# Outcomes of Bilateral Globus Pallidus Internus Deep Brain Stimulation in *GNAO1*-Related Disorder: An International Multicenter Experience

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**Objective:** *GNAO1*-related disorder is a severe childhood-onset hyperkinetic movement disorder punctuated by life-threatening dyskinetic crises. Small series suggest benefit from bilateral globus pallidus internus deep brain stimulation (GPi-DBS), but optimal timing, patient selection, long-term outcomes, and genotype-specific response remain unclear. We define the clinical impact of GPi-DBS in the largest cohort assembled to date.
**Methods:** Retrospective multicenter cohort study conducted through the DBSMatchMaker platform, including children and young adults with genetically confirmed *GNAO1*-related disorder treated with bilateral GPi-DBS across 17 centers. The primary outcome was change in dyskinetic crisis burden; secondary outcomes included BFMDRS, Clinical Global Impression (CGI), functional classifications, medication burden, and complications.
**Results:** Forty-six patients underwent implantation at a mean age of $10.4 \pm 4.8$ years with mean follow-up of $4.5 \pm 3.7$ years (longest = 17 years). Over half (52.2%) were implanted emergently during dyskinetic status. Dyskinetic crises were reduced in 38 of 40 patients (95%) and intensive care unit (ICU) admissions in 86.1%. The Burke Fahn Marsden Dystonia Rating Scale (BFMDRS) motor scores improved by 27.5% ($p < 0.001$, Cohen's $d = 1.12$); CGI was improved in 93.5%, with greater benefit for chorea than dystonia. Pain, sleep, and medication burden improved; functional classification was largely unchanged. Complications occurred in 19.6%, predominantly in emergent cases.
**Interpretation:** Bilateral GPi-DBS was associated with sustained prevention of dyskinetic crises and reduction of overall disease burden in *GNAO1*-related disorder, with limited impact on functional classification. These findings support earlier elective neuromodulation before recurrent crises drive cumulative morbidity and identify GPi-DBS as a crisis-preventive, symptom-modifying intervention rather than a restorative one.

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*GNAO1*-related disorder encompasses a wide clinical spectrum covering the core features of hyperkinetic movement disorders, epilepsy, developmental delay, and intellectual disability.[1,2] *GNAO1* encodes the α-subunit of the heterotrimeric G protein Gαo, a regulator of inhibitory G protein-coupled receptor signaling within striatal medium spiny neurons. Through modulation of dopaminergic and cyclic adenosine monophosphate (cAMP) pathways, Gαo plays a central role in basal ganglia circuit function.[3] Disruption of this signaling cascade is thought to destabilize striatopallidal network activity, leading to abnormal motor output and recurrent dyskinetic crises.[4] These circuit abnormalities provide a rationale for targeting pallidal output using globus pallidus internus deep brain stimulation (GPi-DBS).

Since its first description in 2013, the clinical spectrum has expanded from developmental and epileptic encephalopathy 17 (DEE17; Online Mendelian Inheritance in Man [OMIM] #615473) and neurodevelopmental disorder with involuntary movements (NEDIM; OMIM #617493) to include milder phenotypes with late-onset dystonia and variable degrees of intellectual disability.[5–8] Hyperkinetic movements typically emerge in early childhood and usually consist of generalized dystonia and chorea on a background of severe axial hypotonia and weakness.[9,10] A defining feature is the occurrence of dyskinetic crises, which may be spontaneous or triggered by infection, pain, or emotional stress and can escalate to life-threatening status dystonicus requiring intensive care.[11]

Conventional pharmacologic therapies, including dopamine-depleting agents, anticholinergics, and benzodiazepines, usually only provide partial benefit, even in the setting of extensive polypharmacy.[12,13] Dyskinetic crises often necessitate prolonged sedation, mechanical ventilation, and repeated hospitalizations, contributing to substantial cumulative morbidity and mortality.[14,15]

GPi-DBS has emerged as a promising therapeutic approach for pharmacoresistant *GNAO1*-related disorder, including chronic refractory dystonia and acute dyskinetic crises.[16–18] Case reports and small series describe meaningful motor improvement and quality-of-life benefits,[19–21] and the largest cross-sectional analysis to date (28 patients) reported significant improvement on the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) and resolution of dyskinetic crises.[22] However, critical questions remain regarding optimal timing of intervention, long-term benefit, predictors of response, genotype-specific trajectories, and the role of elective versus emergency implantation.

