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Short communication

Residual signs of dopa-responsive dystonia with *GCH1* mutation following levodopa treatment are uncommon in Korean patients

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ABSTRACT

Introduction: Dopa-responsive dystonia (DRD) related to *GCH1* mutation is a biochemical disorder. DRD is majorly characterized by dystonia and/or parkinsonism. Although clinical disorders show a dramatic positive response to levodopa, there are controversies over the residual signs following treatment. This study was designed to investigate the residual signs following levodopa treatment in Korean DRD patients with *GCH1* mutation.

Methods: A structured questionnaire was prepared to obtain information about demographic factors, clinical characteristics, genetic data, neuroimaging data and residual signs following levodopa treatment of the patients, and was sent to movement specialists at tertiary hospitals. The data collected from the returned forms were analyzed using appropriate statistical methods such as Student's *t*-test, Mann-Whitney *U* test, Chi-square test or Fisher's exact test.

Results: Thirty-nine DRD Korean patients with *GCH1* mutation were recruited. One patient was presented with only parkinsonism. Dystonia was completely resolved in 32 out of 38 patients following treatment, while parkinsonism improved without residual signs in 8 out of 9 patients. The frequency of the residual signs in Korean patients (15.8% for dystonia and 11.1% for parkinsonism) is similar to that observed in Chinese patients, but lower in Western patients. Furthermore, these signs were more frequent in those patients with a delay in their diagnosis, and those who were relatively older at the time of diagnosis.

Conclusions: Ethnic differences, age at diagnosis, and a temporal gap between the onset and diagnosis in Korean patients may influence the remaining neurologic abnormalities of DRD.

1. Introduction

The main feature of dopa-responsive dystonia (DRD) is its excellent response to dopamine supplementation [1]. Dopamine itself is produced by a complex enzymatic cascade, in which tyrosine hydroxylase (TH) plays a critical role by converting tyrosine into L-dopa by TH with tetrahydrobiopterin (BH4) as a cofactor. In the biochemical pathway for BH4 production, the conversion of guanosine triphosphate into dihydroneopterin triphosphate by guanosine triphosphate cyclohydrolase 1 (GCH1) is the initial rate-limiting step [2]. Accordingly, mutations in the genes of these key enzymes impair dopamine production in the brain.

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An autosomal dominant mutation in the *GCH1* gene is the most common cause of DRD. In postmortem studies, both dopamine and TH protein concentrations were found to be decreased in the striatum [3,4]. However, further pathologic examination showed only decreased melanin in the dopaminergic neurons of the substantia nigra (SN). There was neither neuronal loss nor Lewy bodies observed in the SN and striatum, supporting the theory that DRD related to *GCH1* mutation is a biochemical disorder [3,4]. Additionally, the intactness of the dopaminergic nerve terminal in the striatum was also demonstrated by normal findings in dopamine transporter (DAT) scans [2]. As L-dopa replacement treatment would bypass the defective step, it is expected to completely reverse the symptoms related to dopamine deficiency [1].

However, a recent study that reviewed 352 cases reported the presence of residual signs in historical cases (residual signs of dystonia in 32.1% and of parkinsonism in 15.7% of cases, respectively) [5]. In this study, the proportion of residual signs in the authors' cases was even higher (residual signs of dystona in 66.7% and of parkinsonism in 22.2% of cases, respectively). In contrast, an incomplete response to levodopa treatment was observed to occur less frequently in the series of Chinese cases (12.5%), raising the issue of ethnical differences between DRD patients [6].

In this study, we investigated the clinical outcomes following levodopa treatment in Korean DRD patients with *GCH1* mutation in order to determine the proportion of residual signs of DRD in the study population.

2. Methods

A structured survey presented as a questionnaire form was initially prepared and sent to movement specialists at tertiary hospitals to obtain clinical information about their patients with genetically confirmed DRD. This questionnaire included age at onset and diagnosis, current age, workups, clinical phenotypes, L-dopa or levodopa doses and response to treatment, with particular attention to any residual signs observed.

