BRIEF REPORT

Bilateral Globus Pallidus Deep Brain Stimulation Improves Motor Function in *ADCY5*-Related Disorder

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ABSTRACT: Background: *ADCY5*-related disorder is characterized by disabling hyperkinetic movement disorders. The therapeutic impact of deep brain stimulation (DBS) has not been systematically evaluated.

Objectives/Methods: This work involved a multicenter cohort study of 8 children with genetically confirmed *ADCY5*-related movement disorders treated with bilateral globus pallidus internus (GPi) DBS.

Results: The mean age at initiation of DBS was 12.9 years (range: 3.5–18). All patients demonstrated improvement in baseline hyperkinesia and paroxysmal exacerbations. Mean Burke–Fahn–Marsden Dystonia Rating Scale motor scores decreased from 50.7 to 22.7 ($p = 0.019$, $d = 1.19$). Functional gains included new or recovered motor milestones, improved speech and swallowing, and resolution of sleep-related dyskinesias. There were no perioperative complications.

Conclusions: GPi-DBS is a safe and effective therapy for *ADCY5*-related movement disorders, offering sustained motor and functional improvement. These findings support earlier consideration of DBS to reduce disease burden, preserve function, and improve long-term outcomes. © 2026 International Parkinson and Movement Disorder Society.

Key Words: childhood-onset movement disorders; deep brain stimulation; dyskinesia; dystonia; genotype–phenotype correlation; hyperkinetic movement disorders; neurogenetics; precision medicine

ADCY5-related movement disorder is a rare autosomal dominant condition caused by pathogenic variants in the *ADCY5* gene, which encodes adenylate cyclase 5—a key enzyme in cyclic adenosine monophosphate

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(cAMP) signaling within the basal ganglia and related networks.[1] Clinically, it encompasses a broad spectrum of hyperkinetic phenotypes ranging from continuous choreiform and dystonic movements to paroxysmal exacerbations.[2] Characteristic features include nocturnal dyskinesias and prominent perioral and facial chorea or myoclonus.[3,4] Symptoms typically emerge in infancy or childhood and fluctuate with stress, illness, or fatigue. Cognitive and developmental involvement is variable, whereas neuroimaging findings are usually normal.[5]

Conventional pharmacologic therapies, such as dopamine agonists, anticholinergics, and benzodiazepines, often provide only limited and transient benefit.[6] Agents targeting cAMP signaling, including caffeine or theophylline, may alleviate symptoms in some cases, but responses are inconsistent and functional impairment frequently persists despite multidrug regimens.[7,8]

Globus pallidus internus deep brain stimulation (GPi-DBS) has emerged as a promising therapeutic approach for pharmacoresistant hyperkinetic movement disorders, including *ADCY5*-related dystonia and chorea, with potential benefit for motor control and quality of life.[9,10] Although several case reports suggest benefit from DBS in *ADCY5*-related disorder, evidence remains limited, and questions regarding patient selection, optimal stimulation parameters, and long-term efficacy persist.[8,11]

Here, we present the outcomes of bilateral GPi-DBS in 8 pediatric patients with genetically confirmed *ADCY5*-related disorder, providing systematic multicenter evidence for this intervention in treatment-refractory hyperkinetic syndromes.

Patients and Methods

This retrospective international, multicenter, observational study included children with genetically confirmed *ADCY5*-related disorder who underwent bilateral GPi-DBS. Collaborating centers were identified through the DBSMatchMaker platform (https://dbsmatchmaker.com/).[12] Participating centers obtained local ethics approval, and participants/legal guardians provided written consent.

Demographic, genetic, and clinical data were collected using a standardized case-report survey developed specifically for *ADCY5*-related disorder. Variables included age at symptom onset, developmental milestones, movement disorder characteristics, comorbidities, and detailed pharmacological history.

