



CASE REPORT

Case Report: Guitarist's cramp as the initial manifestation of dopa-responsive dystonia with a novel heterozygous GCH1 mutation [version 1; peer review: 2 approved, 1 approved with reservations]

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Abstract

Dopa-responsive dystonia (DRD), also known as Segawa syndrome, is a phenotypically and genetically heterogeneous group of neurological disorders that typically presents as early-onset lower limb dystonia with diurnal fluctuation, and exhibits a marked, persistent response to levodopa. Heterozygous loss-of-function mutations in the guanosine triphosphate cyclohydrolase 1 (GCH1) are the most common cause of DRD. In addition to the classic form of the disease, there have been a number of studies addressing atypical clinical features of GCH1 related DRD with variable age of onset. This report describes a 37-year-old Japanese male patient with a 10-year history of focal upper limb dystonia that initially emerged as task-specific, guitarist's cramp. The dystonic symptoms responded very well to levodopa treatment, and genetic analysis identified a novel heterozygous mutation in the C-terminal catalytic domain of GCH1. Insufficient recognition of this treatable condition often leads to misdiagnosis, which causes delays in the patient receiving adequate dopamine replenishing therapy. A diagnostic trial with levodopa should be considered in all patients with relatively young-onset dystonia, whether they have classic features of DRD or not.

Keywords

Guitarist's cramp, dystonia, task-specific, dopa-responsive, dopamine, Segawa syndrome, GCH1, DYT5a

Open Peer Review

Reviewer Status   

	Invited Reviewers		
	1	2	3
version 1			
07 May 2021	report	report	report

1. **Hiroshi Ichinose** , Tokyo Institute of Technology, Yokohama, Japan
2. **Taku Hatano** , Juntendo University, Tokyo, Japan
3. **Juei-Jueng Lin**, Chushang Show-Chwan Hospital, Nantou, Taiwan

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: **Hasegawa T:** Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Validation, Visualization, Writing – Original Draft Preparation; **Hosaka T:** Investigation, Resources; **Harada R:** Investigation, Resources; **Kawahata I:** Funding Acquisition, Investigation, Methodology; **Hoshino K:** Supervision; **Sugeno N:** Investigation, Resources; **Kikuchi A:** Investigation, Resources; **Aoki M:** Supervision

Competing interests: No competing interests were disclosed.

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Introduction

Dopa-responsive dystonia (DRD, Segawa syndrome) is a rare movement disorder typically characterized by childhood-onset walking difficulties due to lower limb dystonia, diurnal fluctuation, and dramatic, sustained response to relatively low-dose levodopa treatment¹. Striatal dopamine deficiency due to loss-of-function mutations in the guanosine triphosphate cyclohydrolase 1 (GCH1, EC 3.5.4.16) is the most common etiology in the autosomal dominant form of DRD (DYT5a, OMIM 128230), in which incomplete penetrance and variable phenotype are observed². Owing to its diverse clinical presentations and poor recognition by general practitioners, DRD is under-reported and may be mistaken for other conditions such as cerebral palsy or psychogenic movement disorder. In this report, an unusual, adult case of DRD/DYT5a initially presenting as guitarist's dystonia is described.

Case report

The 37-year-old, right-handed Japanese man with a professional career as a guitar player, was referred to our hospital for the reassessment of upper limb dystonia. Upon assessment, no family history of neurological disorders was reported, and he did not use any regular medication before onset. At the age of 27 years, he began to spend most of his time practicing guitar and three months later, he felt difficulty in picking a pick due to excessive wrist extension and intermittent, tremulous finger movement in the right hand. At the age of 29 years, he was diagnosed with having guitarist's cramp, for which the oral administration of clonazepam (1.5 mg/day) and trihexyphenidyl (6 mg/day) were prescribed. This treatment proved to be ineffective. After switching from guitar to piano, these strange movements transiently disappeared but later reappeared. Meanwhile, the task-specificity of hand dystonia was gradually lost, and the disabling hand dystonia was induced by other daily activities including opening/closing a screw cap bottle and the brushing of his teeth. After five years from the onset, he had considerable difficulty in playing instruments, and finally, he decided to end his musical activities.

