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Introduction: Dystonia is the third most common pediatric movement disorder and is often difficult to treat. Deep brain stimulation (DBS) of the internal pallidum (GPi) has been demonstrated as a safe and effective treatment for genetic dystonia in adolescents and adults. The results of DBS in children are limited to individual cases or case series, although it has been proven to be an effective procedure in carefully selected pediatric cohorts. The aim of our study was to present the treatment outcome for 7- to 9-year-old pediatric patients with disabling monogenic isolated generalized DYT-*THAP1* and DYT-*KMT2B* dystonia after bilateral GPi-DBS.

Patients and results: We present three boys aged <10 years; two siblings with disabling generalized DYT-*THAP1* dystonia and a boy with monogenic-complex DYT-*KMT2B*. Dystonia onset occurred between the ages of 3 and 6. Significantly disabled children were mostly dependent on their parents. Pharmacotherapy was inefficient and patients underwent bilateral GPi-DBS. Clinical signs of dystonia improved significantly in the first month after the implantation and continued to maintain improved motor functions, which were found to have improved further at follow-up. These patients were ambulant without support and included in everyday activities. All patients had significantly lower Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) values, indicating >25% improvement over the first 15 months. However, there was a decline in speech and upper limb function, manifesting with bradylalia, bradykinesia, and dysphonia, which decreased after treatment with trihexyphenidyl.

Conclusion: Although reports of patients with monogenic dystonia, particularly DYT-*THAP1*, treated with DBS are still scarce, DBS should be considered as an efficient treatment approach in children with pharmacoresistant dystonia, especially with generalized monogenic dystonia and to prevent severe and disabling symptoms that reduce the quality of life, including emotional and social aspects. Patients require an individual approach and parents should be properly informed about expectations and possible outcomes, including relapses and impairments, in addition to DBS responsiveness and related improvements. Furthermore, early genetic diagnosis and the provision of appropriate treatments, including DBS, are mandatory for preventing severe neurologic impairments.

KEYWORDS

pediatric genetic dystonia, DYT6 gene, *KMT2B* dystonia, GPi-DBS, neurosurgery

Introduction

Dystonia (DYT) is *"a movement disorder characterized by sustained involuntary or intermittent muscle contractions causing abnormal, sustained, often repetitive movements, postures, or both"* (1). Dystonia may be focal, segmental, or generalized, resulting in twisting, sustained, and repetitive postures and movements, with the progressive development of severe motor disability and a negative impact on quality of life (1). The etiology, pathophysiology, and clinical presentation are heterogeneous, ranging from pediatric-onset to adult-onset generalized dystonia, with the possible development of life-threatening dystonic storm. In the last couple of decades, a great number of genes have been identified and linked to different types of dystonia, such as torsin family 1 member A (*TOR1A*) in 1997 [linked to dystonia type 1 [DYT-[*TOR1A*]] and thanatos-associated-domain containing apoptosis-associated protein 1 (*THAP1*) in 2009 [linked to dystonia type 6 with onset occurring usually during childhood or adolescence, including segmental or generalized dystonia with initial craniocervical or laryngeal and upper limb involvement (2–4)]. In addition, since 2016, several mutations in the lysine methyltransferase 2B (*KMT2B*) gene have been identified and linked to progressive childhood-onset dystonia, including development from focal toward generalized dystonia with pronounced craniofacial and laryngeal involvement (5).

Deep brain stimulation (DBS) of the internal globus pallidum (GPi) has been demonstrated as a safe and effective treatment for primary dystonia with a genetic cause, such as DYT-*TOR1A* and DYT-*THAP1* in adolescents and adults (6, 7). The number of adolescents and adults with DYT-*THAP1* dystonia who underwent GPi DBS to date is relatively small. The first published small case series, including several patients, reported only moderate responses to DBS (8, 9). However, medically refractory DYT-*THAP1* cases receiving GPi DBS showed favorable outcomes, more similar to those observed in other isolated dystonias (9–16).