All patients with clinical symptoms that came from the same families were counted as individual cases. Ultimately, clinical data form the returned forms were collected for further analyses.

Clinical characteristics were compared between those with and without residual signs. For continuous and binominal variables, Student's *t*-test and Chi-square (or Fisher's exact) test were used, respectively. If normality assumption was not satisfied by Kolmogorov-Smirnov tests, Mann-Whitney *U* test was done. Statistical analyses were performed using SPSS software (version 21.0; SPSS Inc., Chicago, IL, USA), with the significance level set at 0.05 (two-tailed).

Since this study was based on medical records, no direct contact with the patients, such as clinical assessment or medical intervention, was made. The protocol of this study was reviewed by Internal Review Board of Kyung Hee University Hospital (KHUH IRB). KHUH IRB approved this protocol and decided that the requirement for the waiver of informed consent, such as no more than minimal risk to the patients, practical limitation of the research without the waiver, and no adverse effect on the rights and welfare of the patients by the waiver, were fulfilled.

3. Results

Data from 39 DRD cases of Korean patients with *GCH1* mutation (10 men and 29 women; Table 1) were successfully collected, of which 21 cases were familial (from 7 families) and 18 were sporadic. Twenty-six cases (67%) were previously reported and 13 were newly diagnosed (See References of Table 1).

Regarding the study population, the onset of clinical symptoms began to manifest at the mean age of 9.4 rom 7 families) and 18 were sporadic. Twenty-six cases (67%) were previously reported and 13 were newly diagnrkinsonism). The diagnosis was made at the mean age of 17.8 ± 11.9 years, which was a mean of 8.4 ± 8.0 years following the onset of clinical symptoms. Overall, there were 27 cases with generalized dystonia, nine with segmental dystonia and two focal dystonia, while Parkinsonism was present in 9 out of 39 cases (23.1%). Additionally, there was a male patient who presented with resting tremor, rigidity and bradykinesia (age at onset = 51.0 years, mutation = M137R; Case 7) but without dystonia [7].

There was no significant difference between those with and without parkinsonism in terms of the age at onset (13.4 versus 8.2 years, respectively, $p > 0.05$), age at diagnosis (22.1 versus 16.6 years, respectively, $p > 0.05$), and temporal gap between the ages at onset and diagnosis (8.7 versus 8.4 years, respectively $p > 0.05$).

MRI was performed in 16 cases and the DAT scan in 13 cases (six of where with parkinsonism), which were normal. Subsequently, levodopa treatment began at the mean age of 17.4 ± 12.2 years, with the mean dosage of levodopa being 190.5 ± 98.5 mg/day.

With respect to the cases of dystonia (n = 38), the complete response to levodopa medication was successfully achieved in 32 cases without residual signs (84.2%; Table 1) Those with residual signs took larger amount of levodopa (258.3 ± 80.1 versus 168.8 ± 100.6 mg/day, $p < 0.05$). All the patients with residual signs of dystonia were female ($p > 0.05$). Dystonia subtype and familial cases were not different between those with and without residual signs. They were older at the time of diagnosis (25.7 versus 15.3 years, respectively, $p < 0.05$) and had a greater temporal gap between ages at onset and diagnosis (17.5 versus 7.0 years, $p < 0.05$) as compared to those without the signs. Mild limb dystonia was persistent in four cases (10.5%), with one of them additionally showing mild facial dystonia. There were two cases (5.3%) with scoliotic deformity.

Concurrently, with respect to the cases of parkinsonism (n = 9), its symptoms completely disappeared with levodopa treatment in 8 cases, while rigidity was persistent in one case (Case 7 from Family 1), constituting an overall 88.9% response rate (Table 1).

Clinical presentation of DRD was homogeneous in three (Family 3, 4, and 6) and inhomogeneous in four families (Family 1, 2, 5 and 7), while the residual signs were different in two families (Family 1 and 2).

