Deep Brain Stimulation for Generalized Dystonia from Secondary Carnitine Deficiency: A Case Report and Literature Review.

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Case report

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Abstract

BACKGROUND:
Carnitine deficiencies result from a metabolic disorder of fatty acid β-oxidation and may lead to organic acidemia, which are thought to be associated with dystonia, epilepsy, autism and developmental delay. Pharmacotherapy has been the dominant therapy, while many refractory patients still require other treatment. Deep brain stimulation (DBS) of the globus pallidus internus (GPI) has been found to be effective for medically refractory primary dystonia and now it has been proposed to be used for secondary dystonia from mitochondrial metabolic disorder.

OBJECTIVE:
To investigate the efficacy and safety of DBS treatment in secondary dystonia from organic acid metabolic disorder.

METHODS:
We present a patient born with secondary carnitine deficiency who had the onset of generalized seizures at age 4.5 months and developed torsion dystonia at age 14. Multiple medical therapies failed to adequately control her symptoms, therefore she received GPI DBS at age 26 years. In addition, we performed a literature review of this therapy in the treatment of organic acid metabolic disorder.

RESULTS:
Our patient's dystonia resolved without side effects post-DBS surgery, but intermittent spastic symptoms along with severe pain in her lower extremity persist. Concerning the 8 cases from our literature review, 7 received GPI DBS, and had improvement in motor symptoms. Overall, DBS efficacy was lower than in treatment of primary dystonia. One patient with methylmalonic acidemia received STN DBS and had marked improvement in dystonia and reduction in pain afterwards.

CONCLUSION:
DBS has become an effective therapy in refractory secondary dystonia from organic acid metabolic disorder. More prospective studies are needed to determine the eligibility and efficacy of this surgical therapy in these cases.

Introduction
Carnitine plays a critical role in energy production. It transports long-chain fatty acids into the mitochondria to be oxidized for energy production. It also transports toxic compounds out of this organelle to prevent their accumulation. Given these key functions, carnitine is concentrated in tissues such as brain, skeletal and cardiac muscle that utilize fatty acids as a dietary fuel.

Primary carnitine deficiency is an autosomal recessive disorder of the carnitine cycle. This disorder was first described in 1988 in an infant who presented with fasting nonketotic hypoglycemic coma and fatty hepatomegaly associated with extremely low concentrations of carnitine in plasma, liver, and skeletal muscle. Subsequent genetic studies have
shown that this carnitine transporter defect is due to recessively inherited mutations of the OCTN2 (SLC22A5) gene on 5q3.4. Furthermore, the inherited organic acidemia and disorders of fatty acid oxidation could result in an accumulation of short-chain and medium-chain acyl groups, which are excreted into the urine together with acylcarnitine expelling from the mitochondria, and thus result in a depletion of the body's carnitine storage, leading to secondary carnitine deficiency. The carnitine abnormalities in the latter disorders are the consequence, rather than the cause, of the impairment in fatty acid oxidation. Secondary carnitine deficiency may be accompanied by a moderate degree of muscular dysfunction. Despite this, neurological symptoms such as epilepsy, dystonia, myoclonus, diplopia, sensory neuropathy and myopathy are frequently developed in both cases due to this mitochondrial dysfunction. Furthermore, 20 to 30% of patients do not appreciate an adequate control of epilepsy or dystonia with available medications.

DBS has become an established treatment for medically refractory movement disorders such as Parkinson disease and essential tremor in adults. It has also been accepted for medically refractory childhood dystonia, especially for DYT1 primary dystonia. However, there is less consensus regarding the role of DBS in other forms of dystonia. Even though different subtypes may have different surgical outcomes, concerning the high number of medically refractory patients in secondary dystonia, DBS should be considered as an effective procedure in carefully selected pediatric cohorts.

We report the case of a 26-year-old female born with secondary carnitine deficiency who had an onset of generalized seizures at age 4.5 months and developed torsion dystonia at age 14. Multiple medical therapies have failed to adequately control her symptoms, therefore she received GPi DBS at age 26. Dystonic symptoms have resolved without side effects post-surgery. A literature review of this therapy in the treatment of organic acid metabolic disorder is provided.