Dystonia is the third most common pediatric movement disorder and is often difficult to treat (17). Coubes et al. were the first to report on the treatment of a child with dystonia using bilateral GPi-DBS (18). In the last decade, a number of reports of DBS in children have been published, showing excellent outcomes for monogenic isolated dystonia DYT-*TOR1A*, as well as the general consensus that DBS is safe and effective in the treatment of adults (7, 19–21). The results of DBS in children are limited to individual cases or case series, although DBS for childhood dystonia has been proven to be an effective procedure in carefully selected pediatric cohorts. Although it is suggested that DBS should be considered as a treatment approach in pharmacoresistent DYT-*THAP1* early in childhood to prevent more severe symptoms, such as disabling motor development and quality of life decline, including emotional and social aspects, the results are missing. Additionally, bilateral GPi-DBS has been reported as a valuable therapeutic option for DYT-*KMT2B*, especially for regaining motor function and mobility, but less so for speech if significant speech difficulties are developed (5, 22–37).

Thus, the aim of our study was to present efficient treatment outcomes of two siblings with DYT-*THAP1* and a boy with DYT-*KMT2B* with disabling monogenic generalized dystonia after bilateral GPi DBS in childhood.

Patients and results

We present three boys: two siblings at the of 9 (patient I) and 7 (patient II) years of age with DYT-*THAP1* and a boy of 7 years of age (patient III) with DYT-*KMT2B* who had DBS implanted.

Case 1

A boy was born after an uneventful pregnancy and birth; both the mother and father were non-consanguineous, with a negative family history for neurologic disorders. His development was normal until the age of three; he became clumsy, with coordination disturbances and lordotic posturing, with hypotonia, torticollis to the right side, and slurred speech. The initial extensive hospital diagnostic investigations excluded structural, infectious, autoimmune, metabolic, chromosomal, and paraneoplastic pathological conditions; however, the diagnosis and etiology remained unknown. No psychiatric or cognitive dysfunctions or disturbances were associated. Over 7 years, the progressive impairment of clinical signs occurred and he developed generalized torsion-type dystonia and became wheelchair-bound. His speech was severely affected as evidenced by slurring, and exhibited upper limb dysfunction with associated dyskinetic movements and tremor. On exam at admission, the boy was not ambulant and had generalized dystonia at rest and during activity, as well as dysphonic and dysarthric speech along with swallowing difficulties (Supplementary Video 1). A dystonia gene panel using PCR amplification and sequence analysis revealed a *THAP 1*, C270_273del (p.glu91ilefs*28) mutation. The patient was treated with clonazepam, trihexyphenidyl, and baclofen, but without meaningful improvement. The Burke–Fahn–Marsden Dystonia Rating Scale-movement scale (BFMDRS-M) was 116 and the BFMDRS-disability scale (BFMDRS-D) was 28 (Table 1).

Case 2

Patient 2, a male sibling of patient I, born after normal pregnancy and delivery. His motor, mental, speech, and cognitive development were normal. He started to walk unassisted at the age of 12 months. At the age of 4.5 years, he manifested with involuntary dystonic movements of the first upper limbs, and afterwards he became clumsy and could not run without frequent falls. On exam, bradylalia and dysarthria were present, with oromandibular dystonia, resulting in scarce verbal response. He could not maintain left side upper and lower extremities in antigravity positions nor walk downstairs without assistance. He also experienced gear phenomenon on lower limbs and waddling gait, absent tendon reflexes of the left side. He gradually developed generalized dystonia manifested at rest and provoked by activity (Supplementary Video 2). No psychiatric or cognitive dysfunction were registered other than slurred speech. A dystonia

TABLE 1 Preoperative characteristics of dystonia patients included in the study.

