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BRIEF COMMUNICATION

The Effect of Globus Pallidus Interna Deep Brain Stimulation on a Dystonia Patient with the *GNAL* Mutation Compared to Patients with DYT1 and DYT6

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ABSTRACT

Objective The aim of this study was to investigate the efficacy of globus pallidus interna deep brain stimulation (GPi-DBS) for treating dystonia due to the *GNAL* mutation.

Methods We provide the first report of a dystonia patient with a genetically confirmed *GNAL* mutation in the Korean population and reviewed the literature on patients with the *GNAL* mutation who underwent GPi-DBS. We compared the effectiveness of DBS in patients with the *GNAL* mutation compared to that in patients with DYT1 and DYT6 in a previous study.

Results Patients with the *GNAL* mutation and those with DYT1 had higher early responder rates (*GNAL*, 5/5, 100%; DYT1, 7/7, 100%) than did patients with DYT6 ($p = 0.047$). The responder rates at late follow-up did not differ statistically among the three groups ($p = 0.278$). The decrease in the dystonia motor scale score in the *GNAL* group was 46.9% at early follow-up and 63.4% at late follow-up.

Conclusion GPi-DBS would be an effective treatment option for dystonia patients with the *GNAL* mutation who are resistant to medication or botulinum toxin treatment.

Key Words Deep brain stimulation; *GNAL*; Dystonia; DYT25.

GNAL (OMIM #615073) mutations have recently been identified as responsible for primary dystonia.[1] The *GNAL* mutation typically presents as adult onset (mean 32 years) craniocervical dystonia. Focal or segmental dystonia has also been reported, but generalized dystonia is relatively rare.[1] Deep brain stimulation (DBS) is an important therapeutic strategy for patients with

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dystonia who are unsuccessfully treated with medication or botulinum toxin injections. The efficacy and safety of globus pallidus interna (GPi) DBS has been well established for generalized or segmental primary dystonia in previous trials.[2] However, treatment for patients with the *GNAL* mutation has not been studied, and the efficacy and safety of DBS for these patients is not yet known. We reviewed previous reports of patients with the *GNAL* mutation who underwent GPi-DBS and reported the case of a patient with generalized dystonia due to the *GNAL* mutation who was successfully treated with bilateral GPi-DBS.

MATERIALS & METHODS

Patient and molecular genetic diagnosis using next-generation sequencing

We provide the first report of a Korean patient genetically confirmed to have the *GNAL* mutation by using next-generation sequencing. Genomic DNA was extracted from a patient blood sample. Whole exome sequencing (WES) was performed as follows. First, raw data were filtered for splice sites of known target genes and nonsynonymous coding regions related to dystonia. Second, variants with a minor allele frequency < 1% were filtered out based on population databases, including in-house and normal Korean datasets. Subsequently, strong candidates were evaluated according to American College of Medical Genetics, 2015 guidelines.[3]

Comparison with previous reports of *GNAL* treated with GPi-DBS

We obtained studies from the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/) and Google Scholar by searching for keywords including *GNAL*, DYT25, and deep brain stimulation. We selected patients genetically confirmed to have the *GNAL* mutation who underwent GPi-DBS. The control group was identified by searching for keywords including DYT1, DYT6, TOR1A, THAP1, deep brain stimulation, and long-term follow up. We selected a study that included both DYT1 and DYT6 patients who underwent DBS surgery and reported follow-up data for more than 2 years. We excluded studies that did not identify the clinical character of each dystonia group or only included a specific phenotype. For the selected reports, we summarized the clinical characteristics and the effectiveness of the surgery compared with DYT1 and DYT6.

Statistical analysis

We compared the patients with the *GNAL* mutation with previous reports of patients with DYT1 and DYT6.[4] Group comparisons were performed with the chi-squared test or analysis of variance depending on the variable. A responder was defined as a patient who showed more than a 25% improvement in motor score on the dystonia scale.[5] A p value < 0.05 was considered statistically significant. Statistical analysis was performed with IBM SPSS (version 25.0; IBM Corp., Armonk, NY, USA) software for Windows.

Ethical approval

This study was approved by the Institutional Review Board of Samsung Medical Center, Seoul, Korea (IRB No. 2019-01-012), and the patient provided informed consent to participate.

