Scholars LITERATURE

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Case Report

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

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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 an acquired dystonia from mitochondrial metabolic disorder.

Objective: We present the first case of carnitine deficiency treated with DBS for dystonia and investigate the efficacy and safety of DBS treatment in acquired dystonia from organic acid metabolic disorder.

Methods: The patient was born with secondary carnitine deficiency who had an onset of generalized seizures at age 4.5 months and developed general dystonia at age 14. Multiple medical therapies have failed to adequately control her symptoms, therefore she received GPi DBS at age 26. In addition, we performed a literature review of this therapy in the treatment of inherited organic acid metabolic disorder.

Results: Our patient's dystonia has resolved without side effects post-DBS surgery, but intermittent spastic symptoms along with severe pain in her lower extremity persist. Concerning the 14 cases from our literature review, 13 of them received GPi DBS, and had an improvement in motor symptoms. One patient with methylmalonic acidemia received STN DBS and had marked improvement in dystonia and reduction in pain afterwards. Overall, DBS efficacy was lower than in treatment of primary dystonia.

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

Keywords: Treatment; Deep brain stimulation; Carnitine deficiency; Organic acid metabolic disorder; Generalized dystonia

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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 [1].

Primary carnitine deficiency (OMIM 212140) 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 [2]. Subsequent genetic studies have shown that this carnitine transporter defect is due to recessively inherited mutations of the *OCTN2* (*SLC22A5*) gene on 5q [3, 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[5]. 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 [6]. Furthermore, 20 to 30% of patients do not appreciate an adequate control of epilepsy or dystonia with available medications [7]. Carnitine deficiency in the context of childlike hypoglycemia can lead to a range of extra neural manifestations. Impaired fatty acid metabolism can disrupt the normal balance of energy substrates, leading to a decrease in overall energy levels and potentially affecting cardiac function [8]. Furthermore, the deficiency can impact the immune system, leading to increased susceptibility to infections and impairing overall health [5]. Timely recognition and management of carnitine deficiency in the context of childlike hypoglycemia are crucial to prevent these extra neural manifestations and ensure optimal growth and development.

DBS has become an established treatment for medically refractory movement disorders such as Parkinson disease [9-11] and essential tremor [12-15] in adults. It has also been accepted for medically refractory childhood dystonia, especially for DYT1 primary dystonia[16]. However, dystonia caused by inherited metabolic disorders may have a more variable response to DBS therapy [16]. Even though different subtypes may have different surgical outcomes, concerning the high number of medically refractory patients in acquired dystonia, DBS should be considered as an effective procedure in carefully selected pediatric cohorts [17].

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 general 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 (Table 1). 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 4 years of age, she developed leg pain, but no myopathy was detected from her muscle biopsy. Her electroencephalography 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.

Table 1: The metabolic biochemical studies indicated that she was deficient in the enzymes in Krebs cycle which led to her secondary carnitine deficiency.

Carnitine results	**Result**	**Control range**
Total urine carnitine (nmol/mg creat.)	776.3 ↑	332.3 - 574.4
Free urine carnitine (nmol/mg creat.)	175.0 ↑	148.9 - 174.4
Urine acyl/Free Ratio	3.4 ↑	1.0 - 2.9
Total plasma carnitine (nmol/ml)	54.2 ↓	60.8 - 63.8
Free plasma carnitine (nmol/mg creat.)	19.9 ↓	21.1 - 39.3
Plasma acyl/Free ratio	1.9	0.6 - 1.9
Plasma organic acids results	**Result**	**Control range**
Citric (umol/L)	2653 ↑↑	60 - 480
Isocitric (umol/L)	0 ↓	7 - 19

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. She underwent gene sequencing of primary dystonia (including *ANO3, ATP1A3, CIZ1, DRD2, GCH1, GNAL, HPCA, KCTD17, PARK2, PNKD, PRRT2, SGCE, SLC2A1, SLC6A3, SPR, TH, THAP1, TOR1A, TOR1AIP1,*and *TUBB4A*) and metabolic tests but no significant pathogenic mutation was detected (a normal profile excludes translocase/CPT II, VLCAD, LCHAD/trifunctional protein deficiency, MCAD, SCAD, and severe RTF dehydrogenase deficiency).

Before surgery, she was on L-carnitine (30ml three times/day) for carnitine deficiency, baclofen (20mg three times/day) and diphenhydramine (50mg three times/day) for dystonia, gabapentin (50mg three times/day) for myalgia, diazepam (7.5mg every 6 hours) and levetiracetam (1000mg 2 times/day) for seizures.