**Case Report**

**History and Examination**

Our patient was born in a family with several carnitine deficiency offspring and was tested for carnitine soon after birth. Her urine carnitine levels and acylcarnitine/free carnitine ratio were abnormally high and plasma carnitine was relatively low. From her plasma organic acids screen, she was high in citric acid, however isocitric acid was scarce. These findings indicated that she was deficient in the enzymes in Krebs cycle which led to her secondary carnitine deficiency. She was diagnosed with gross motor development retardation and had her first onset of generalized seizures at 4.5 months. Since then she was started on Phenobarbital and L-carnitine. At age 4 years of age, she developed leg pain, but no myopathy was detected from her muscle biopsy. Her EEG was abnormal indicating diffuse cerebral dysfunction. At age 14, she began to take Fluoxetine for her depression, and her dystonia then emerged. She had inversion of the left foot at first progressing to the spasms of the left leg, each episode lasting 3 to 4 hours and up to 4 to 5 times per day, leading to a series of emergency room visits. She finally required IV phenytoin to abort these hyperkineses and was put on 100 mg phenytoin TID. However, she would have increased hyperkineses if phenytoin levels were either too low or too high.

At age 20, she began to have paroxysmal dystonic movements involving neck, both arms and legs starting from the left foot. She was started on botulinum toxin injection trials for the dystonic movement of the left leg with marked improvement, however she continued to have paroxysmal episodes once every month on average. According to
neurological examination, she was alert and oriented. She had increased tone of the left foot and left leg without adventitious movements. Her strength was 5/5 throughout all extremities. Her brain MRI and MRA were normal.

Before surgery, she was on L-carnitine for carnitine deficiency, baclofen and diphenhydramine for dystonia, gabapentin for myalgia, diazepam, lacosamide and levetiracetam for seizures.

When she was 25 years old, she began to experience a significant amount of discomfort and falls with her dystonic attacks despite medical management, and was found to be a suitable candidate for DBS. Her surgery goals were to reduce her bilateral lower extremity pain, to reduce the spasms that occurs in her extremities and to reduce her medication regimen. She underwent a Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) before surgery. Her Torticollis Severity Scale was 24/35, the disability scale was 28/30, and the pain scale was 16.25/20. Her Burke-Fahn-Marsden (BFM) Dystonia Rating Scale score was 27.5.

**Operation procedure**

The DBS surgery was accomplished in two stages. During the first stage, bilateral Medtronic 3389 leads were implanted stereotactically into both GPi nuclei. The operation was performed in a stereotactic frame using local anesthesia, and microelectrode recordings and intraoperative test stimulation were performed to confirm the location of the GPi. An intraoperative CT scan was also obtained to confirm final lead locations prior to completing the operation. The pre- and postoperative brain MRI were shown in Fig. 1.

The second stage of the DBS surgery, during which the implantable pulse generator (IPG) and extension cables were implanted and connected to the leads, was performed one week later. The IPG was implanted under the skin of the anterior chest wall connected to the lead wires via subcutaneously tunneled extension cables. This was an outpatient procedure and there were no immediate surgical or hardware complications afterwards.

Devices were programmed within the first month after surgery, during which the clinician controlled the combination of four stimulus parameters: electrode configuration, amplitude, pulse width and frequency to generate maximum motor function improvement and reduce pain without causing adverse effects. After initial adjustments, she did best on a bipolar setting (LGPi 1-/2+, 2.1v, PW 60 microsec, Rate 130 Hz; RGPi 9-/10+, 2.1v, PW 60 microsec, Rate 130 Hz).

**Post-surgery reports**

Our patient’s dystonia had resolved at her seven-month review, but the pain stayed the same. The spastic movements of her left leg occurred occasionally, which could last up to 12 hours at most when she was in pain. She also reported one episode of tremors in her arms which progressed to her lower extremities. She has been attending physical therapy to help with her gait balance and pain. She has returned to school and is carrying out more activities than before surgery. She continues her medications of diphenhydramine, gabapentin and levocarnitine at the present time.

At her eight-month review, her TWSTRS showed definitive improvement following DBS. Her Torticollis Severity Scale was 6/35, the disability scale was 18/30, and the pain scale was 18/20. Her Videotaped Fahn-Marsden BFM Dystonia Rating Scale was 2 in total.

**Literature review**

A literature review was performed by searching the key words of ‘secondary dystonia’, ‘DBS’ and ‘organic acid metabolic disorder’ through the electronic database PubMed, to identify cases and cohort studies reporting DBS...
treatment for secondary dystonia from organic acid metabolic disorder. Eight reported cases were retrieved from 2010 to 2017 (Table 1). The most common organic acid metabolic disorder was glutaric acidemia type 1 (4/8). According to our literature review, the case of DBS for secondary dystonia from carnitine deficiency has never been reported. The onset age of dystonia ranged from 5 months to 16 years, with a medium age of 5, which was much younger than our patient. The patients with an onset age earlier than one year tended to develop more severe generalized dystonia.

In case 1, the patient’s BFMDRS motor score was 105 for movement and 30 for disability before surgery. The preoperative goal was to alleviate his seating intolerance, the inability to change position, and difficulty with communication. From his MRI, the bilateral globus pallidus manifested complete liquefaction, thus he was the only patient to undergo STN stimulation in our series.