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Here, we report outcomes of bilateral GPi-DBS in 46 children and young adults with *GNAO1*-related disorder, representing the largest cohort assembled to date. We find that GPi-DBS primarily reduces dyskinetic crises and motor symptom burden while exerting more limited effects on functional outcomes. By integrating long-term follow-up with multidimensional clinical measures, this study defines the role of pallidal neuromodulation in *GNAO1*-related disorder.

## Methods

### Study Design

This multicenter observational study included children and young adults with genetically confirmed *GNAO1*-related disorder who underwent bilateral GPi-DBS. Participating centers were identified through the DBSMatchMaker platform (https://dbsmatchmaker.com/).[23] No untreated comparator cohort was included. Each center obtained institutional ethics approval in accordance with the Declaration of Helsinki, and written informed consent was obtained from the patients or their legal guardians according to local regulations.

### Data Collection

Demographic, genetic, and clinical data were collected using a standardized case-report form developed for *GNAO1*-related disorders. Variables included demographic information, genotype, age at symptom onset, developmental milestones, movement disorders, comorbidities, and medication history.

Dyskinetic crises were defined as acute, severe, and sustained exacerbations of dystonia and chorea requiring hospital admission and/or intensive care management. For each patient, we recorded age at first crisis, total number of hospitalizations, number of intensive care admissions, and timing of DBS implantation relative to crises.

Surgical data included age at implantation, emergent versus elective procedure, lead targeting strategy, stimulation parameters, and perioperative complications. Complications were categorized as hardware-related, surgical, or neurological. Surgical targeting and postoperative programming were not standardized and reflected routine practice at each center. Emergent DBS implantation was defined as surgery performed during dyskinetic crisis or status requiring intensive medical management; elective procedures were performed in clinically stable patients.

Clinical outcomes included motor severity, dyskinetic crises burden, hospitalization and intensive care utilization, medication requirements, and functional status. Motor severity was evaluated using the BFMDRS (motor and disability subscales). Global disease burden was assessed using the GNAO1 Severity Score. Functional abilities were classified using Gross Motor Function Classification System-like (GMFCS-like) and Manual Ability Classification System-like (MACS-like) scales. When longitudinal data were available, pre- and post-DBS scores were compared using the most recent follow-up assessment.

The primary outcome was change in dyskinetic crises burden after GPi-DBS, assessed by crisis frequency, hospitalizations, and intensive care admissions. Secondary outcomes included changes in motor severity (BFMDRS), clinical global impression improvement (CGI) scale, functional classification scales (GMFCS-like and MACS-like), overall disease severity score, medication requirements, and long-term clinical trajectory. CGI ratings were assigned by treating clinicians based on longitudinal clinical assessment and caregiver report, reflecting routine clinical assessment rather than blinded evaluation.

### Statistical Analysis

Normality of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed variables are presented as mean ± standard deviation and non-normally distributed variables as median with interquartile range. Pre- and post-DBS BFMDRS motor scores were compared using paired $t$ tests with Cohen's d effect size. Wilcoxon signed-rank tests were used for BFMDRS disability, GMFCS-like, MACS-like, and GNAO1 Severity Score comparisons. Two-tailed $p < 0.05$ was considered statistically significant. Missing data were handled using available-case analysis. Analyses were performed using SPSS Statistics version 29.0 (IBM Corp., Armonk, NY).

Because several participating centers contributed small patient numbers, adjustment for center-level clustering or mixed-effects modeling was not performed, and analyses were conducted at the overall cohort level. Accordingly, statistical findings should be interpreted as hypothesis-generating rather than confirmatory. Considering the multidimensional clinical outcomes evaluated, emphasis was placed on magnitude and clinical relevance of change in addition to statistical significance.