When she was 25 years old, she began to experience a significant amount of discomfort and falls with her dystonic episodes 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 stereo tactically 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 post-operative brain MRI were shown in figure 1.

The second stage of the DBS surgery, during which the implantable pulse generator and extension cables were implanted and connected to the leads, was performed one week later. The implantable pulse generator 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,

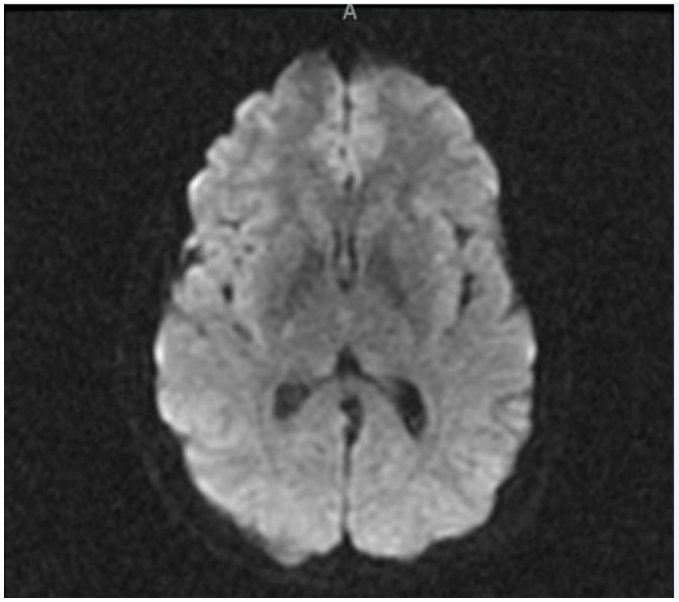

Figure 1a: The preoperative axial MRI of the patient showing a normal basal ganglia structure.

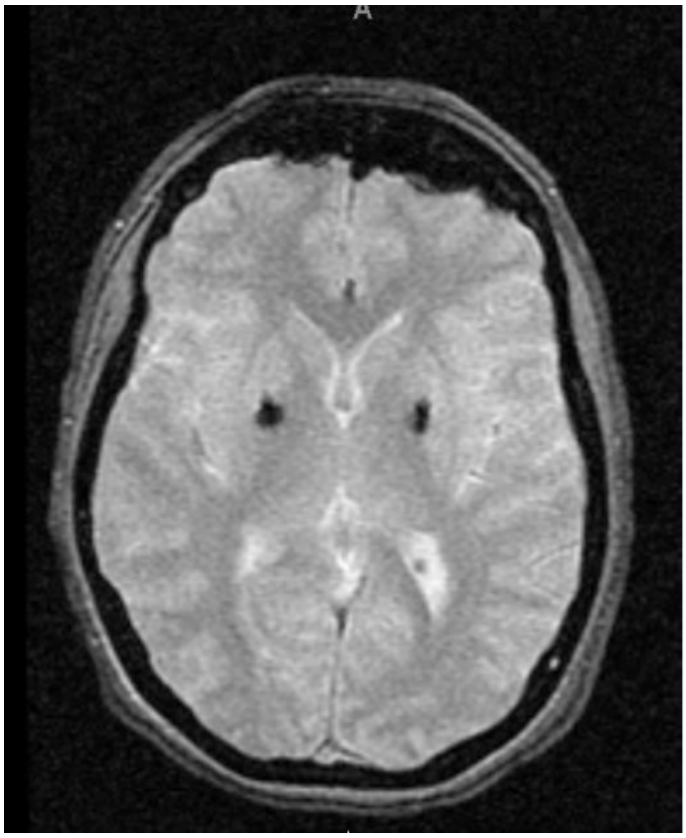

Figure 1b: Postoperative MRI demonstrating bilateral GPi positioning of deep brain stimulation leads.

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 2020 (Table 2). The most common organic acid metabolic disorder was Lesch-Nyhan syndrome (7/14). 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. According to our literature review, the case of DBS for secondary dystonia from carnitine deficiency has never been reported.

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 16 months (range 3 - 144 months). 12 of the 14 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 1 was interacting and smiling more often, which had never been observed before surgery. The patients with Lesch-Nyhan syndrome experienced remission of self-injurious behavior.