Surgical details, stimulation parameters, and adverse events were systematically recorded. Clinical outcomes assessed the effects of GPi-DBS on baseline movement disorder severity, frequency of paroxysmal exacerbations, and sleep-related dyskinesias, as well as psychiatric comorbidities, medication reduction, and changes in Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) scores before and after DBS. Local field potentials (LFP) were recorded during clinical follow-up visits in 2 patients.

BFMDRS-M scores pre- and post-DBS were compared using the Wilcoxon signed-rank test, with effect size calculated as rank-biserial correlation. Statistical significance was set at $p < 0.05$. Analysis included patients with complete paired assessments (n = 7).

Results

Demographic Information

Eight children with *ADCY5*-related disorder were included, with a female predominance (n = 6). Six carried the recurrent *p.Arg418Trp* variant, 1 had *c.2080_2088del*, and 1 harbored a novel *p.Leu370Pro* variant not previously reported (Table S1). Most patients (n = 7) developed symptoms within the first year of life, including 3 before 6 months; 1 patient presented after age 5 years. Motor development varied: 2 patients (2 and 4) never achieved independent mobility, whereas 6 attained ambulation. Speech delay was present in 5 patients, ranging from a few words to age-appropriate speech in 3.

Intellectual disability occurred in 4 patients, and psychiatric comorbidities, mainly anxiety, occurred in 3. Additional neurological features included epilepsy and stuttering (1 patient each) (Table S2). Non-neurological manifestations comprised gastrointestinal, respiratory, or orthopedic complications. Patient 2, previously reported by Dy et al.,[13] is presented here with a 10-year follow-up, and patient 6, originally described by Garofalo et al.[14], includes updated outcomes.

Movement Disorder Spectrum

Initial motor symptoms were heterogeneous, most commonly axial and appendicular hypotonia (n = 6), followed by chorea (n = 2) and focal limb dystonia (n = 1). Over time, all patients developed complex, mixed hyperkinetic movement disorders comprising overlapping chorea, dystonia, and myoclonus. Generalized dystonia was present in 5 patients, focal dystonia in 3, choreoathetosis in 6, and myoclonus in 5. Tics and spasticity each occurred in 1 patient.

Daily paroxysmal exacerbations were universal prior to DBS, typically triggered by emotional stress, fever/infections, or voluntary movements. Sleep-related dyskinesias were reported in 4 patients, 2 experiencing severe nocturnal episodes. All patients received multiple medications (two to seven medications per individual); benzodiazepines were most common (n = 7). Caffeine was tested in 6 patients, providing transient benefit in 2 but precipitating status dystonicus in 1. Medication details and movement disorder characteristics are summarized in Table 1.

TABLE 1 Movement disorders characteristics

ID	Sex	First motor symptom and age at onset	Movement disorders (most disabling symptom in bold font)	Frequency of hyperkinetic exacerbations, trigger	Sleep-associated dyskinesia	Motor milestones achieved	Pharmacotherapy (most effective in bold font)
P1	Female	Limb dystonia, >5 yr	**Generalized dystonia and chorea**	>1 per day	Yes	FS, CR, FW	**Caffeine**, acetazolamide, benzodiazepines, gabapentin, levodopa, tetrabenazine, trihexyphenidyl
P2	Male	Hypotonia, <6 mo	**Chorea**, generalized dystonia, hypotonia, spasticity	>1 per day, evening, stress	Yes, >2 times a day	None	**Eslicarbazepine, trazadone**, benzodiazepines, chloralhydrate, levodopa, phenobarbital, tetrabenazine
P2	Female	Chorea, >1 yr	**Generalized dystonia**, chorea, hypotonia	>1 per day, voluntary movements	No	FS, CR, FW	**Benzodiazepines**, gabapentin
P4	Female	Hypotonia, <1 yr	**Chorea, limb and cervical dystonia**, hypotonia, myoclonus of face and limbs	>1 per day, afternoon, emotions	No	HC	**Benzodiazepine**, caffeine, levocarnitine, trihexyphenidyl
P5	Female	Hypotonia, tremor, <6 mo	**Generalized dystonia, myoclonus of the face and limbs**, hypotonia	6–10, infection, emotions, voluntary movements	No	FS, CR, FW	**Benzodiazepine**, baclofen, botulinum toxin injections, caffeine (inducing status dystonicus), clonidine, levodopa, trihexyphenidyl, zonisamide
P6	Female	Hypotonia, chorea, <1 yr	**Limb dystonia**, dystonia of the face and neck, hypotonia, myoclonus of the face and limbs, chorea	>1 per day, whole day, infection, emotions	Yes, 1 time a day	FS, CR, FW	**Benzodiazepines**, caffeine, gabapentin, theophylline
P7	Male	Hypotonia, <1 yr	**Myoclonus of the limbs**, face, and neck, chorea, generalized dystonia, motor tics	>1 per day, whole day, emotions, voluntary movements	Yes, >2 times a day	FS, CR, FW	**Caffeine**, acetazolamide, baclofen, benzodiazepines, clonidine, tetrabenazine
P8	Female	Hypotonia, <6 mo	**Generalized dystonia**, chorea, myoclonus of the face and limbs	>1 per day, afternoon, evening, emotions, stress	No	FS, CR, FW	**Benzodiazepines, levompepromazin**, acetazolamide, caffeine, clonidine, chloralhydrate

