Parkinsonism and Related Disorders 65 (2019) 277–278

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

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Deep brain stimulation shows high efficacy in two patients with *GCH1* variants

ARTICLE INFO

Keywords:
Genetics
Dopamine responsive dystonia
GCH-1
Parkinson's disease
Deep brain stimulation

Dopa-responsive dystonia (DRD) is characterized by diurnally fluctuating limb onset dystonia and responds well to levodopa [1]. DRD is caused by a deficiency of GTP cyclohydrolase 1, encoded by *GTP-cyclohydrolase 1* (*GCH1*). *GCH1* variants also relate to Parkinson's disease (PD), where the frequency of the variant is significantly higher in PD than in control subjects [2]. We previously reported the complex inheritance patterns of families with members who are PD or DRD harboring *GCHI* variants [3]. Patients harboring *GCH1* variants may yield effects of both PD and DRD phenotypes. Recently, increasing evidence has supported the positive efficacy of deep brain stimulation (DBS) of the subthalamic nucleus (STN) for PD patients. Good outcomes have been obtained for STN-DBS in two patients with *GCH1* variants [4,5]. One was a 6-year-old boy with DRD whose initial symptom was dyskinesia and the other was a 32-year-old PD patient with the *GCH1* variant c.671A > G, p.K224R, whose initial symptom was status dystonicus [4,5]. Here, we encountered two patients harboring *GCH1* variants, one with DRD and the other with PD. Following long-term treatment with levodopa, both presented with parkinsonism and motor fluctuations, which we ameliorated using STN-DBS.

Our patients were both female of Japanese origin and have been reported on previously by us [3]. The first was patient A–II–2 from Family A, and second was patient C–III–2 from Family C (Table 1). Two patients gave informed and written consent before participation. Complications of cognitive decline or psychosis were absent throughout the course for either patient.

A–II–2 was 66 years old, harboring c.626 + 2T > A, and presented with diurnal dystonia in her right foot since 10 years of age. She was diagnosed with DRD. Levodopa drastically improved her symptoms. At 53 years of age, she presented frequently with wearing-off, dyskinesia and levodopa-induced dyskinesia (LID) despite frequent levodopa/carbidopa administration (six times a day, total 300 mg/day) and transdermal rotigotine (27 mg/day). ^{123}Iodine-labelled N-(3-fluoropropyl) -2β-carbomethoxy-3β-(4-iodophenyl) nortropane (^{123}I-FP-CIT) single photon emission computerized tomography (SPECT) revealed the left-dominant reduction of non-displaceable binding ratios (SBR) and dot-shape. Thus, we conducted a bilateral STN-DBS operation at 66 years of age. After the operation, levodopa/carbidopa was ceased and the amount of rotigotine was decreased to 22.5 mg/day; diminished troublesome dyskinesia was noted (Table 1).

C–III–2 was a 41-year-old patient with a clinical diagnosis of PD, harboring the variant c.626C > T, p.T209I in *GCH1*. Her initial symptom was resting tremor in the upper limb on the right side at the

Table 1
Summary of two patients harboring *GCH1* variants.

	A–II–2		C–III–2	
Clinical diagnosis	DRD		PD	
GCH1 mutations	c.626 +2T > G		c.626C > T, p.T209I	
Gender	Female		Female	
Age at onset (years old)	10		31	
Age at operaton (years old)	66		41	
Disease duration at operation (years)	56		10	
Device	Vercise TM PC (Boston Scientific, Massachusetts, USA)		Vercise TM PC (Boston Scientific, Massachusetts, USA)	
Stimulation settings one year after operation	Left	Right	Left	Right
Amplitude (mA)	3.6	3.2	2.7	3.6
Pulse width (μs)	40	40	50	90
Pulse frequency (Herz)	130	130	130	130
	Before DBS	After DBS	Before DBS	After DBS
Modified Rankin Scale	3	2	3	1
Hoen and Yahr stage (on)	3	3	2	2
Hoen and Yahr stage (off)	4	3	4	2
MDS-UPDRS part III (on)	12	9	19	3
MDS-UPDRS part IV	18	3	11	3
MMSE	28		29	
MoCA-J	25		29	
HAM-D17	6		0	
Beck's Depression Inventory	22		1	
The total daily levodopa equivalent dose	660	300	1358	820

Abbreviation: *GCH1*, GTP cyclohydrolase 1; DRD, dopa-responsive dystonia; PD, Parkinson's disease; DBS, deep brain stimulation; MDS-UPDRS, Movement Disorder Society- Unified Parkinson's Disease Rating Scale; MMSE, the Mini-Mental State Examination; MoCA-J, Japanese version of Montreal Cognitive Assessment; HAM-D17, the Hamilton Rating Scale for Depression-17.

https://doi.org/10.1016/j.parkreldis.2019.06.002
Received 2 April 2019; Received in revised form 27 May 2019; Accepted 1 June 2019

Abbreviations

PD	Parkinson's disease
DRD	Dopa-responsive dystonia
YOPD	young onset Parkinson's disease
LID	levodopa induced dyskinesia
DBS	deep brain stimulation
^{123}I-FP-CIT	^{123}Iodine-labelled N-(3-fluoropropyl) -2β-carbomethoxy-3β-(4-iodophenyl) nortropane
SPECT	single photon emission computerized tomography
SBR	specific to non-displaceable binding ratios
MDS	Movement Disorder Society
UPDRS	The Unified Parkinson's Disease Rating Scale

age of 31 years, along with a good response to levodopa. ^{123}I-FP-CIT SPECT depicted the left-dominant reduction of SBR and dot shape. Since 40 years of age, she showed prominent wearing-off and troublesome dyskinesia under frequent levodopa/carbidopa medication (500 mg, five times per day) and rotigotine (36 mg/day). Wearing-off and levodopa-induced dyskinesia disappeared completely after a bilateral STN-DBS operation and levodopa/carbidopa was decreased to 400 mg/day and rotigotine to 31.5 mg/day.