No.	Gender	Age at disease onset (years)	Initial anatomical distribution	Sequence variant	Preop BFMDRS-M	Preop BFMDRS-D	Preop medication
I	M	3	Upper limb dystonia and slurred speech	THAP 1, C270_273del (p.glu91ilefs∗28)	115	28	Clonazepam, tryhexyphenidyl, and baclofen
II	M	6	Upper limb dystonia and slurred speech	THAP 1, C270_273del (p.glu91ilefs∗28)	96	20	Clonazepam, tryhexyphenidyl, and baclofen
III	M	4.5	Speech developmental delay, anarthria, and lower limb dystonia	KMT2B c.5572dupC; pArg1858Profs ∗ 114	106	22	Valproat, clobazam, ethosuximide, levetiracetam, and petinimid

gene panel revealed a *THAP1*, C270_273del (p.glu91ilefs*28) mutation, the same as in his brother (patient 1). Treatment with trihexyphenidyl, clonazepam, and baclofen was introduced but without clinical significance. The preoperative BFMDRS-M was 96 and the BFMDRS-D was 20 (Table 1).

Case 3

Patient 3, a boy was born after an uneventful pregnancy, with the umbilical cord wrapped around his neck during childbirth. The Apgar score was 9/10 and he was discharged from hospital as a healthy newborn. He started to walk unassisted at the age of 12 months. Pronounced developmental speech delay was significant. At the age of 3, his speech was totally undeveloped and he manifested with anarthria. Motor development except speech was normal until the age of 3.5 years when tremor, chorea, and walking difficulties occurred; his gait became clumsy and ataxic, and he often fell. He could run only backwards with trunk rotation, and manifested occasional jerky arm tremor associated with attention deficit disorder. On exam, thoracic kyphosis, choreoathetoid movements, occasional jerky hand tremor, and coordination disturbances were observed. The patient could not hold extremities in antigravity positions due to muscle weakness. At the time he also manifested with significant speech developmental delay and anarthria. Owing to delayed speech development, EEG was recorded and revealed bilateral multifocal epileptiform discharges. Treatment with antiepileptics, including valproate, clobazam, ethosuximide, levetiracetam and petinimid, was introduced. A brain MRI showed small hypothalamic hamartoma and lipoma, and a conservative approach was suggested. The patient manifested further progressive speech regression, upper limb tremor, bizarre walking patterns, severe hand tremor, and anarthria (Supplementary Video 3). Diagnostic work up except brain MR and EEG was normal (EMNG, VEP and BAER, cerebrospinal fluid, and metabolic analysis), including spinal MRI and brain SPECT. A gene panel for dystonia revealed a pathogenic *de novo* variant in gene *KMT2B* c5572dupC;p.Arg1858Profs*114. The BFMDRS-M was in total 106 and the BFMDRS-D was 22 (Table 1).

All patients underwent bilateral GPi-DBS at the age 7 and 9. After surgical planning using anatomical targeting through preoperative frameless MRI and CT obtained with a mounted

Leksell frame (Electa, Stockholm, Sweden) on patients head the electrodes have been implanted bilaterally in GPi (11). In patient I, Activa RC neurostimulator and model 3389 electrodes (Medtronic) were implanted, whereas in patients II and III, the Vercise rechargeable neurostimulator and directional electrodes (Boston Scientific) were implanted. The stimulation started with the following parameters: for patient I an amplitude of 1.9 V, a frequency of 125 Hz, and a pulse duration of 60 μs, and for patient II and III, an amplitude of 2 mA, a frequency of 130 Hz, and a pulse duration of 60 μs. The pulse amplitude was gradually increased over the 6 months following implantation.

On the first follow up, the first patient's signs improved significantly, enabling the patient to sit independently and to walk with the assistance of one person (Supplementary Video 1). In the weeks and months following the DBS procedure, he regained some manual abilities (he became able to write with moderate difficulty), discrete speech improvement was registered (dysarthria and dysphonia were still present and now bradylalia), mobility (he walked with minimal assistance), and could perform basic self-care tasks with some help (feeding, dressing, etc.). In general, his quality of life improved dramatically. The BFMDRS-M decreased to 64 after GPi DBS, and this persisted after more than 2 years of follow up, while the BFMDRS-D decreased to 8 and persisted (Table 2). However, dysphonia, bradykinesia, bradylalia, fatiguability, and dystonic posturing were still present and mildly increased 2 years after implantation.