Abbreviations: FS, free sitting; CR, crawling; FW, free walking; HC: head control.

Deep Brain Stimulation

DBS was performed at a mean age of 12.9 years (range: 3.5–18), including one emergency implantation during status dystonicus. All patients received bilateral GPi electrodes without perioperative complications (surgical workflows are summarized in Table S3; confirmation of lead position is shown in Fig. S2). Clinical improvement was universal, with significant reduction in dystonia, choreoathetosis, and paroxysmal exacerbations, including nocturnal dyskinesia. Weight gain occurred in several patients reflecting decreased motor expenditure. Speech improved in patients 3, 5, and 6; swallowing improved in patient 5, and patients 4 to 6 demonstrated better hand function.

Motor skill acquisition and recovery were significant: patient 3 regained assisted ambulation, patient 5 achieved independent sitting, patient 6 attained free walking, and patient 7 recovered independent walking. Representative pre- and post-DBS videos for patients 1, 3, and 4 show these gains (Videos 1–3). Sleep-related dyskinesias improved in 3 of 4 affected patients, with complete resolution in patient 6. Psychiatric symptoms improved in 2 patients, and medication burden decreased in 5.

Stimulation parameters varied across centers: mean pulse width: 93.8 μs (left) and 120 μs (right); frequency: 135.5 Hz (left) and 133 Hz (right); amplitude 2.0 mA (left) and 1.9 mA (right). Patient 6 required high-intensity stimulation (4.2/3.7 mA, 179/159 Hz), whereas 3 patients achieved optimal benefit with low amplitudes (0.5–1 mA). Of those, patient 5 exhibited significant asymmetric stimulation, with a pulse width of 300 μs on the right side and 90 μs on the left. In this case, initial symmetric parameters yielded suboptimal outcomes, whereas progressive asymmetric titration resulted in sustained improvement, which aligned with the baseline clinical asymmetry of symptom severity. All DBS parameters are summarized in Table 2.

Median BFMDRS-M scores improved from 53 (range: 10–96) pre-DBS to 35.5 (range: 4–46.5) post-DBS, indicating a significant reduction in motor symptoms ($p = 0.016$, $r = 0.89$). For descriptive purposes, mean scores decreased from 50.7 to 22.7. Mean BFMDRS-D scores declined modestly from 25 (range: 18–30) to 19.7 (range: 15–30).