4. Discussion

Our study demonstrated that residual signs of dystonia and parkinsonism following levodopa treatment are uncommon (17.9%, 7 of 39 cases) in cases of Korean DRD patients. The frequency of the residual sings from our study is similar to that observed in case of Chinese patients but different to that of Western patients [5,6]. The ethnic modification of monogenetic disorders has been observed in other forms of genetic dystonia such as *DYT1* dystonia [8]. In addition to ethnicity-dependent genetic modification of *GCH1*, due to the concentration level of dopamine being a function of its production and metabolism, the role of other enzymes involved in dopaminergic metabolic pathway such as catechol-O-methyltransferase and monoamine oxidase could be also of importance. Such ethnic differences associated with dopamine metabolism have been demonstrated in the patients with Parkinson disease (PD), such as with a lower levodopa equivalent dose and the same efficacy of a low-dose COMT inhibitor in Asian PD patients, which has not been studied in patients with DRD [9].

Furthermore, residual signs were found only in those families, whose members had heterogeneous phenotypes in this study (Table 1). Intra-familial diversity in monogenetic hereditary disorders may be under the influence of a genetic modifier. In line with this assumption, GCH1 enzyme level was found to be 20% that of the normal rather than 50%, suggesting that haploinsufficiency of *GCH1* may be not the sole determinant of enzyme activity and the expression of *GCH1* be vulnerable to genetic modifier [10].

A delay in the diagnosis could also contribute to the development of residual signs in DRD patients. In this study, those with residual signs were diagnosed at relatively older ages and thus had a long delay in the

Table 1
Clinical features and diagnostic workups.

Case	Family Number	Sex	Age at onset (years)	Age at diagnosis (years)	Temporal gap between the diagnosis and treatment (years)	Current age (years)	Levodopa (mg/day)	Treatment duration (years)	Neurologic diagnosis	Genetic diagnosis	Neuroimaging	Residual signs
1	NA	F	9	28	19	47	300	19	generalized dystonia/parkinsonism	IVS2+3A > T	normal MRI	dystonia in both hands and right foot
2	NA	F	8	20	12	38	200	18	generalized dystonia	M1L	normal MRI	fixed scoliotic deformity of spine
3	NA	F	3	17	14	22	250	5	generalized dystonia	V226Dfs*23	ND	fixed scoliotic deformity of spine
4	1	F	5	17	12	40	400	23	generalized dystonia	M137R	ND	both leg dystonia
5	NA	F	13	31	18	35	200	4	generalized dystonia	A74D	normal MRI, normal DAT scan	both feet dystonia
6	2	F	11	41	30	53	200	12	generalized dystonia	IVS5-1-2insA	normal DAT scan	facial and limb dystonia
7	1	M	51	52	1	68	200	16	Parkinsonism without dystonia	M137R	normal MRI, normal DAT scan	left hand rigidity
8	NA	M	9	15	6	19	150	4	focal dystonia (left leg)/parkinsonism	A208E	normal MRI, normal DAT scan	none
9	3	F	7	10	3	27	50	17	segmental dystonia	Q48X	ND	none
10	3	F	9	31	22	50	100	19	segmental dystonia	Q48X	ND	none
11	NA	M	8	10	2	27	100	17	segmental dystonia	R198W R59G	normal MRI, normal DAT scan	none
12	NA	F	7	9	2	22	100	13	generalized dystonia	R216*	normal MRI	none
13	NA	F	8	8	0	21	100	13	generalized dystonia	V204I	normal MRI	none
14	NA	F	7	10	3	23	100	13	generalized dystonia	P23L	normal MRI	none
15	NA	M	7	9	2	19	50	10	segmental dystonia	H209DfsX5	normal MRI, normal DAT scan	none
16	NA	M	8	10	2	17	100	7	focal dystonia	A98T	normal MRI	none
17	2	F	5	7	2	24	100	17	segmental dystonia	IVS5-1-2insA	normal MRI	none
18	NA	F	8	10	2	21	100	11	generalized dystonia	R178del	normal MRI	none
19	4	M	2	8	6	18	250	10	generalized dystonia	T186I	normal MRI	none
20	4	F	14	35	21	46	200	11	generalized dystonia	T186I	ND	none
21	1	F	13	19	6	42	200	23	generalized dystonia	M137R	ND	none
22	1	F	2	2	0	19	100	17	generalized dystonia	M137R	ND	none
23	NA	F	21	31	10	43	50	12	segmental dystonia	T186I	ND	none
24	NA	F	20	33	13	34	50	1	generalized dystonia	IVS3+2T > C	ND	none
25	NA	M	4	5	1	21	250	16	generalized dystonia/spasticity/parkinsonism	G203R	normal DAT scan	none
26	NA	F	6	8	2	25	250	17	generalized dystonia/parkinsonism	M230fs	ND	none
27	NA	F	11	12	1	23	200	11	generalized dystonia/parkinsonism	P40fs	ND	none
28	5	F	5	8	3	24	500	16	generalized dystonia	S114X	ND	none
29	5	M	6	9	3	19	250	10	segmental dystonia	S114X	ND	none
30	5	F	11	30	19	43	200	13	generalized dystonia	S114X	normal MRI, normal DAT scan	none
31	5	F	12	33	21	61	200	28	generalized dystonia/parkinsonism	S114X	normal DAT scan	none
32	5	F	7	22	15	49	100	27	generalized dystonia/parkinsonism	S114X	normal DAT scan	none
33	5	F	1	8	7	25	400	17	generalized dystonia	S114X	normal DAT scan	none
34	5	M	6	8	2	23	200	15	generalized dystonia	S114X	ND	none
35	6	F	11	32	21	46	250	14	segmental dystonia	IVS2+1G > C	ND	none
36	6	M	4	5	1	19	100	14	segmental dystonia	IVS2+1G > C	normal MRI	none
37	NA	F	6	10	4	21	200	11	generalized dystonia	IVS5-1-2insA	ND	none