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 [6]. Dystonia, one of the most common pediatric movement disorders [18], exists on a spectrum of severity which can include persistent debilitating clinical states affecting the life quality of patients and caretakers [19]. The role of DBS in pediatric dystonia remains only partially characterized [20]. Various multi-center 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 [21-23]. However, the results in acquired dystonia are heterogeneous, which may result from the mixed etiology of the disorder [24].

Table 2: Case reports of patients with organic acid metabolic disorder who received DBS treatment.

Case	First Author	Etiology	Symptom	Onset Age (year)	Target	DBS programming	Follow-up time (months)	Outcome
1	Chakraborti, S [23]	Methylmalonic Acidemia	Generalized dystonia	21 months	Bilateral STN	60 ms, 130 Hz bilaterally at 0.5 V	6	Marked improvement in dystonia and reduction in pain
2	Lipsman, N [42]	Glutaric Acidemia type 1	Dystonia	Unknown	Bilateral GPi	NA	77	Mild improvement in motor symptoms
3	Air, E. L [32]	Glutaric Acidemia type1	Dystonia	16.8	Bilateral GPi	90 - 200 ms, 185 Hz	3	BADS from 28 to 23 (18% reduction)
4	Gimeno, H [43]	Glutaric Acidemia type 1	Severe generalized dystonia	5 months	Bilateral GPi	NA	12	Mild improvement
5	Tsering, D [20]	Glutaric Acidemia type I	Dysarthria	16	Bilateral GPi	120 Hz, 150 ms, at 2 V	24	No improvement
6	Air, E. L [32]	Lesch-Nyhan syndrome	Dystonia	5.4	Bilateral GPi	90 - 200 ms, 185 Hz	12	80% and 75% decreases in frequency and severity in Behavior Problems Inventory. 6% decrease in BFMDRS motor subscore
7	Abel. T. J. [44]	Lesch-Nyhan syndrome	Generalized dystonia, Self-mutilation behavior	6 months	Bilateral GPi	60 ms, 120 Hz at 0.5 V bilaterally	NA	Moderate improvement in the motor and self-mutilationsymptoms
8	Deon, L.L. [45]	Lesch-Nyhan syndrome	Severe dystonia and Self-injurious behaviors	7	Bilateral GPi	NA	3	Improvement in dystonia with acomplete remission of self-injurious behavior
9	Tambirajoo, K. [46]	Lesch-Nyhan syndrome	Dystonic dyskinesia, Oro-lingualand hand to face self-mutilation	4	Bilateral GPi	120 ms, 130 Hz at 1.3 V	97	3.8% increase in BFMDRS Movement, 6.9% increase in BFMDRS Disability
10		Lesch-Nyhan syndrome	Self-mutilating behavior, Worsening dystonia with extensor posturing	5	Bilateral GPi	450 ms, 130 Hz at 0.9 V	144	1.3% increase in BFMDRS Movement, 4.0% increase in BFMDRS Disability
11		Lesch-Nyhan syndrome	Severe disabling dystonia, Hand to mouthmutilation, Self-harming behavior	7	Bilateral GPi	450 ms, 125 Hz at 1.3 V	37	6.7% increase in BFMDRS Movement, 8.3% increase in BFMDRS Disability
12		Lesch-Nyhan syndrome	Severe total bodydystonia, Dystonic choreoathetosis, Self-injurious behavior, Globaldevelopmental delay, and Learning disability	6	Bilateral posteroventral GPi	450 ms, 130 Hz at 1.3V	20	1.6% increase in BFMDRS Movement, no increase in BFMDRS Disability
13	Air, E. L [32]	Unknown metabolic disorder	Dystonia	2	DBS of Bilateral GPi	90 - 200 ms, 185 Hz	NA	Did not experience benefit
14	Ghosh, P. S [33]	Mitochondrial disorder	Generalized dystonia	5	DBS of Bilateral GPi at the Age of 13	90 - 120ms, 60 Hz at 2-3 V	24	Mild improvement compared with primary dystonia

Note: NA: Not Applicable.

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. Due to inadequate symptom control with medication management, she underwent bilateral GPi DBS. At her 8-month follow up, not only have her movement disorders 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. In addition to our case, our literature review also showed eight cases where DBS appeared to be effective in improving motor symptoms and alleviating degree of disability.