All the other patients were treated with bilateral GPi DBS. The median follow-up duration was 12 months (range 3–24 months). Seven of the eight patients achieved clinical improvement to various extents from their baseline. We noted that, apart from their dystonia, certain concurrent psychiatric disorders were also alleviated. The patient in case one was interacting and smiling more often, which had never been observed before surgery. The patient with Lesch-Nyhan syndrome experienced a decrease in self-injurious behaviors.

Discussion

Carnitine is a key player in mitochondrial generation of energy and metabolism of acetyl coenzyme A. The mitochondrial dysfunction due to carnitine deficiency has been identified as a potential cause of therapy-resistant forms of severe movement disorders. Dystonia, one of the most common pediatric movement disorders, exists on a spectrum of severity which can include persistent debilitating clinical states affecting the life quality of patients and caretakers. The role of DBS in pediatric dystonia remains only partially characterized. Various multicenter studies and randomized controlled trials have verified the efficacy of GPi DBS for patients with primary dystonia, indicating partial to complete symptom relief in 90% of patients. The results in secondary dystonia are heterogeneous, however, which may result from the mixed etiology of the disorder.

Here we report the first case of a 26-year-old female who acquired refractory generalized dystonia as a result of secondary carnitine deficiency. She was poorly responsive to the medication trials of anticholinergic drugs, benzodiazepine derivatives, botulinum toxin injections, oral baclofen and neuroleptics. She finally received bilateral GPi DBS. At her 8-month follow up, not only have her movement disorders evidently been alleviated, but her social functions have also been restored to some extent. However, because of her persisting myalgia, the patient is still receiving physical therapy and medications of Gabapentin. According to our review of the eight cases, DBS appeared to be effective in improving motor symptoms and alleviating degree of disability.

Despite many years of research, the effects of DBS on the basal ganglia in dystonia remains mysterious. Recording of neuronal activity in the awake state of primary dystonia model mice revealed reduced spontaneous activity with bursts and pauses in both internal and external segments of the globus pallidus. Reductions of the inhibitory input from the GPi may cause increased thalamic and cortical activity, resulting in the involuntary movements observed in dystonia. From the ‘excitation hypothesis’, DBS excites local neuronal elements just as single stimulation does. Directly evoked spikes induced by GPi-DBS could reduce firings in thalamic neurons therefore control the movement disorder. While more recent studies showed that the effect of DBS is more complex than simply an increase or decrease in firing rate in a single state. Vitek suggested that dystonia results mainly from a hypersynchronization of GPi and motor thalamic neurons. Pallidotomy as well as DBS of GPi would reduce the hypersynchronous inhibitory input to the motor thalamus as well as to other brain areas connected to the motor
thalamus such as the pedunculopontine nucleus. This loss of GPi-induced hypersynchronization would correct the abnormal firing of the motor thalamus cells by changing thalamic neurons synchronization without necessarily affecting their firing rate, which fits with the ‘disruption hypothesis’. From the existing study, pallidal DBS is especially effective for patients with a normal brain structural MRI\textsuperscript{28}.

In our case series, early improvement in the mobile, phasic movements of dystonia have been observed, whereas the fixed postures may require months for improvement. However, its efficacy for symptoms other than those arising from movement disorders such as myalgia or emotional disturbances is still obscure. Secondary dystonia from organic acid metabolic disorder has its own characteristics that should be considered during peri-operation period and follow-up visits.

From our case and literature review, the movement disorders of this type tend to have their onset at an early age, thus the patients who underwent DBS were mostly juveniles. Even though no complications were reported in our series, electrode dislocation can occur in pediatric patients\textsuperscript{29}. Cerebral growth leads to a relative posterior dislocation of the electrodes\textsuperscript{30}. This potential complication must be considered, particularly if the patients are younger than 7 years of age\textsuperscript{21}. In addition, dystonic postures can exert traction on the leads, displacing them from the targeted nucleus, which seldom happens to the adult patients\textsuperscript{31}.

Mitochondrial dysfunction could aggressively affect neurodevelopment. In some severe cases\textsuperscript{22,32}, targeting the GPi was impossible because of their structural abnormality, leaving the STN as a possible alternative. The STN is directly connected to a wide range of structures including the cerebral cortex, the GPe, the centromedian nucleus of the thalamus, and brainstem structures such as the pedunculopontine and raphe nuclei\textsuperscript{22}. Furthermore, high-frequency stimulation of the STN may modulate local pathological activity including residual GPi neurons\textsuperscript{25}. A body of literature demonstrating the benefits of STN DBS in dystonia is accumulating\textsuperscript{33–35}.