We experienced two patients with clinical diagnoses of DRD and PD, harboring the *GCH1* variants c.626 + 2T > G and p.T209I, respectively. Our bioinformatics analysis proven the disease causing, splice site changes, amino acid changes, and no records in the public gene database [3]. We selected STN-DBS to improve their parkinsonism and motor fluctuations, particularly the dyskinesia and wearing-off. Amelioration of these symptoms persisted well after one year since the operation. Severe bilateral motor fluctuations and dystonia of the lower limbs emerged when A–II–2 was over 50 years old. C–III–2 also had troublesome dyskinesia and wearing-off. These symptoms severely limited their daily life activities. STN-DBS produces a good outcome, improving motor fluctuations for patients harboring *GCH1* variants.

GCH1 variants cause GTP cyclohydrolase 1 deficiency and decrease tyrosine hydroxylase activities. This results in decreased dopamine expression in the striatum and can cause hyperactivity of the STN, resulting in parkinsonism. Thus, DBS may dissociate input/output signals in the STN and interrupt abnormal information in the cortico-basal ganglia loop, resulting in an amelioration of their symptoms. Intriguingly, both patients showed a decrease in dopamine transporter densities on ^{123}I-FP-CIT SPECT, a result commonly seen in PD but not in DRD, indicating presynaptic dopaminergic neuron degeneration. This is inconsistent with common findings in DRD patients where ^{123}I-FP-CIT SPECT results are normal [3]. We speculate that the upregulated compensatory dopaminergic activity at the presynaptic level could mask dopaminergic neuron degeneration in these cases. Although the mechanisms of motor fluctuations in DRD remain unclear, our results indicate that STN-DBS may result in positive outcomes for symptoms of motor-fluctuations in DRD patients and will expand the application of STN-DBS to patients with *GCH1* variants.

Disclosure

The authors report no conflicts of interest relevant to the manuscript. There is no specific grant support for this study.

Acknowledgements

None.

References

[1] S. Wijemanne, J. Jankovic, Dopa-responsive dystonia–clinical and genetic heterogeneity, Nat. Rev. Neurol. 11 (7) (2015) 414–424.
[2] N.E. Mencacci, I.U. Isaias, M.M. Reich, C. Ganos, V. Plagnol, J.M. Polke, J. Bras, J. Hersheson, M. Stamelou, A.M. Pittman, A.J. Noyce, K.Y. Mok, T. Opladen, E. Kunstmann, S. Hodecker, A. Munchau, J. Volkmann, S. Samnick, K. Sidle, T. Nanji, M.G. Sweeney, H. Houlden, A. Batla, A.L. Zecchinelli, G. Pezzoli, G. Marotta, A. Lees, P. Alegria, P. Krack, F. Cormier-Dequaire, S. Lesage, A. Brice, P. Heutink, T. Gasser, S.J. Lubbe, H.R. Morris, P. Taba, S. Koks, E. Majounie, J. Raphael Gibbs, A. Singleton, J. Hardy, S. Klebe, K.P. Bhatia, N.W. Wood, C. International Parkinson's Disease Genomics, U.C.-e. consortium, Parkinson's disease in GTP cyclohydrolase 1 mutation carriers, Brain 137 (Pt 9) (2014) 2480–2492.
[3] H. Yoshino, K. Nishioka, Y. Li, Y. Oji, G. Oyama, T. Hatano, Y. Machida, Y. Shimo, A. Hayashida, A. Ikeda, K. Mogushi, Y. Shibagaki, A. Hosaka, H. Iwanaga, J. Fujitake, T. Ohi, D. Miyazaki, Y. Sekijima, M. Oki, H. Kusaka, K.I. Fujimoto, Y. Ugawa, M. Funayama, N. Hattori, GCH1 mutations in dopa-responsive dystonia and Parkinson's disease, J. Neurol. 265 (8) (2018) 1860–1870.
[4] M.J. Tormenti, N.D. Tomycz, K.A. Coffman, D. Kondziolka, D.J. Crammond, E.C. Tyler-Kabara, Bilateral subthalamic nucleus deep brain stimulation for dopa-responsive dystonia in a 6-year-old child, J. Neurosurg. Pediatr. 7 (6) (2011) 650–653.
[5] J. Lobato-Polo, D. Ospina-Delgado, E. Orrego-Gonzalez, J.F. Gomez-Castro, J.L. Orozco, A. Enriquez-Marulanda, Deep brain stimulation surgery for status dystonicus: a single-center experience and literature review, World Neurosurg 114 (2018) e992–e1001.

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