Twelve months after DBS implantation, patient II had only mild and occasional upper limb dystonia, a stable gait, was able to run fast, had a stronger voice, and had more fluent and understandable speech (Supplementary Video 2). The BFMDRS-M decreased to 50 after GPi DBS, and this persisted after almost 1 year of follow up, while the BFMDRS-D decreased to 9 and persisted (Table 2).

After DBS implantation, only transitory but very discrete speech improvement occurred in patient III (although it was agrammatic and dysphonic), whose upper limb function and gait improved so he was able to walk unaided (Supplementary Video 3). His dystonia was worsened by specific activities (such as running, walking, chewing, swallowing, writing, and less targeting the objects) and he still had some cognitive and behavioral dysfunctions issues. His follow up EEG showed pronounced and intensive bilateral focal and multifocal discharges. His AEDs were tapered off prior to DBS implantation. He manifested freezing of the

TABLE 2 Outcome after GPi DBS of dystonia patients included in the study.

No.	Age at GPi DBS (years)	Disease duration prior to GPi DBS (years)	Follow up (years, months)	Change in BFMDRS-M, last follow-up compared to baseline	Change in BFMDRS-D, last follow-up compared to baseline	Responder (>25% improvement)	Effect on speech and/or swallowing	Long-term follow-up	DBS parameters at last follow up
I	9	6	2 years, 8 months	115 > 64	28 > 8	✓	✓	Bradykinesia and bradylalia (after 24 months)	GPi L (8+, 9−, 10+) 3.9 mA, 60 µs, 180 Hz GPi R (0+, 1−, 2+) 4.9 mA, 60 µs, 180 Hz
II	7	1	1 year	96 -> 50	20 > 9	✓	✓	No impairment	GPi L (C+, L3-10%, L4-11%, L5-18%, L6-53%, L7-8%) 2.8 mA, 90 µs, 113 Hz GPi R (C+, L1-1%, L4-22%, L5-62%, L6-6%, L7-9%) 3.6 mA, 90 µs, 113 Hz
III	7	2	1 year 11 months	106 -> 67	22 > 12	✓	+/-	Dysphonia (dys/anarthria), swallowing and chewing difficulties, and freezing of the gait impairment (after 15 months)	GPI L (C+, L1-20%, L2 2−22% 3−38%, L3 5−20%) 4.5 mA, 100 µs, 130 Hz GPI R (C+, L1-11%, L2 2−22% L3 5−13%, 6−28%) 4.0 mA, 90 µs, 130 Hz

gait 15 months after DBS and developed anarthria, and again manifested with upper limb dystonia during activity associated with swallowing and bolus clearance difficulties. The BFMDRS-M scale decreased to 58 after GPi DBS. After 6 months, as the progression of dystonia occurred, the BFMDRS-M score increased to 67 but still showed significant improvement, while the BFMDRS-D decreased to 12 (Table 2). During postoperative follow up no complications occurred in any of the presented patients.

Literature review

We did not follow the exact methodology of a systematic review, i.e., we performed a PubMed Search using the terms "KMT2B" or "THAP1" and "dystonia" and "Deep Brain stimulation".

In the period between 2010 and 2022, we identified 10 studies, including 38 patients with DYT-THAP1 who underwent GPi DBS describing significant improvements in both BFMDRS-M and BFMDRS-D (Supplementary Table 1). Furthermore, in the period between 2017 and 2022, we identified 16 studies, including 64 patients with DYT-KMT2B who underwent DBS (Supplementary Table 2). In the vast majority of cases, the lead was implanted in the GPi bilaterally, and STN-DBS was only performed in one patient. Furthermore, during follow-up, significant changes were described in BFMDRS-M and BFMDRS-D, ranging from 20% to more than 95% improvement.