Video 1. Patient 1: pre–GPi-DBS (globus pallidus internus deep brain stimulation): at 16 years of age, the patient is wheelchair dependent. At rest, lower-limb chorea is evident, more pronounced on the right. During postural tasks, upper-limb myoclonus emerges, and finger-to-nose testing elicits action-induced dystonia. Post–GPi-DBS: At 18 years, gait assessment with single-person support shows significant improvement. Myoclonus, chorea, and dystonia no longer interfere with ambulation. Transient deactivation of DBS leads to rapid reemergence of generalized dystonia.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.70181

Video 2. Patient 3: pre–GPi-DBS (globus pallidus internus deep brain stimulation): at 16 years, the patient is cachectic and wheelchair dependent, exhibiting generalized dystonia at rest. Post–GPi-DBS: at 18 years, there is clear weight gain and improved motor control, with only mild distal choreiform movements. Gait assessment requires two-person support, limited by residual lower-limb weakness and chorea.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.70181

LFP recordings were obtained during routine clinical follow-up visits using standardized BrainSense Survey acquisitions in patients 1 and 3. Patient 1 underwent recordings at 24 and 27 months after GPi-DBS implantation, and patient 3 at 1 and 4 months postimplantation. In all sessions, LFPs were collected in the resting state, with stimulation ON, and exclusively using survey-mode acquisitions. Across all time points, prominent β-band (13–30 Hz) activity was observed bilaterally across multiple contacts in both patients (Fig. S1).

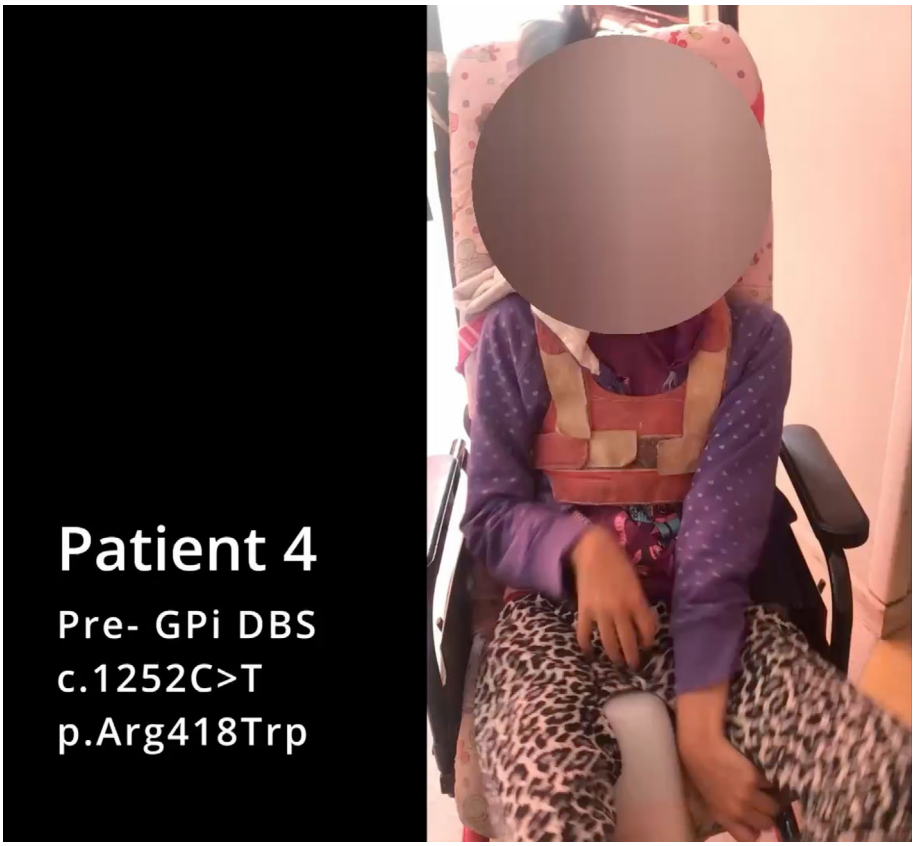
Discussion

This study presents the largest pediatric cohort of *ADCY5*-related disorder treated with bilateral GPi-DBS, expanding upon the 15 previously published cases across all ages.[11,14–18] *ADCY5*-related movement disorder is a rare but disabling hyperkinetic syndrome that profoundly impairs daily function and night sleep, and may lead to failure to thrive or progressive weight loss from continuous involuntary movements.[19]

Conventional pharmacologic therapy is often ineffective despite extensive polypharmacy. Although caffeine and theophylline can provide transient benefit in some,[7,20] responses are inconsistent and functional limitations usually persist. In this cohort, none achieved meaningful improvement with medications alone, underscoring the need for alternative therapies such as DBS.