RESULTS

Clinical description and genetic findings

A 19-year-old, right-handed male was referred with generalized dystonia from age 12. He had no perinatal problems and reached normal developmental milestones by the age 12. He had no family history of dystonia or other neurologic diseases. The dystonia started at his trunk and spread to the other parts of the body. Upon neurological examination, his trunk deviated to the right side, and he had left shoulder elevation, left torticollis, and right laterocollis. Dystonia was present in both hands, especially when straightening his arms. The patient did not show any other abnormal movements, such as parkinsonism or myoclonus. Ceruloplasmin, a 24-hour urine test for copper levels, brain MRI, and whole spine MRI were normal. Levodopa (200 mg/day), trihexyphenidyl (12 mg/day), and baclofen (20 mg/day) were not effective. Additionally, botulinum toxin was injected to treat the truncal dystonia, but this treatment had little effect on the symptoms.

Bilateral GPi-DBS surgery was performed because of the insufficient response to the medication and botulinum toxin therapy. At the pre-DBS evaluation, the Burke-Fahn-Marsden dystonia rating scale (BFMDRS) motor section was scored 30 out of 120, and the disability scale was scored 10 out of 30 (Supplementary Video 1 in the online-only Data Supplement). Bilateral GPi-DBS was performed with standard stereotactic and microelectrode recording techniques (Supplementary Figure 1A in the online-only Data Supplement). Dystonia gradually improved after surgery. One year after surgery, the patient's symptoms were improved, the BFMDRS motor section was rated 18 out of 120 and the disability score was 8 out of 30. The BFMDRS motor section was 9, and the disability score was 5 at two years after surgery (Supplementary Video 2 in the online-only Data Supplement). The patient showed an approximately 70% improvement in dystonia symptoms after surgery as estimated by the BFMDRS score (from 30 to 9).

Genetic tests for DYT1 (TOR1A) and DYT6 (THAP1) were negative. WES was performed and analyzed for known dysto-

nia target genes, and the test revealed heterozygosity for c.1060G >A(p. Val354Met), a missense mutation in exon 12 of the *GNAL* gene that was previously reported as a pathogenic variant (Supplementary Figure 1B in the online-only Data Supplement).[6]

Literature review of the efficacy of GPi-DBS in dystonia patients with the *GNAL* mutation

We reviewed patients with the *GNAL* mutation who underwent GPi-DBS.[7-10] A total of eight patients were evaluated, and demographic and dystonia-related information are summarized in Table 1. Three patients had generalized dystonia, four had segmental dystonia, and one had cervical dystonia. Five patients had early follow-up clinical data and showed good responses to GPi-DBS. All four patients who had late follow-up records showed a significant reduction in the dystonia motor scale score.

Comparisons of *GNAL* patients with DYT1 and DYT6

Brüggemann et al.[4] reported short- and long-term outcomes for chronic GPi-DBS in DYT1, DYT6, and non-DYT patients. We excluded non-DYT patients because the previous study did not perform a genetic test for the *GNAL* mutation. We compared the clinical characteristics and effect of GPi-DBS for *GNAL* patients with a previous study (Table 2). Patients with the *GNAL* mutation had an older age of onset than did patients with DYT1 and DYT6 ($p < 0.001$). Time until first DBS ($p = 0.055$) did not differ statistically. Four patients with the *GNAL* mutation were assessed with the BFMDRS, and the other three patients were assessed with the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). The baseline dystonia motor scale score did not differ in patients assessed with the BFMDRS ($p = 0.100$). Five patients in the *GNAL* group had early follow-up data, and these individuals had a higher responder rate (5/5, 100%) than did those in the DYT6 group. Patients with DYT1 also showed a higher responder rate than did patients with DYT6 ($p = 0.047$). The responder rates at late follow-up did not differ statistically among the three groups ($p = 0.278$). The decrease in the dystonia motor scale score in the *GNAL* group was 46.9% at early follow-up and 63.4% at late follow-up.

DISCUSSION

This study reviewed dystonia patients with the *GNAL* mutation who underwent DBS and found that these individuals had good responses to DBS. We also reported the first genetically confirmed case of generalized dystonia with the *GNAL* mutation in a Korean patient.

