dr. Ahmed M. Raslan, Department of Neurological Surgery, Oregon Health & Sciences University, Mail Code CH8N, 3303 South Bond Ave, Portland, OR, 97239, USA; E-mail: raslana@ohsu.edu
Keywords: deep brain stimulation, chorea, inherited movement disorder, globus pallidus interna.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 2 September 2021; revised 10 November 2021; accepted 12 November 2021.
Published online 21 December 2021 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.13383

LETTERS: GENOTYPE AND PHENOTYPE

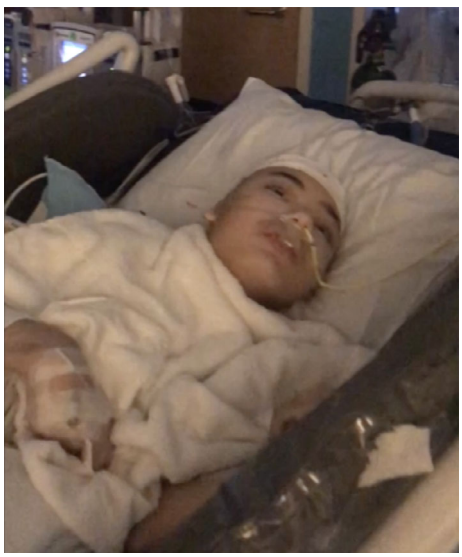
Video 1. Seventeen-year-old female (Case 1) who is diagnosed with GNAO1-associated movement disorder is debilitated by another chorea storm. She is shown here 4 days prior to primary placement of bilateral DBS targeting bilateral GPi.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13383

placement, which was not placed given the high likelihood that his movements would dislodge the tube. He was considering hospice care.



Video 3. Patient with neuroacanthocytosis (Case 2) is shown eating a small piece of bread. His oral intake is hampered by severe orolingual dyskinesias which has resulted in significant weight loss. Caretaker assistance is required to help bring food to his mouth. He lays down to eat because food falls out of his mouth if he eats sitting upright.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13383

Bilateral GPi DBS was offered as a last effort given his poor response to treatment. DBS leads (Boston Scientific 2202) and generator placement were performed using the same techniques as described in Case 1. On POD 3, the DBS system was activated



Video 2. Patient (Case 1) with GNAO1-associated movement disorder following bilateral GPi DBS placement. Here shown on post-operative day 2 off of sedation with immediate improvement in control of limb dyskinesias.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13383

Video 4. Patient with neuroacanthocytosis (Case 2) within the first week following primary placement of bilateral GPi DBS. He is able to brush his own teeth, demonstrating immediate significant improvement in motor control.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13383

Video 5. Patient with neuroacanthocytosis (Case 2) shown 6-months following DBS implantation. He is walking independently and confidently down the hall. At this follow-up, the patient reports that he is able to write, feed himself, and has regained his weight.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13383

using double monopolar setting and ring stimulation, and the second and third distal contacts as cathode with a frequency of 104 Hz bilaterally and pulse width of 60 microseconds (right) and 90 microseconds (left), amplitude of 3.6 mA (right) and 4.0 mA (left). The patient noticed immediate improvement in swallowing and regained the ability to brush his teeth (Video 4). He discharged on POD 6 to a skilled nursing facility. By 4 months, he was feeding himself and gained 26 kg, and at 6 months he was writing and ambulating independently (75% reduction in Unified Huntington's Disease Rating Scale; Video 5).

Mortality is the natural history in end-stage NA and GNAO1. Although DBS does not alter this disease course, both patients presented above experienced dramatic improvement in chorea. Case 2 experienced significant control of motor symptoms, deferred hospice care, and is ambulating independently. The family in Case 1 reported that the patient had become interactive with DBS, adding a few quality months prior to her passing. Although complications developed and she ultimately died, it is possible that she may have clinically decompensated to require hospice care sooner without the palliation of her movements by DBS.

Patients with genetic choreas represent a small, underrepresented population who may benefit from DBS. Evaluation by an interdisciplinary team and careful risk–benefit assessment is suggested. International registries focused on the use of DBS for these rare patient populations are essential to quantify DBS efficacy and complications, and identify which patients might benefit from earlier intervention.

Acknowledgment

The authors thank Dr. Shirley McCartney for their editorial support during preparation of this manuscript. The authors acknowledge and thank patients and their families for sharing their stories and clinical videos.

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.

E.A.Y.: 1A, 1B, 1C, 3A
M.B.: 1A, 1C, 2A
W.H.: 1C
M.N.S.: 1C
J.L.W.: 1A, 1B, 3B
D.S.: 1A, 1B, 3B
A.M.R.: 1A, 1B, 3B

Disclosures

Ethical Compliance Statement: Institutional Review Board approval is not requited for publication of less than three cases. The work was performed in accordance with ethical clinical standards. Written informed consent for publication of the clinical details, clinical images and video their case was obtained from patients. 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.

Funding Sources and Conflicts of Interest: No specific funding was received for this work. The authors have no conflicts of interest to declare.

Financial Disclosures for the Previous 12 Months: The authors have no conflicts of interest to declare. ■

References

1. Cardoso F, Seppi K, Mair KJ, Wenning GK, Poewe W. Seminar on choreas. *Lancet Neurol* 2006;5(7):589–602. https://doi.org/10.1016/s1474-4422(06)70494-x.
2. Koy A, Cirak S, Gonzalez V, et al. Deep brain stimulation is effective in pediatric patients with GNAO1 associated severe hyperkinesia. *J Neurol Sci* 2018;391:31–39. https://doi.org/10.1016/j.jns.2018.05.018.