DBS has been used sparingly in *ADCY5*-related disorder, often as a last-resort intervention or for status dystonicus.[17] Consistent with previous reports,[15,13] all patients in our cohort demonstrated improvement in hyperkinetic exacerbations and sleep-related dyskinesias. Chronic baseline dystonia also improved, reflected by significant reductions in BFMDRS-M scores comparable to earlier pediatric studies.[9] These motor benefits translated into tangible functional gains, including improved truncal control, hand use, and ambulation. That the BFMDRS-D nevertheless showed no major improvement is likely due to its limited sensitivity to focal changes in complex movement disorders.

Particularly, 3 patients exhibited improved speech and swallowing, suggesting a broader therapeutic range of GPi-DBS than previously recognized.[21] Similar



Video 3. Patient 4: pre–GPi-DBS (globus pallidus internus deep brain stimulation): at 13 years, the patient is wheelchair dependent, showing generalized chorea that intensifies during assisted standing. Post–GPi-DBS: at 15 years, there is substantial improvement, with only mild, intermittent chorea of the upper and lower limbs.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.70181

findings in earlier reports[15,13] indicate that bulbar function may represent an additional treatment target in *ADCY5*-related disorder.

Evaluation of DBS efficacy in *ADCY5*-related disorder remains limited due to the paroxysmal character of the movement disorder and the lack of standardized rating scales for chorea. Although the BFMDRS provides objective scoring, it incompletely captures the mixed hyperkinetic phenotype. Future studies integrating wearable motion sensors and patient-reported outcomes may yield more comprehensive assessments[22].

Patient selection is crucial. Individuals with profound developmental impairment or minimal voluntary movement may experience stability with DBS rather than substantial functional recovery, as illustrated by patient 2. Nonetheless, this patient exhibited durable suppression of hyperkinesia, with symptom recurrence upon brief deactivation—demonstrating sustained stimulation benefit consistent with long-term outcomes in prior studies[15].

Due to the accumulating evidence and a favorable safety profile, GPi-DBS should be considered earlier in the disease course to enhance daily function and quality of life, and to prevent fixed contractures or severe disability. Earlier intervention may capitalize on neuroplasticity, as observed in other pediatric dystonias,[23,24] and mitigates the long-term risks of polypharmacy.

Stimulation parameters varied, but several patients achieved robust benefit at low amplitudes (0.5–1.0 mA), suggesting heightened pallidal circuit sensitivity in *ADCY5*-related disorder. Rapid symptom recurrence after short deactivation in most patients underscores this responsiveness (Video 1).

LFP recordings from 2 patients revealed prominent β-band (13–30 Hz) oscillations, typically considered a hallmark of parkinsonian syndromes, which could play a role in the pathophysiology of *ADCY5*-related dyskinesias. If a larger cohort is validated, this observation could influence our understanding of network dynamics in this disorder and potentially impact neuromodulation strategies for symptomatic relief.

Experience with GPi-DBS in childhood-onset genetic movement disorders is expanding, historically anchored by successful outcomes in DYT-*TOR1A* dystonia.[25] Results in *ADCY5*-related disease parallel those in *KMT2B*-associated dystonia.[26] Unlike ***GNAO1***-related disorder, where DBS is often lifesaving during status dystonicus,[27] *ADCY5*-related disorder typically allows