Discussion

We present two siblings with DYT-THAP1 and a child with DYT-KMT2B, all pharmacoresistant with remarkable clinical improvement after GPi-DBS.

DYT-THAP1 is an early-onset initially craniofacial and later typical generalized dystonia with autosomal-dominant inheritance, rostrocaudal progression, and a sex-independent penetrance of 60%, with causative mutations in the THAP1 gene on chromosome 8 (38). The THAP1 gene is part of a family of THAP proteins that bind specific DNA sequences and regulate cell proliferation through pRB/E2F cell cycle target genes, a pathway recently proposed to be involved in cell death in Parkinson's disease (21, 39). The phenotype of patients with DYT-THAP1 is highly variable, with age of onset ranging from 8 to 69 years and the site of onset predominantly cervical, laryngeal, and in the upper limbs, and associated with tremor and signs of parkinsonism in some patients. The involvement of cranial muscles, leading to disabling dysarthria or dysphonia, as was also the case in our patients, is typical for DYT-THAP1 (40).

DYT-KMT2B is a progressive childhood-onset disorder, evolving from a focal to a generalized pattern, either from lower-limb dystonia in the first decade of life, which accounts for up to 10% of cases, or first affecting the laryngopharyngeal region, speech development, and upper limb function, and developing into generalized dystonia in a craniocaudal manner (41). Gene mutations occur de novo, and are usually non-sense mutations,

rather than missense mutations. DYT-*KMT2B* is often associated with endocrinological symptoms, short stature, early onset with a median of 5 years of age, laryngeal dystonia, and onset on lower extremities. Developmental and pronounced delay in speech development, as in our patients, precede dystonia in 30% of patients (25). Further clinical characteristics, such as cognitive disability, psychiatric comorbidities, and dysmorphic features, have been reported in several patients (27–29). Bilateral GPi-DBS has been reported as an efficient therapeutic option, especially for improving movement disorder and regaining independent mobility (5, 22–37). GPi-DBS is sometimes associated with "dramatic" amelioration in gait but more commonly associated with truncal dystonia and scoliosis; it is rarely associated with speech dysfunction in severely affected patients with KMT2B gene mutations prior to DBS (23).

The first-line treatment for multifocal or generalized dystonia is trihexyphenidyl and baclofen, which provide limited and transient improvement in some patients. Intramuscular injections of botulinum toxin A are used mainly for the treatment of focal dystonia (42). L-dopa at low doses (50–200 mg) represents the first-line treatment for dopa-responsive dystonia. AnT empirical trial of L-dopa is usually offered to all patients with early-onset dystonia without evidence of neurodegeneration or brain structural lesions, partly due to a delay in treatment onset and a lack of feasibility of next-generation sequencing and the genetic screening of dystonia (42).

As already mentioned, the results of DBS in children are limited to individual cases or case series, although DBS for childhood dystonia has been proven to be an effective procedure in carefully selected pediatric cohorts. A positive response to treatment has been demonstrated in DYT-*TOR1A* patients after GPi-DBS (43, 44). Several adult and pediatric patients underwent GPi-DBS due to DYT-*THAP1* and DYT-*KMT2B*. Although the number of pediatric patients was lower, the results prove that bilateral GPi-DBS is a valuable therapeutic option for DYT-*THAP1* (8–16) and DYT-*KMT2B,* particularly for movement disorders and regaining mobility, but less so for speech issues (5, 22–37) (Supplementary Tables 1, 2). So far, the aforementioned patients presented with severe dystonic postures, majorly impacting their quality of life, as well as those of their families and caregivers. In the vast majority of patients who underwent bilateral GPi-DBS, a significant improvement was reported in both BFMDRS-M and BFMDRS-D, ranging from 20% to more than 95% during follow-up, from which the longest was 22 years (Supplementary Tables 1, 2). Systematic review and meta-analysis of GPi-DBS for DYT-*KMT2B* with a median follow-up of 12 months reported a 42% improvement in the BFMDRS scale, with better outcomes with more severe dystonia at baseline (24), which is compatible with our results.