The patient with the *GNAL* mutation showed a good response at early and late follow-up. Five patients with the *GNAL* mutation had data available within one year after DBS. All five patients

Table 1. Demographic and clinical characteristics of patients with the *GNAL* mutation

	Case 1[9]	Case 2[9]	Case 3[9]	Case 4[7]	Case 5[8]	Case 6[8]	Case 7[10]	Case 8 (index patient)
Distribution	Segmental	Cervical	Generalized	Segmental	Segmental	Segmental	Generalized	Generalized
Sex	Female	Male	Female	Female	Male	Female	Female	Male
Family history	Y	Y	Y	Y	Y	Y	N	N
Age at onset, year	38	42	18	54	36	42	47	12
Years until first DBS	15	11	23	6	19	20	n.a	7
DBS settings	Left GPi: 0–3+, 4 V, 90 μs, 185 Hz Right GPi: 8–11+, 6 V, 120 μs, 185 Hz	Left GPi-1: C+0-, 3 V, 90 μs, 125 Hz Left GPi-2: C+1, 3 V, 90 μs, 125 Hz Right GPi-1: C+1-, 3 V, 90 μs, 125 Hz Right GPi-2: C+0-, 3 V, 90 μs, 125 Hz	Left GPi: C+1-, 4.5 V, 60 μs, 145 Hz Right GPi: C+5-, 4.2 V, 90 μs, 145 Hz	Left GPi: C+8-, 2.3 V, 120 μs, 180 Hz Right GPi: C+0-, 2.3 V, 120 μs, 180 Hz	Left GPi: C+1-, 2.5 V, 90 μs, 130 Hz Right GPi: - 8+9, 2 V, 90 μs, 130 Hz	Left GPi-1: C+0-, 1.25 V, 60 μs, 125 Hz Left GPi-2: C+1-, 2 V, 60 μs, 125 Hz Right GPi-1: C+1-, 2.15 V, 60 μs, 125 Hz Right GPi-2: C+2-, 60 μs, 125 Hz	n.a	Left GPi: C+2-, 2.5 V, 150 μs, 150 Hz Right GPi: C+2-, 2.5 V, 150 μs, 150 Hz
Dystonia Motor Scale, Preoperative	n.a	24†	21†	26*	16*	12*	22†	30*
Response rate (%)								
Early follow-up (1–12 months)	n.a	29.2†	28.6†	n.a	68.7*	n.a.	68.2†	40.0*
Late follow-up (12–96 months)	n.a	45.8†	57.1†	80.8*	n.a	n.a	n.a	70.0*

*Burke-Fahn-Marsden Dystonia Rating Scale, †Toronto Western Spasmodic Torticollis Rating Scale. DBS: deep brain stimulation, GPi: globus pallidus interna.

Table 2. Comparison of the clinical characteristics and effectiveness of DBS

	GNAL[7-10]	DYT1[4]	DYT6[4]	*p* value
No. of patients	8	9	8	
Distribution generalized/segmental/focal	3/4/1	8/0/1	5/3/0	0.143‡
Male/female	3/5	3/6	7/1	0.051‡
Family history positive/negative/unknown	6/2/0	5/4/0	4/3/1	0.551‡
Age at onset (year)				
Mean (SD)	36.4 (13.8)	11.2 (6.6)	10.0 (3.3)	< 0.001§
Range	14– 54	2–23	6–15	
Years until first DBS				
Mean (SD)	14.4 (6.6)	20.1 (11.1)	27.0 (10.8)	0.055§
Range	6–23	5–41	11–46	
Dystonia scale, preoperative				
Motor, mean (SD)	21.0 (8.4)*, 22.3 (1.5)†	43.8 (30.7)*	37.0 (15.9)*	0.100§‖
Responder rate motor BFMDSR, n (%)				
Early follow-up (1–16 months)	5/5 (100)	7/7 (100)	4/7 (57.1)	0.047‡
Late follow-up (22–96 months)	4/4 (100)	5/8 (62.5)	6/7 (85.7)	0.278‡
Reduction of dystonia scale (%)				
Early follow-up (1–16 months)	46.9	60	32	n.a
Late follow-up (22–96 months)	63.4	44	42	n.a

*Burke-Fahn-Marsden Dystonia Rating Scale (BFMDSR), †Toronto Western Spasmodic Torticollis Rating Scale, ‡statistical analysis was performed with chi-square test, §statistical analysis was performed with analysis of variance, ‖comparison of the patients who were assessed by the BFMDSR. DBS: deep brain stimulation.

were classified as DBS responders and had a high reduction in the dystonia motor scale score. Brüggemann et al.[4] reported that the effect of DBS appears to be less predictable in patients with DYT6. These authors also reported that DYT6 had a lower responder rate at early follow-up and a similar responder rate at late follow-up. In our study, patients with the *GNAL* mutation had a higher response rate than did patients with DYT6 at early follow-up, and the response to DBS was sustained at late follow-up, similar to the response observed in the DYT1 and DYT6 groups. This result suggests that similar to patients with DYT1, bilateral GPi-DBS would be an effective treatment for patients with the *GNAL* mutation. Whether this robust effect of DBS surgery for patients with the *GNAL* mutation is due to their clinical characteristics, such as older age at onset, short time from onset to DBS, or dystonia distribution, remains uncertain. However, the genotype of dystonia patients contributes to the DBS response. In this regard, we suggest that GPi-DBS would be a good treatment option for dystonia patients with the *GNAL* mutation if they have the proper phenotype, such as cervical, craniocervical, or generalized dystonia, especially in patients who show unsatisfactory results with medication or botulinum toxin treatment.