TABLE 2 Deep brain stimulation characteristics

ID	Age at implantation	Follow-up duration	Effects on movement disorder	Other effects	Effect after long-term follow-up DBS (>1 yr)	Most effective DBS settings	BFMDRS-M pre-DBS (0–120)	BFMDRS-M post-DBS (0–120)	BFMDRS-D pre-DBS (0–30)	BFMDRS-D post-DBS (0–30)
P1	16 yr	3 yr 3 mo	Chorea reduced, exacerbations reduced, sleep-associated dyskinesia improved	Sleep improved	Continued improvement	L: 90 μs, 130 Hz, 1.0 mA; R: 90 μs, 130 Hz, 0.5 mA	12.5	6.6	26	24
P2	3 yr 6 mo	10 yr 3 mo	Chorea reduced		Unchanged	L/R: 190 μs, 140 Hz, 2.1 V	10	4	30	30
P3	18 yr	2 yr	Chorea reduced, restored assisted walking, speech improved		n.a.	L/R: 60 μs, 125 Hz, 0.9 mA	28	7	27	25
P4	15 yr 4 mo	2 yr 4 mo	Dystonia in limbs and neck improved, chorea reduced	Medication burden reduced	n.a.	L/R: 60 μs, 130 Hz, 2.5 mA	85	26.5	27	23
P5	15 yr 3 mo	2 yr	Dystonia improved, rare action myoclonus of the limbs and face improved, tremor reduced, reduced exacerbations, speech and swallowing improved, started sitting independently	Medication burden reduced, anxiety improved	n.a.	L: 90 μs, 130 Hz, 0.5 mA R: 300 μs, 130 Hz, 0.5 mA	70.5	46.5	22	15
P6	6 yr 8 mo	5 yr 10 mo	Dystonia improved, reduced exacerbations, sleep-associated dyskinesia improved, speech hand function improved, started free walking	Medication burden reduced	Continued improvement	L: 60 μs, 179 Hz, 4.2 mA; R: 60 μs, 159 Hz, 3.7 mA	96	33	n.a.	n.a.
P7	11 yr 9 mo	4 yr 7 mo	Dystonia improved, myoclonus of the face and limbs improved, restored free walking, sleep-associated dyskinesia improved	Medication burden reduced, behavioral disorder improved	Continued improvement	L/R: 110 μs, 130 Hz, 2.5 mA	Status dystonicus	20	Status dystonicus	6
P8	16 yr 6 mo	2 yr 7 mo	Dystonia improved, reduced exacerbations	Medication burden reduced, anxiety improved	n.a.	L/R: 90 μs, 120 Hz, 3.0 mA	53	35.5	18	15

Abbreviations: DBS, deep brain stimulation; BFMDRS, Burke–Fahn–Marsden Dystonia Rating Scale.

for elective implantation, offering a safer therapeutic window.

Future research should explore pallidal network topology, connectivity, and alternative targets[28] to optimize neuromodulation strategies. Limitations of this study include its retrospective design, variable follow-up, and heterogeneity in disease severity. Nonetheless, consistent benefit across international centers supports the robustness of these findings.

In summary, bilateral GPi-DBS is a safe and effective treatment for *ADCY5*-related disorder, resulting in sustained reduction in hyperkinetic movement disorders and meaningful functional improvement. Early intervention may preserve motor abilities and improve long-term outcomes. Prospective multicenter studies using standardized, multimodal assessments are warranted to refine patient selection and DBS timing in this rare disorder. ■

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Partnerships, none. Inventions, none. Contracts, none. Honoraria, none. Royalties, none. Patents, none. Grants, none. Other, none. **D.E.-F.:** stock ownership in medically related fields, none. Intellectual property rights, none. Consultancies, Guidepoint LLC, Kramon & Graham, and Blackfin Bio Inc. Expert testimony, none. Advisory boards, scientific advisory board (unpaid): the Lilly & Blair Foundation, Genetic Cures for Kids Inc., Dystonia Medical Research Foundation, and ADCY5 Foundation. Employment, Boston Children's Hospital. Partnerships, none. Inventions, none. Contracts, joint research agreement/clinical trials: Astellas Pharma Inc., Neurocrine Inc., and Blackfin Bio Inc. Honoraria, speaker honoraria from the Movement Disorders Society. Royalties, Cambridge University Press. Patents, PCT/US2024/029856. 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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

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