Despite many years of research, we are still understanding the complexities of the effects of DBS on the basal ganglia in dystonia. 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 pallid us. Reductions of the inhibitory input from the GPi may cause increased thalamic and cortical activity, resulting in the involuntary movements observed in dystonia [25]. According to the 'excitation hypothesis' [26], 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 [27] (Figure 2). Vitek [28] suggested that dystonia results mainly from a hyper synchronization of GPi and motor thalamic neurons. Pallidotomy as well as GPi-DBS 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 hyper synchronization 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 [29].

Movement disorders are important and one of the most common neurological manifestations of inherited metabolic disorders[30], and dystonia is the most common type (54%)[31]. It has been proposed that DBS should be considered to modify the course of dystonia in the young patient once it is clear that pharmacological therapies are

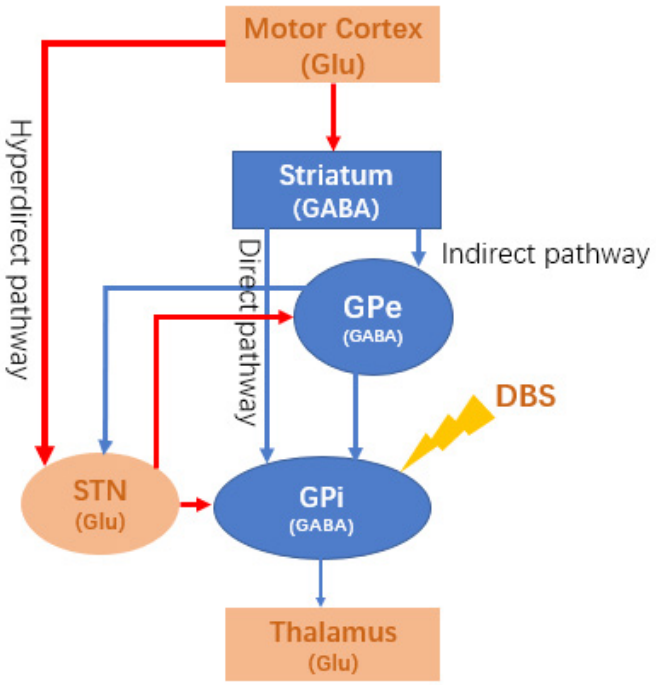

Figure 2: Reductions of the inhibitory input from the GPi leading to the increase of thalamic and cortical activity. Involuntary movements observed in dystonia GPi-DBS could reduce firings in thalamic neurons therefore control the movement disorder (Red and blue arrows represent glutamatergic excitatory and GABAergic inhibitory terminals).

inadequate, and before the onset of fixed musculoskeletal deformities set in[23, 32]. Nevertheless, the functional benefit is modest compared to the patients with primary dystonia[33]. In patients with contractures or fixed skeletal deformities due to severe generalized dystonia, DBS is not likely to have a positive outcome[34]. 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. Acquired dystonia from inherited metabolic disorder has its own characteristics as follows that should be considered during peri-operation period and follow-up visits.

From our case and literature review, the movement disorders of inherited metabolic diseases 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 [35]. Cerebral growth leads to a relative posterior dislocation of the electrodes [36]. This potential complication must be considered, particularly if the patients are younger than 7 years of age [22]. In addition, dystonic postures can exert traction on the leads, displacing them from the targeted nucleus, which seldom happens to the adult patients [37].

Inherited metabolic dysfunction could aggressively affect neurodevelopment. In some severe cases [23, 38], 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 [23]. Furthermore, high-frequency stimulation of the STN may modulate local pathological activity including residual GPi neurons [26]. A body of literature demonstrating the benefits of STN DBS in dystonia is accumulating [39-41].

Conclusion

DBS could be an effective therapy in refractory acquired 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.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Credit Author Statement

Yixuan Zhang: Data mining, Analysis, Manuscript preparation; Laura Sperry: Case preparations, Medical record analysis, Manuscript editing; Michelle Chan: Scientific analysis of the cases, Manuscript editing; Suma Shankar: Scientific analysis of the cases, Manuscript editing; NorikaMalhado-Chang: Scientific analysis of the cases, Manuscript editing; Vicki Wheelock: Scientific analysis of the cases, Manuscript editing; Kevin O'Connor: Data mining and correcting, Manuscript proofreading and editing; Fady Girgis: Surgical data mining, Manuscript editing; Farias Sarah: Data analysis and mining, Manuscript editing; Kiarash Shahlaie: Surgical data analysis and mining, Manuscript editing; Lin Zhang: Data analysis, Submission proofreading, Scientific editing, Manuscript lining up and submission.

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