## Results

### Cohort Characteristics

Forty-six patients were included, of whom 26 (56.5%) were previously unpublished cases with no prior data on DBS. The cohort comprised 25 female patients (54.3%) and 21 male patients (45.7%). Symptom onset ranged from early infancy to early childhood (mean = 0.8 ± 1.2 years, range = 0–7). Mean age at last follow-up was 15.4 ± 6.2 years (range = 3.2–32).

Twenty-one unique *GNAO1* variants were identified. The most frequent were c.625C>T;(p.R209C) (n = 11, 23.9%), c.607G>A;(p.G203R) (n = 7, 15.2%), and c.709G>A;(p.E237K) (n = 5, 10.9%) with additional

recurrent variants including c.626G>A;(p.R209H), c.736G>A;(p.E246K) (each n = 3, 6.5%), and c.626G>T;(p.R209L) (n = 2, 4.3%). The remaining variants (n = 15) were predominantly missense changes. Two patients harbored a splicing variant (c.724-8G>A).

Early developmental impairment was near universal. Gross motor delay occurred in 45 patients (97.8%), with only 7 (15.2%) achieving independent ambulation. Speech delay was present in 44 patients (95.7%); at last follow-up, 34 patients (73.9%) were nonverbal, and 8 patients (17.4%) produced single words. Failure to thrive affected 33 patients (71.7%) and gastrostomy feeding was required in 30 patients (65.2%). Axial hypotonia was documented in 43 patients (93.5%), epilepsy in 20 patients (43.5%) including drug-resistant epilepsy in 5 patients (10.9%), and sleep disturbance in 28 patients (60.9%; Supplementary Table S1).

### Movement Disorders

Dystonia was universal and generalized. Limb involvement occurred in >90% of patients (upper limbs 43, 93.5% and lower limbs 44, 95.7%), axial dystonia in 40 patients (87%), and orofacial or cervical involvement in 41 patients (89%). Bulbar dysfunction causing dysarthria or dysphagia was present in 40 patients (87%). Chorea occurred in 41 patients (87%) and was typically generalized. Less common features included parkinsonism (n = 5, 10.9%), myoclonus (n = 3, 6.5%), lower limb spasticity (n = 2, 4.3%), motor stereotypies (n = 1, 2.2%), oculogyric crises (n = 5, 10.9%), and paroxysmal tonic upgaze (n = 3, 6.5%).

Dyskinetic crises occurred in 40 patients (87%), with a mean age at first crisis of 6.5 ± 4.2 years (range = 0–13.5). Hospitalization burden was substantial with recurrent admissions in most patients. Polypharmacy was common, with 35 patients (76.1%) receiving 3 or more medications for movement disorders. Frequently used agents included benzodiazepines (69.6%), gabapentin (52.2%), clonidine (50.0%), tetrabenazine (45.7%), trihexyphenidyl (37.0%), chloral hydrate (34.8%), and baclofen (34.8%; see Supplementary Table S1).

### Deep Brain Stimulation

All patients underwent bilateral GPi-DBS. Mean age at surgery was 10.4 ± 4.8 years (range = 2.7–23.1). DBS was performed emergently during dyskinetic crises in 24 cases (52.2%), including 6 during their first crisis.

Postoperative complications occurred in 9 patients (19.6%), 6 of whom had been implanted during a dyskinetic crisis. Complications included hardware infection requiring removal and reimplantation (n = 1), lead migration requiring repositioning (n = 2), wound complications (n = 2), asymptomatic intracranial hemorrhage (n = 2), and perioperative exacerbation of the movement disorder during staged surgery requiring intensive care (n = 1). One patient required system removal due to recurrent infection, eventually followed by pallidotomy.

Stimulation parameters varied (Supplementary Table S2). For current-controlled stimulation (n = 29), median amplitude was 2.7 mA bilaterally (interquartile range [IQR] = 2.1–3.5). For voltage-controlled stimulation (n = 16), median amplitude was 2.4 volts (V; IQR = 1.8–2.8) on the left and 2.0 V (IQR = 1.4–2.8) on the right. Median frequency was 130 hertz (Hz) bilaterally (IQR = 130–159 Hz, range = 90–205 Hz). Median pulse width was 110 μs (IQR = 60–130) on the left and 90 μs (IQR = 70–130) on the right. One patient required high-intensity stimulation (6.0/6.2 mA; 180/180 Hz; 420/420 μs), whereas several patients achieved optimal benefit with low amplitudes (0.3–1.0 mA or 0.7–1.0 V).

