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Case Report

Efficacy of Deep Brain Stimulation in a Patient with Genetically Confirmed Chorea-Acanthocytosis

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Keywords
Deep brain stimulation · Chorea-acanthocytosis · Globus pallidus

Abstract
Chorea-acanthocytosis (ChAc) is a rare autosomal recessive neurodegenerative disease due to mutation of the VPS13A gene encoding the protein chorein. ChAc is a slowly progressive disorder that typically presents in early adulthood, and whose clinical features include chorea and dystonia with involuntary lip, cheek, and tongue biting. Some patients also have seizures. Treatment for ChAc is symptomatic. A small number of ChAc patients have been treated with bilateral deep brain stimulation (DBS) of the globus pallidus interna (GPi), and we now present an additional case. Patient chart, functional measures, and laboratory findings were reviewed from the time of ChAc diagnosis until 6 months after DBS surgery. Here, we present a case of ChAc in a 31-year-old male positive for VPS13A gene mutations who presented with chorea, tongue biting, dysarthria, weight loss, and mild cognitive dysfunction. DBS using monopolar stimulation with placement slightly lateral to the GPi was associated with significant improvement in chorea and dysarthria. This case adds to the current state of knowledge regarding the

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efficacy and safety of bilateral GPi-DBS for symptomatic control of drug-resistant hyperkinetic movements seen in ChAc. Controlled trials are needed to better assess the impact and ideal target of DBS in ChAc.

Background

Chorea-acanthocytosis (ChAc) is a rare autosomal recessive neurodegenerative disease caused by mutation of the VPS13A gene, which encodes the chorein protein. A slowly progressive hyperkinetic movement disorder, ChAc typically presents in early adulthood with chorea, dystonia, and self-mutilation due to involuntary biting of the cheek, tongue, and lips. Patients may also exhibit seizures, myopathy, peripheral neuropathy, and neuropsychiatric symptoms [1]. Pathological markers include acanthocytosis, defined as erythrocytes that exhibit a specific spiny morphology, and striatal degeneration with a proclivity for the head of the caudate nucleus [2].

The mainstay of therapy for ChAc is symptomatic [3]. The relative paucity of effective medical treatments has led to the exploration of neurosurgical interventions such as lesional approaches [4] and deep brain stimulation (DBS) of the globus pallidus interna (GPi) [5]. A recent cross-sectional study of ChAc patients has suggested that bilateral GPi DBS is effective in alleviating chorea [6]. We now present a patient with genetically confirmed ChAc who responded well to pallidal DBS.

Case Presentation

The patient is a 31-year-old right-handed man whose initial symptoms began at the age of 22 with involuntary tongue protrusion, dysphagia, and tongue biting. He later developed mild dysarthria and chorea in the arms and legs, and basic workup revealed elevated muscle creatine kinase at 10,500 IU/L (normal range: 47–322). There was significant unintentional weight loss (~10 kg), and his symptoms progressed to the extent that he had to wear mouthguards continuously to mitigate persistent oral self-mutilation. He was treated with clonazepam, amantadine, tetrabenazine, and deutetrabenazine with only mild improvement. Eventually, he stopped working as a high school teacher due to increasing frequency of involuntary movements, in addition to worsening cognitive issues. There is no consanguinity in the family.

Neurological examination prior to DBS surgery revealed orolingual hyperkinesia with motor impersistence on tongue protrusion, dysarthria, moderate truncal and appendicular chorea, gait instability, hyporeflexia, and bradykinesia. Unified Huntington's Disease Rating Scale chorea sub-score (UHDRS-c) was 13 (maximum 28), and neuropsychological testing was notable for mild attentional difficulties. Brain MRI with and without contrast revealed no significant abnormalities (caudate nucleus volume was normal bilaterally), and acanthocytes were detected on peripheral blood smear. Whole exome sequencing (GeneDx, MD, USA) revealed two heterozygous, likely pathogenic mutations (c.4856 + 1G>A, splice mutation;

c9431_9432delAG, 2-bp deletion) in the VPS13A gene, confirming the diagnosis of autosomal recessive ChAc.

In consultation with the multidisciplinary DBS team at our institution, bilateral GPi DBS was offered for symptomatic treatment of his refractory chorea and dyskinesia. Informed consent was obtained, and the patient understood that DBS would not alter the progressive course of the illness. Deep brain stimulating leads (Model 3387; Medtronic Inc., MN, USA) were stereotactically implanted under general anesthesia within the GPi bilaterally employing a frame-based, MRI-guided technique. Placement within the GPi was confirmed via intraoperative CT and postoperative MRI (Fig. 1). One week after electrode implantation, a dual channel pulse generator (Activa PC, Medtronic) was connected to the leads and implanted within a subclavicular subcutaneous pocket. DBS settings were programmed and optimized for chronic stimulation over 3 months following surgery. The final monopolar stimulation parameters were as follows: right case (+), contact 1 (−); amplitude 2.6 V; pulse-width 60 μs; frequency 100 Hz; left case (+), contact 10 (−); amplitude 2.6 V; pulse-width 60 μs; frequency 100 Hz. Lead localization was generated by the fusion of 1-mm slice thickness postoperative CT with preoperative MRI [7] and revealed slightly lateral placement of the electrodes relative to the intended GPi target (Fig. 2). It can be appreciated from the volume of tissue activation that the area of stimulation is closer to the globus pallidus externa.