Although highly effective in some patients, it is known that the stimulation response can be variable and difficult to predict, emphasizing the need for controlled studies in pediatric cohorts exclusively (7, 19, 20). As presented in the literature, stimulation parameters vary widely among patients; therefore, optimal programming is individual (Supplementary Tables 1, 2).

Furthermore, genetic or acquired causes of dystonia and other movement disorders lead to the development of basal ganglia, thalamus, cortex, dentate cerebellar nucleus, and brain stem lesions

or dysfunction (45). GPi-DBS can affect neuronal activity in functional connections of the cortico-basal ganglia neural network and cause long-term plasticity changes at the cortical level, which can then reestablish normal movement (46, 47). Additionally, beside modulation in neuronal networks, DBS may play an important role in the neurochemical system, e.g., modulating neurotransmitter (dopamine, glutamate, and gamma-aminobutyric acid) release (46, 48). It is known that various genetic etiologies and dystonia pattern respond differently to DBS (49). The best results are achieved in DYT-*THOR1*. DBS efficiency in DYT-*THAP1* has been described as variable but improvement occurs in 50–70% of patients. Early identification of a genetic etiology for dystonia is critical because a correct diagnosis can ensure timely and appropriate treatment, such as DBS, before disability or deformity occurs (6). Impairments after initial improvement could be the result of either associated or induced parkinsonism related to specific gene mutation or induced after DBS implantation (50). Mild parkinsonian signs are an additional manifestation of dystonia arising from basal ganglia dysfunction. In DYT-*KMT2B* patients, decline is progressive after 7–22 years of post DBS implantation assessment (31).

Several studies have investigated the potential predictive factors (i.e., biomarkers) of DBS treatment outcome for early-onset dystonia in pediatric population. It was shown that the age at onset of dystonia, severity, and previous duration of disease and not age at surgery are associated with good treatment response and outcome, while a shorter time between diagnosis and DBS was significant. Although some studies did not show a correlation of preoperative dystonia severity and DBS efficacy, others indicated that a lower preoperative BFMDRS score is related to better treatment efficacy and outcome (20, 47). In addition, DBS treatment outcome is less efficient if speech has been severely affected prior to DBS implantation, if the disease duration is longer, and if disease onset is later; the outcome is also less efficient for complex or combined monogenic dystonia (20, 21). Factors such as age at onset, disease duration, specific gene mutation, dystonia pattern, and severity of preoperative dystonia will definitely be included and discussed in future studies. A better understanding of outcomes in pediatric dystonia is leading to the refinement of the indications for DBS, which continue to evolve (20, 21). Nevertheless, GPi-DBS should be considered in a timely manner once the symptoms cannot be controlled by medications.

Conclusions

Although the number of patients with dystonia, particularly DYT-*THAP1*, treated with GPi-DBS is still small, we believe that DBS should be considered in patients as an early treatment approach in pediatric pharmacoresistant dystonia to prevent more severe symptoms decreasing the quality of life, including emotional and social aspects. Parents should be properly informed about the expected and possibly variable improvement after DBS implantation. Using whole-exome sequencing, it is possible to establish the correct diagnosis early, which can be helpful in determining the appropriate treatment, such as DBS, before disability or deformity occur. Furthermore, we emphasize the

importance of genetic analysis in pediatric dystonia patients, particularly those with monogenic isolated generalized dystonia with normal brain MR, who are possible candidates for DBS treatment, especially because the identification of an underlying molecular defect could significantly help predict the efficacy and functional outcome of DBS. DBS treatment outcome is less efficient if speech has been severely affected prior to DBS implantation and in complex or combined monogenic dystonia.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) and/or minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

DC, NB, and VV contributed equally to the conception and design of the study, investigation, and formal data analysis. NB, MR, VR, and EP organized the data and prepared Supplementary material. NB and DC wrote the first draft of the manuscript. VV, NN, NB, and MR wrote sections of the manuscript.

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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1151900/full#supplementary-material

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