Conclusion

DBS is an effective therapy in refractory secondary dystonia from organic acid metabolic disorder. The characteristics of the disease should be carefully evaluated during the perioperative period and follow-up visits to avoid complications. Larger prospective studies are needed to determine if it is versatile, reversible and adequate.

Declarations

Ethics approval and consent to participate: The study was fully approved by IRB of UCDavis (Continuing Review # HRP-212)

Consent for publication: Obtained from the case patient (on file). This work received the full consent from the patient from whom the case was reported and data collected.

Availability of data and material: Data and material will be made fully available upon email contact to the corresponding author

Competing interests: None

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Authors’ contributions:
The author's contributions are as follows:

Yixuan Zhang, MD, PhD: contributed to conception and design of the study, data collection, drafting the article, and final approval of the version to be published.

Laura Sperry, NP: contributed to data collection, data analysis and interpretation.

Michelle Chan, PhD: contributed to data collection, data analysis and interpretation, critical revision of the article

Suma Shankar, PhD: contributed to data collection, data analysis and interpretation, and critical revision of the article

Norika Malhado-Chang, MD: contributed to data collection, data analysis and interpretation

Kevin O'Connor, PhD: Contributed to data collection, data interpretation, and critical revision of the article

Fady Girgis, MD, PhD: contributed to data collection, data analysis and interpretation

Sarah Farias, PhD: contributed to data collection, data analysis and interpretation, and critical revision of the article

Vicki Wheelock, MD: contributed to data collection, data analysis and interpretation, and critical revision of the article

Kiarash Shahlaie, MD, PhD: contributed to the conception of the work, data analysis and interpretation.

Lin Zhang, MD, PhD (corresponding author): contributed to conception of the work, data analysis and interpretation, critical revision of the article, and final approval of the version to be published.

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**Tables**

Table 1. Case reports of patients with organic acid metabolic disorder who received DBS treatment.
<table>
<thead>
<tr>
<th>Case</th>
<th>First Author</th>
<th>Etiology</th>
<th>Symptom</th>
<th>Onset Age</th>
<th>Treatment</th>
<th>Follow-up time(months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>Methylmalonic Acidemia</td>
<td>Generalized Dystonia</td>
<td>21 months</td>
<td>DBS of Bilateral STN</td>
<td>6</td>
<td>Marked improvement in dystonia and reduction in pain</td>
</tr>
<tr>
<td>2</td>
<td>Lipsman, N[19]</td>
<td>Glutaric Acidemia Type 1</td>
<td>Dystonia</td>
<td>Unknown</td>
<td>DBS of Bilateral GPI</td>
<td>77</td>
<td>Mild improvement in motor symptoms</td>
</tr>
<tr>
<td>3</td>
<td>Air, E. L[20]</td>
<td>Glutaric Acidemia Type 1</td>
<td>Dystonia</td>
<td>16.8</td>
<td>DBS of Bilateral GPI</td>
<td>3</td>
<td>BADS from 28 to 23 (18% reduction)</td>
</tr>
<tr>
<td>4</td>
<td>Air, E. L[20]</td>
<td>Lesch-Nyhan syndrome</td>
<td>Dystonia</td>
<td>5.4</td>
<td>DBS of Bilateral GPI</td>
<td>12</td>
<td>80% and 75% decreases in frequency and severity in Behavior Problems Inventory 6% decrease in BFMDRS motor subscore</td>
</tr>
<tr>
<td>5</td>
<td>Air, E. L[20]</td>
<td>Unknown metabolic disorder</td>
<td>Dystonia</td>
<td>2</td>
<td>DBS of Bilateral GPI</td>
<td>NA</td>
<td>Did not experience benefit</td>
</tr>
<tr>
<td>6</td>
<td>Gimeno, H[21]</td>
<td>Glutaric Acidemia Type 1</td>
<td>Severe Generalized Dystonia</td>
<td>5 Months</td>
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<td>Mild improvement</td>
</tr>
<tr>
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</tr>
<tr>
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<td>Glutaric Acidemia Type 1</td>
<td>Dysarthria</td>
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<td>DBS of Bilateral GPI</td>
<td>24</td>
<td>No improvement</td>
</tr>
</tbody>
</table>

**Figures**
Figure 1

The preoperative axial T2-weighted MRI of the patient showing a normal basal ganglia structure (a). Postoperative MRI demonstrating bilateral GPi positioning of deep brain stimulation leads (b).
Figure 2

Reductions of the inhibitory input from the GPi leading to the Increase of thalamic and cortical activity. Involuntary movements observed in dystonia GPi-DBS could reduce firings in thalamic neurons therefore control the movement disorder (Red and blue arrows represent glutamatergic excitatory and GABAergic inhibitory terminals).