(*continued on next page*)

Table 1 (*continued*)

Case	Family Number	Sex	Age at onset (years)	Age at diagnosis (years)	Temporal gap between the diagnosis and treatment (years)	Current age (years)	Levodopa (mg/day)	Treatment duration (years)	Neurologic diagnosis	Genetic diagnosis	Neuroimaging	Residual signs
38	7	F	12	24	12	43	200	19	generalized dystonia/ parkinsonism	P95R	normal DAT scan	none
39	7	F	10	19	9	38	200	19	generalized dystonia	P95R	normal DAT scan	none

Abbreviations: NA, not applicable; ND, not done; M, male; F, female; DAT, dopamine transporter.

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diagnosis compared to those without the signs. Although it was suggested that the risk of complications is associated with the diagnostic delay, the correlation between the delay and residual signs was uncertain with respect to a previous study [5].

Though the frequency of parkinsonism (22.2%, 8 of 32 cases) in those Korean patients with early-onset (< 15 years old) was similar to that of Western patients, parkinsonism patients were found to be highly responsive to medical treatment and the DAT scan was normal (Table 1). Even in the male patient, who exclusively developed parkinsonism at 51 years of age, the DAT scan was normal, which is similar to the diagnosis of a scan without evidence of dopaminergic deficiency (SWEDD) or benign parkinsonism. While a group of patients with full-blown parkinsonism and abnormal DAT scans was reported as neurodegenerative DRD, and the DAT scan was found to be abnormal in an asymptomatic gene carrier, we could not find similar patients in our study [11]. Moreover, since an autopsy of a 90-year-old DRD patient revealed no pathologic findings that were suggestive of PD, despite the patient showing parkinsonian features, further studies, including a pathologic examination, are required for a better understanding of PD-like presentation in DRD [12].

Our study can be limited by a small number of the patients. However, since DRD is a very rare disease (0.0001%), the number of the patients included in this study (n = 39) approaches the expected number of cases (Korean population = 51 million; expected DRD cases = 51), which is adequate to represent the characteristics of Korean patients. Since the number of patients are limited, a significant number of the patients from the same families was analyzed as separate entities. However, the number of familial cases were not different between those with and without residual signs, The results of our study show the unique characteristics of Korean patients with DRD following levodopa treatment, in that, they underscore the importance of early diagnosis, prompt treatment, and possible genetic modification based on ethnicity in patients with DRD.

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