### Subjective Clinician-Rated Outcomes

Clinical outcomes are summarized according to predefined primary and secondary measures. CGI ratings indicated "very much improved" in 22 patients (47.8%) and "much improved" in 21 patients (45.7%). Representative pre- and post-DBS videos from 9 patients are provided in the Supplementary Videos S1 to S9.

Overall improvement rates were similar for dystonia (93.5%, 43/46) and chorea (95.1%, 39/41). However, improvement classified as "very much improved" or "much improved" according to CGI ratings was more frequent for chorea (87.8%, 36/41) than dystonia (67.4%, 31/46). Myoclonus improved in 1 of 3 patients.

Among patients with baseline dyskinetic crises (n = 40), crisis frequency was reduced in 38 patients (95%). In patients who experienced post-intervention dyskinetic crises, these occurred in the context of significant triggers, such as major hip surgery or following device deactivation. Hospital admissions declined in 35 of 39 patients (89.7%) and intensive care admissions in 31 of 36 (86.1%). Improvements in ambulation were observed in 10 patients (21.7%) and hand function in 15 patients (32.6%), although MACS-like scores did not significantly change. Additional reported benefits included reduced discomfort or pain (84.8%), weight gain (71.7%), improved sleep (58.7%), and improved communication (28.3%). Importantly, medication burden following GPi-DBS was reduced in the majority of patients (60.9%; Fig 1).

### Objective Motor and Functional Outcome Measures

BFMDRS-motor scores improved significantly following DBS (pre-DBS 82.7 ± 24.6 vs post-DBS 59.9 ± 21.6; mean reduction 22.7 points; $p < 0.001$; Cohen's