Six months after surgery, bilateral DBS was associated with significant improvements both symptomatically and functionally. Speech and swallowing are ameliorated, while he is steadily gaining weight and exhibiting significantly less chorea (UHDRS-c: 4). He has been able to resume activities that were not possible before surgery (see online suppl. Videos; for all online suppl. material, see www.karger.com/doi/10.1159/000500951).

Conclusion

Here, we present a case of a 31-year-old man with genetically confirmed ChAc who presented with chorea, tongue biting, dysarthria, weight loss, and mild cognitive dysfunction. This case is notable for documented VPS13A gene mutations and a strongly positive outcome at 6 months following DBS, though an important limitation is the open-label nature of the treatment. The excellent clinical outcome in the setting of lead placement lateral to the internal globus pallidus raises questions as to the optimal target in patients with ChAc. Finally, controlled trials for better impact assessment and target identification of DBS in ChAc will be of interest going forward.

Statement of Ethics

The authors confirm that the approval of an institutional review board was not required for this work. Informed consent was obtained from the patient for use of online supplementary videos and details of case history. 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.

Disclosure Statement

No conflicts of interest and no financial disclosures are declared for all authors.

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Author Contributions

Author contributions are listed in Table 1.

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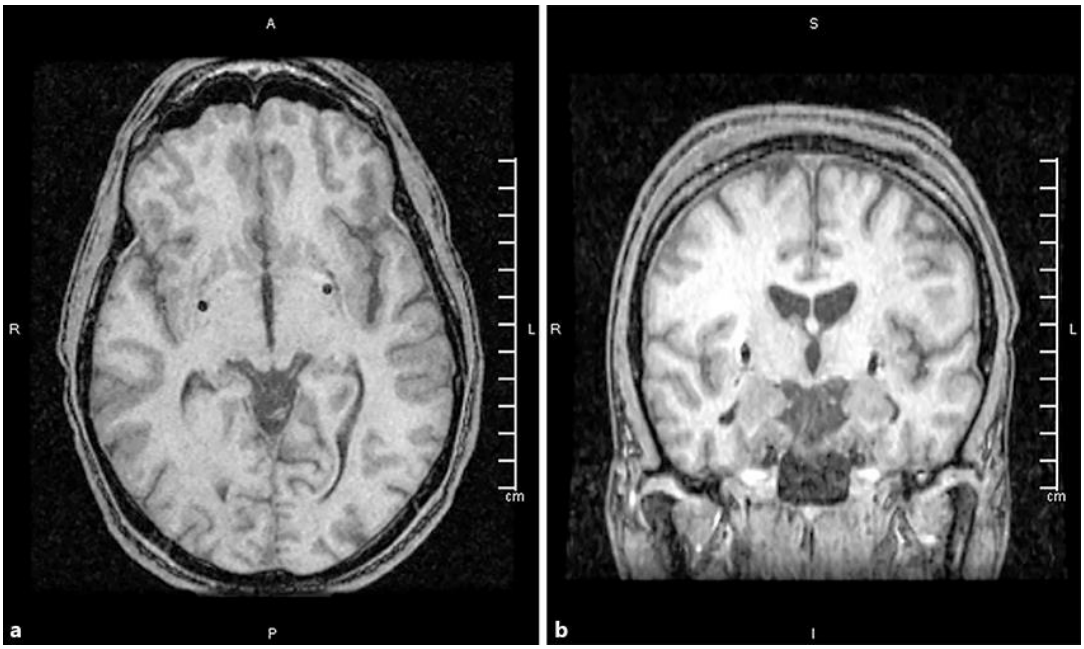

Fig. 1. Postoperative axial (**a**) and coronal (**b**) T1-weighted MRI, demonstrating placement of DBS electrodes. The tips of the electrodes are located in the globus pallidus bordering the putamen bilaterally.

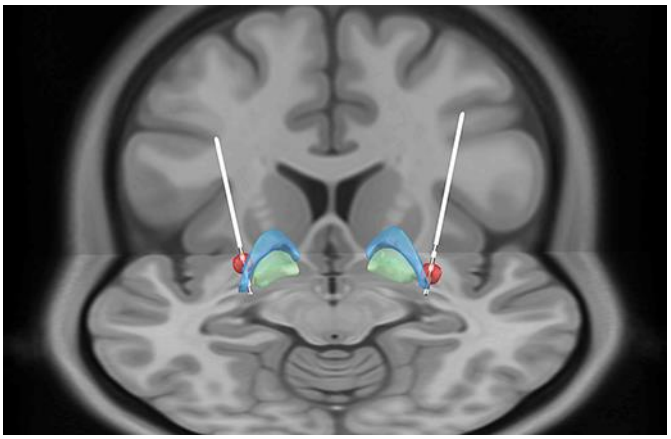

Fig. 2. Three dimensional reconstructed positions of leads with volume of tissue activation in red for the active contacts: right case (+), contact 1 (−), and left case (+), contact 10 (−). Globus pallidus interna and externa are highlighted in green and blue, respectively. Image was generated with Lead DBS v2.1.81 (lead-dbs.org) and visualized with brain shift correction in DISTAL atlas [7].

Table 1. Author contributions

Name	Location	Role	Contribution
Alby Richard, PhD, MD	Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA	Author	Conceptualized idea for manuscript Major role in data analysis Drafted the manuscript for intellectual content
Joey Hsu, BS	Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA	Author	Major role in data analysis Revised the manuscript for intellectual content
Patricia Baum, NP	Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA	Author	Conceptualized idea for manuscript Revised the manuscript for intellectual content
David K. Simon, MD, PhD	Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA	Author	Conceptualized idea for manuscript Revised the manuscript for intellectual content
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