The *GNAL* mutation was identified as causative for dystonia in 2013.[1] The prevalence of the *GNAL* mutation in dystonia is estimated to be less than 1%.[1,6] Cervical dystonia is the most common phenotype (93%) associated with the *GNAL* mutation, followed by cranial (57%) and speech (44%) involvement.[1] Generalized dystonia is reported to have an incidence of only 11% among *GNAL* mutations. Our patient had childhood-onset generalized dystonia, which is an unusual phenotype among patients with the *GNAL* mutation. WES revealed heterozygosity for c.1060G>A(p.Val354Met), a missense mutation in exon 12 of the *GNAL* gene. This variant was previously reported as pathogenic in a 48-year-old male patient with familial segmental dystonia.[6] There is a significant clinical difference between the two patients. The previous patient had a family history of dystonia and segmental dystonia (cranial-laryngeal-cervical). However, our patient had no familial history and presented with childhood onset truncal dystonia, which progressed to generalized dystonia. To date, various dystonia phenotypes, including craniocervical dystonia, focal limb dystonia, and laryngeal dystonia, have been associated with the *GNAL* mutation. Further studies are needed to determine the phenotype-genotype matching of this mutation.

This study had several limitations. Our results were based on a literature review and a reported clinical feature. Thus, limited clinical information was available. Additionally, different clinical scales were used to assess dystonia severity depending on the study. Another limitation is the possibility of publication bias, and this study included only a limited number of patients. Therefore, the results should be interpreted carefully.

In summary, bilateral GPi-DBS can be an effective treatment

option for dystonia patients with the *GNAL* mutation who are resistant to medical therapy or botulinum toxin treatment.

Supplementary Video Legends

Video 1. Preoperative state: dystonic posture was present in both hands, cervical and trunk and was aggravated by turning or walking.

Video 2. Postoperative state: dystonic posture improved after bilateral globus pallidus interna deep brain stimulation surgery, especially while walking.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.19006.

Conflicts of Interest

The authors have no financial conflicts of interest.

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REFERENCES

1. Fuchs T, Saunders-Pullman R, Masuho I, Luciano MS, Raymond D, Factor S, et al. Mutations in GNAL cause primary torsion dystonia. Nat Genet 2013;45:88-92.
2. Kupsch A, Benecke R, Müller J, Trottenberg T, Schneider GH, Poewe W, et al. Pallidal deep-brain stimulation in primary generalized or segmental dystonia. N Engl J Med 2006;355:1978-1990.
3. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-424.
4. Brüggemann N, Kühn A, Schneider SA, Kamm C, Wolters A, Krause P, et al. Short- and long-term outcome of chronic pallidal neurostimulation in monogenic isolated dystonia. Neurology 2015;84:895-903.
5. Volkmann J, Wolters A, Kupsch A, Müller J, Kühn AA, Schneider GH, et al. Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. Lancet Neurol 2012;11:1029-1038.
6. LeDoux MS, Vemula SR, Xiao J, Thompson MM, Perlmutter JS, Wright LJ, et al. Clinical and genetic features of cervical dystonia in a large multicenter cohort. Neurol Genet 2016;2:e69.
7. Ziegan J, Wittstock M, Westenberger A, Dobričić V, Wolters A, Benecke R, et al. Novel GNAL mutations in two German patients with sporadic dystonia. Mov Disord 2014;29:1833-1834.
8. Carecchio M, Panteghini C, Reale C, Barzaghi C, Monti V, Romito L, et al. Novel GNAL mutation with intra-familial clinical heterogeneity: expanding the phenotype. Parkinsonism Relat Disord 2016;23:66-71.
9. Sarva H, Trosch R, Kiss ZHT, Furtado S, Luciano MS, Glickman A, et al. Deep brain stimulation in isolated dystonia with a GNAL mutation. Mov Disord 2019;34:301-303.
10. Pandey S, Sankhla CS, Ramprasad VL, Geetha TS. Novel GNAL mutation in an Indian patient with generalized dystonia and response to deep brain stimulation. Parkinsonism Relat Disord 2019 Jan 14 [Epub]. https://doi.org/10.1016/j.parkreldis.2019.01.011.