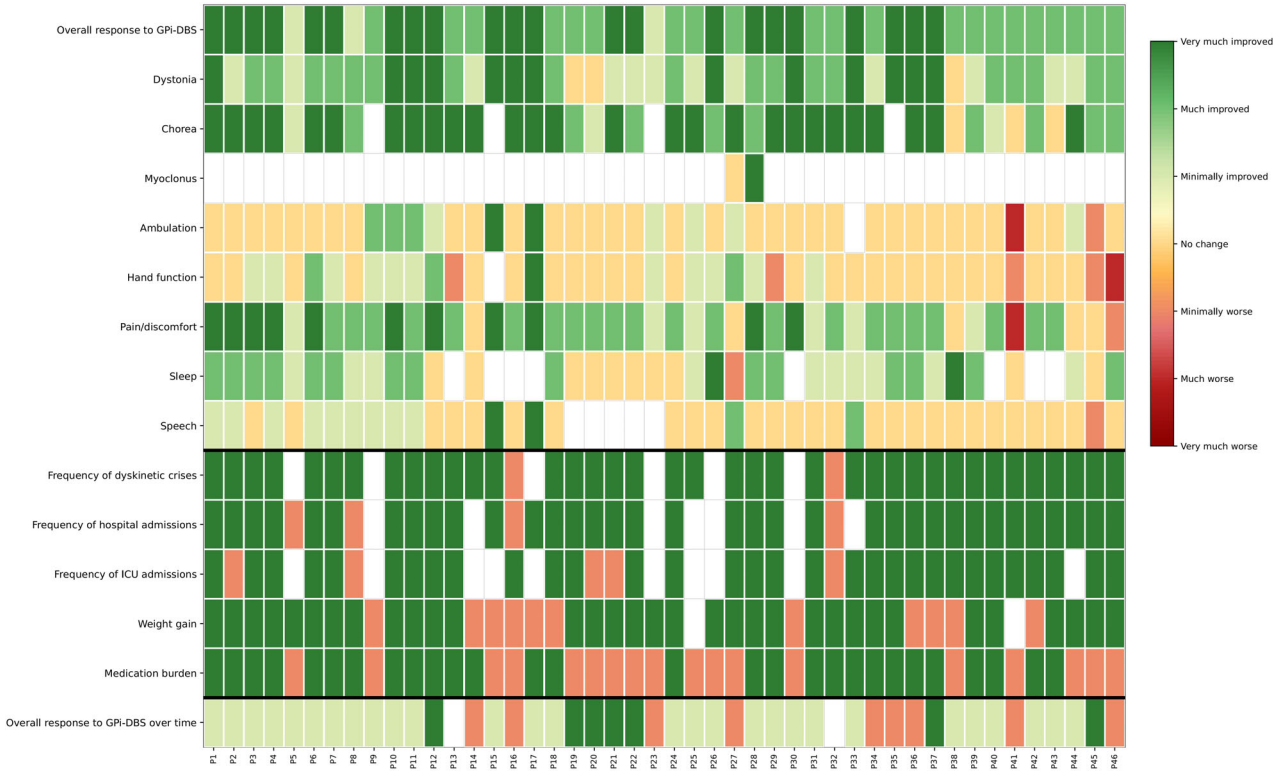


**FIGURE 1: Multi-dimensional DBS outcomes across 46 patients with *GNAO1*-related disorder. Each column represents an individual patient (Pt 1–Pt 46), each row an outcome domain. DBS = deep brain stimulation.**

d = 1.12), representing a 27.5% reduction in severity (Fig 2A). In contrast, BFMDRS-disability scores did not significantly change (median 29.5 vs 29.0; $p = 0.447$). Among patients with available data (n = 24), 13 remained stable and 6 improved.

GMFCS-like and MACS-like scores remained largely unchanged following DBS. At baseline, most patients were classified at GMFCS-like levels IV to V (40/46, 87.0%). After DBS, 5 patients (11.1%) improved and 35 (77.8%) remained unchanged (n = 45; Wilcoxon Z = 0.000, $p = 1.000$). Similarly, baseline MACS-like scores were predominantly severe (levels IV–V in 39/46, 84.8%); post-DBS, 4 patients (8.9%) improved and 34 (75.6%) remained unchanged (n = 45; Wilcoxon Z = −0.800, $p = 0.366$).

GNAO1 Severity Score data were available for 11 patients. No significant change was observed following DBS (pre-DBS median = 9.0 [Q1-Q3: 7.9-9.9]; post-DBS median: 6.8 [Q1-Q3: 5.3-10.5]; Wilcoxon Z = −1.070, $p = 0.321$), although 6 patients (54.5%) showed improvement.

### *Temporal Characteristics*

The mean time from symptom onset to DBS implantation was 9.54 ± 4.50 years (median = 9 years, 95% confidence interval [CI] = 8.19–10.89, range = 2.17–22.66 years, N = 45), exceeding 15 years in 5 patients. From the first medical documentation of dyskinetic status to DBS implantation, the mean interval was 3.90 ± 3.82 years (median = 2.50 years, 95% CI = 2.63–5.17, range = 0.00–13.60 years, N = 37). No formal analysis was performed to evaluate the association between timing of DBS implantation and clinical outcome. The mean post-DBS follow-up duration was 4.53 ± 3.66 years (median = 3.87 years, 95% CI = 3.38–5.67, range = 0.00–17.00 years, N = 42), with the longest follow-up extending to 17 years (Fig 2B).

### *Long-Term Follow-Up and Mortality*

DBS outcomes remained stable in 28 patients (60.9%) with sustained reduction of dyskinetic crises. Seven patients (15.2%) showed further improvement, whereas 9 patients (19.6%) worsened over time (Figure 1; Supplementary Table S3a). Many patients demonstrated marked stimulation dependence, with brief device deactivation resulting in rapid recurrence of chorea or dystonia (Supplementary Videos S8 and S9).

One patient with over 10 years of follow-up developed stimulation-induced parkinsonism that resolved after frequency reduction. In some patients, complex medical comorbidities ultimately limited DBS benefit.

Eight patients (17.4%) had died at the time of data collection. Only one death was directly attributable to recurrent dyskinetic status, occurring 4 years after DBS

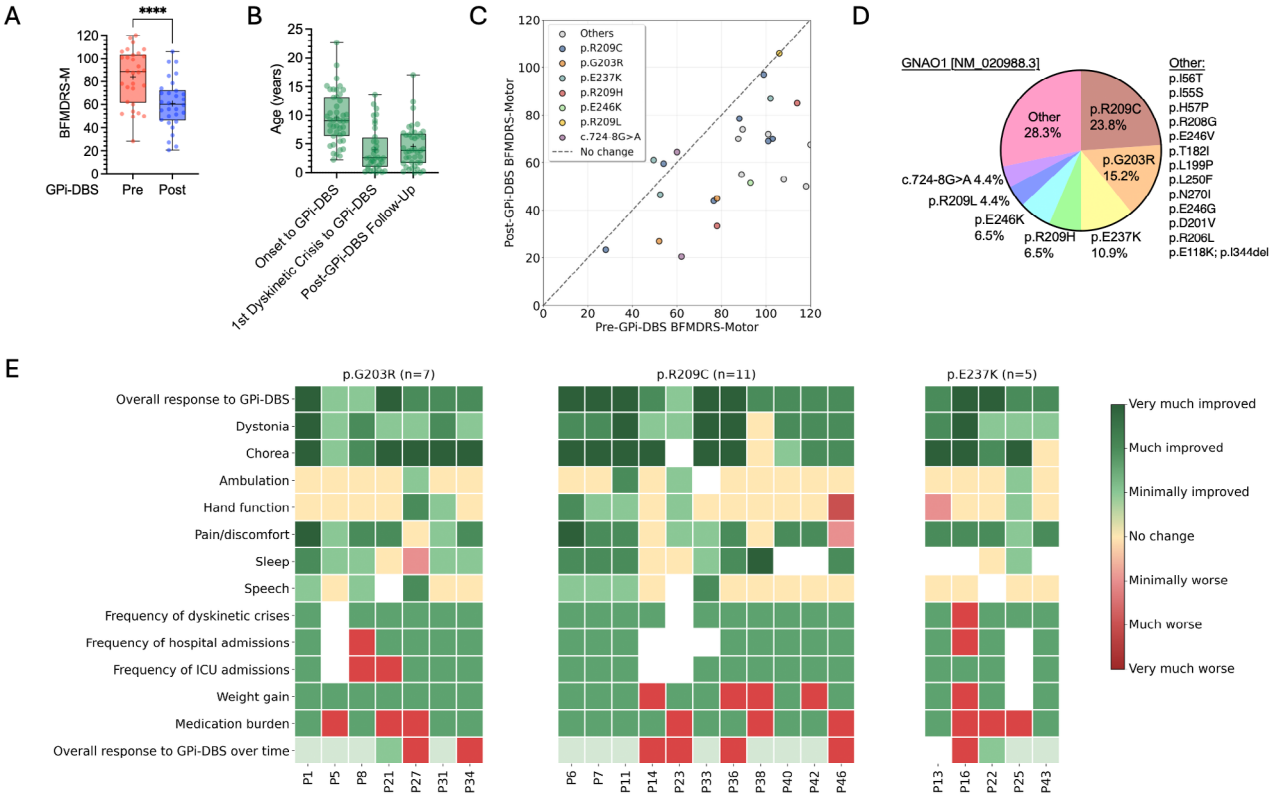


**FIGURE 2: Clinical characteristics and DBS outcomes. (A) BFMDRS–motor scores before and after DBS. (B) Temporal characteristics of the cohort. (C) Scatter plot of individual pre- versus post-DBS BFMDRS-M scores, color-coded by variant. Each dot represents one patient. Points below the diagonal dashed line (no change reference) indicate improvement; points above indicate worsening. (D) Distribution of *GNAO1* variants across the cohort. (E) Variant-specific multidimensional DBS outcome heatmaps for the three most frequent variants: p.G203R, p.R209C, and p.E237K. BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale; DBS = deep brain stimulation.**

implantation. Other causes included respiratory infection (n = 3), sepsis with multiorgan failure (n = 3), and sudden unexpected death (n = 1; Supplementary Table S3b).

### *Genotype–Phenotype Correlations*

Given the marked genetic heterogeneity (21 unique variants), genotype–outcome analyses were exploratory. The 3 most frequent variants (p.R209C, p.G203R, and p.E237K; 50% of the cohort) showed broadly similar DBS responses with substantial improvement in dystonia and chorea and marked reduction in dyskinetic crises (Fig 2C–E). Long-term trajectories differed somewhat: worsening occurred in 42.9% of patients with p.G203R, compared with 27.3% for p.R209C and 20% for p.E237K. The only death attributable to a refractory dyskinetic crisis occurred in a patient with p.E237K. A subgroup of 5 patients (10.9%), including 2 who carried the splice variant c.724-8G>A, had milder motor phenotypes (GMFCS-like I–II and MACS-like I–II) with independent ambulation and no epilepsy or gastrostomy dependence (see Supplementary Table S1). Three experienced dyskinetic crises. DBS improved chorea and dystonia and prevented further crises in all, with minimal change in functional classification.

## Discussion

This study represents the largest cohort of patients with *GNAO1*-related disorder treated with bilateral GPi-DBS to date. Across different centers, pallidal neuromodulation was associated with substantial and sustained reduction of dyskinetic crises and health care utilization, which constituted the predefined primary outcome of this study. However, given the observational design and absence of a non-DBS comparator group, these findings should be interpreted as demonstrating association rather than definitive disease modification.

More than half of the patients underwent implantation emergently during dyskinetic status, often under clinically unstable conditions. The mean interval of approximately 4 years between the first documented dyskinetic crisis and DBS implantation reflects prolonged exposure to recurrent life-threatening exacerbations, repeated hospitalizations, and cumulative morbidity.

These findings suggest that, in the past, DBS has generally been reserved for rescue situations rather than earlier in the disease course. Our results support consideration of earlier referral and elective implantation once dyskinetic crises emerge, particularly in genotypes associated with severe phenotypes (p.R209C, p.R209H, p.E246K, and p.E237K) where the medication burden and risk of catastrophic decompensation appears highest.[7,24]

These observations should be interpreted within the broader natural history of *GNAO1*-related disorder, which is characterized by recurrent dyskinetic crises, repeated intensive care admissions, and substantial mortality related to respiratory complications or dyskinetic status.[9–11,25] The marked reduction in crisis burden observed after DBS suggests an important role for pallidal neuromodulation in mitigating the most life-threatening manifestations of the disorder.

BFMDRS-motor scores improved significantly following DBS, consistent with prior reports.[22] The magnitude of improvement was somewhat lower than in earlier series, possibly reflecting inclusion of more severely affected individuals. It should be cautioned that available scales incompletely capture clinically meaningful change in complex pediatric movement disorders.[26] In particular, the absence of a validated pediatric chorea scale limits assessment of hyperkinetic disorders, such as *GNAO1*-related disease. Similar limitations have been noted in other monogenic movement disorders, including *ADCY5*-related disorders.[27]

CGI scores suggest broader benefits beyond motor scores, including reductions in pain, improved sleep, weight gain, and decreased medication burden – domains consistently prioritized by caregivers.[28] Notably, functional classification scales (GMFCS-like and MACS-like) remained largely unchanged. This motor-functional dissociation may represent the profound and static neurodevelopmental impairment characteristic of this population, including intellectual disability, axial weakness/hypotonia, and comorbid epilepsy. For many families, prevention of dyskinetic crises and improvement in comfort represent the primary therapeutic goals rather than restoration of independent function.

Long-term trajectories warrant particular attention. Approximately one-fifth of patients experienced clinical worsening despite continued stimulation, which may reflect disease progression, evolving comorbidities, or stimulation-related factors. Prior meta-analysis suggested that longer follow-up may correlate with attenuated motor improvement[22]; our findings partially align with this observation but also demonstrate sustained crisis prevention in the majority. Brief interruption of stimulation was followed by rapid recurrence of dystonia and chorea.

From a circuit perspective, *GNAO1* encodes the Gαo subunit, a critical regulator of inhibitory GPCR signaling within striatal medium spiny neurons. Disruption of dopaminergic-cAMP modulation likely destabilizes striato-pallidal network activity, resulting in aberrant pallidal output and thalamocortical disinhibition. The robust response to GPi-DBS observed here is consistent with the hypothesis that pathological activity within the internal pallidum represents a final common pathway for dyskinetic crisis generation.

Genotype-informed analyses remain exploratory given heterogeneity; nevertheless, the 3 most frequent variants showed broadly consistent crisis reduction. Differences in long-term clinical trajectories were observed among genotype groups (p.G203R, p.R209C, and p.E237K carriers). The sole death attributable to refractory dyskinetic crisis occurred in a p.E237K carrier, suggesting that even with DBS, extreme phenotypes may retain vulnerability. As datasets expand, genotype-informed risk stratification may refine patient selection and surgical timing.

A small subgroup of patients (5/46, 10.9%) with relatively mild motor phenotypes demonstrated preserved ambulation and independence despite the presence of hyperkinesia. In these individuals, DBS improved chorea and dystonia and prevented dyskinetic crises, but functional scales changed minimally, suggesting a ceiling effect once baseline motor abilities are relatively preserved. Two of these patients carried the splice variant c.724-8G>A, previously associated with milder or later-onset phenotypes, raising the possibility that specific variants may define distinct clinical trajectories. This has implications for counseling and anticipatory guidance.

From a surgical standpoint, complication rates were comparable to other pediatric dystonia cohorts.[22,29] The occurrence of dyskinetic status between staged procedures in one patient highlights the vulnerability of this population to surgical stress and supports single-stage implantation where feasible (Supplementary Table 3c). Future studies may benefit from physiology-guided targeting strategies and emerging biomarkers of basal ganglia network activity that could enable more individualized neuromodulation approaches.[30,31]

Several limitations should be considered. The cohort is subject to referral bias, as participating centers identified patients considered suitable candidates for neuromodulation, potentially limiting generalizability to milder or more complex phenotypes. Survivor bias may also be present, as patients surviving long enough to undergo DBS may represent a subgroup with distinct clinical trajectories. Conversely, inclusion of 26 previously unpublished cases may partially mitigate the publication bias favoring positive outcomes that

characterizes earlier small-series literature. Outcome measures were incomplete for some patients, follow-up duration was heterogeneous, and surgical targeting and programming strategies varied across centers. Validated disease-specific quality-of-life and chorea instruments remain limited. Genotype–outcome analyses were exploratory and underpowered. The absence of a non-DBS comparator group precludes causal inference regarding disease modification. Finally, mortality data should be interpreted descriptively: the majority of deaths were attributable to respiratory and systemic complications rather than to refractory dyskinetic status, and survival observations should not be construed as evidence of a protective effect of GPi-DBS on long-term mortality in *GNAO1*-related disorder.

Beyond motor outcomes, the substantial reductions in hospitalizations, intensive care admissions, and medication burden observed in this cohort suggest important health-system implications. Dyskinetic crises in *GNAO1*-related disorder frequently require prolonged intensive care support and represent major healthcare utilization and caregiver burden. Although formal cost-effectiveness analyses are beyond the scope of this study, earlier elective DBS implantation may reduce cumulative health care utilization and caregiver strain.[15]

In summary, GPi-DBS is associated with sustained prevention of dyskinetic crises and reduction of overall disease burden in patients with *GNAO1*-related disorders, whereas functional outcomes remained largely unchanged. These findings support pallidal neuromodulation primarily as a crisis-preventive and symptom-modifying strategy rather than a restorative intervention. Prospective registries integrating genotype stratification and standardized multidimensional outcomes will be essential to refine patient selection and optimal timing of intervention.

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## Author Contributions

K.Y., D.E.F., and K.B. contributed to the conception and design of the study; K.B. and J.R. contributed to the acquisition and analysis of data; K.B., J.R., D.E.F., and K.Y. contributed to drafting the text or preparing the figures. All authors commented on and revised the final manuscript.

## Potential Conflicts of Interest

The authors declare no conflicts of interest.

### *Data Availability*

Data are available from the corresponding author upon reasonable request.

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