During consultation, neurological examination of cranial nerves, motor function, coordination, sensory function, and autonomic function showed unremarkable results. This was with the exception of action-induced dystonic posturing of the right upper limb with excessive wrist extension and hyperextension of the fingers, though these findings only became prominent during voluntary, skilled movement (Video S1, *Extended data*³). Neither sensory trick nor diurnal variation was observed. Other abnormalities, including cognitive dysfunction, parkinsonism, pyramidal signs, and cerebellar ataxia, were not detected. Workup including electrolytes, renal function tests, complete blood count, liver function tests and urinalysis were unremarkable. In addition, the levels of serum copper and ceruloplasmin were normal. Cranial magnetic resonance imaging and dopamine transporter (DAT) imaging with ¹²³I-β-CIT (2β-carbomethoxy-3β-(4-iodophenyl) tropane) single-photon emission computed tomography were normal (Figure 1). The diagnosis of DRD was suspected since the oral administration of levodopa (300 mg per day) showed dramatic, sustained improvement of the dystonic symptoms on the following day (Video S2, *Extended data*³), and cerebrospinal fluid analyses revealed a significant decrease in homovanillic acid (22.6 ng/ml, normal range: 41.6–178 ng/ml), 5-hydroxyindoleacetic acid (9.1 ng/ml, normal range: 20.0–96.0 ng/ml), and total neopterin (2.0 pmol/ml, normal range: 9.0–20.0 pmol/ml) levels⁴. The clinical suspicion of DRD was further strengthened by exome analysis and Sanger sequencing showing a novel heterozygous mutation c. 542T>G (p. Val181Gly) in the first amino acid of exon 5 in GCH1 gene (Figure 2A). The first Val in the 5th exon was located in the enzymatic core of GCH1 at the C-terminus⁵, and is highly conserved across species (Figure 2B). This amino acid substitution was predicted to be pathogenic using the *in silico* analysis tools, SIFT and PolyPhen-2. In the half-year follow-up, the patient's dystonic symptom was well-controlled by the levodopa therapy without any adverse side effects.

Discussion

In most cases of adult-onset focal limb dystonia, the exact, underlying etiology remains unclear, but in some cases, dystonia

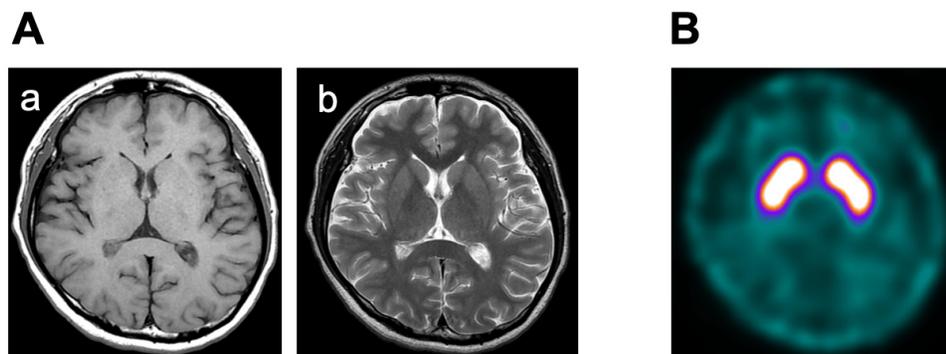


Figure 1. **A:** Cranial magnetic resonance imaging shows no abnormality in (a) T1 and (b) T2 axial sequences. **B:** Transverse dopamine transporter image with ¹²³I-β-CIT (2β-carbomethoxy-3β-(4-iodophenyl)tropane) single-photon emission computed tomography demonstrates normal binding of radioligand in both caudate nuclei and putamina.

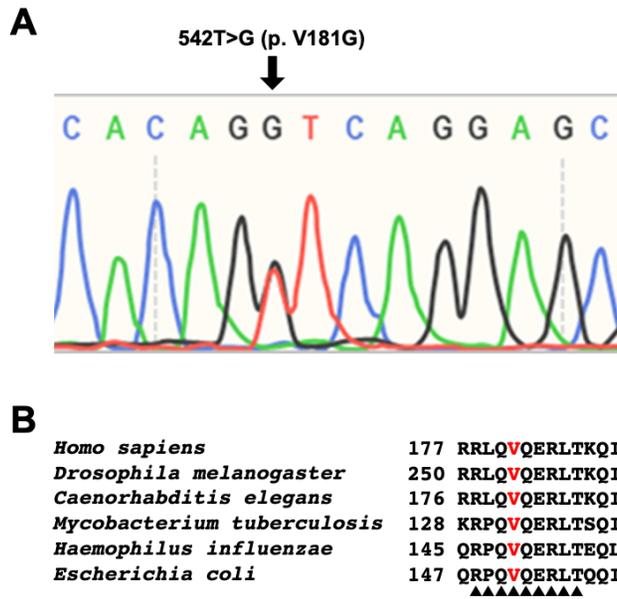


Figure 2. A: Sanger sequencing chromatogram which shows a novel heterozygous mutation c. 542T>G (p. Val181Gly) in the first amino acid of exon 5 in the GCH1 gene (*black arrow*). **B:** Amino acid sequence alignment of the GCH1. Note that the first Val in exon 5 (highlighted in *red*) is highly conserved across species. Residues involved in catalysis are highlighted with *black triangles*

occurs due to specific biochemical defects and genetic alterations⁶. A good example is the DRD caused by genetic defects in dopamine biosynthesis. Deficiency of GCH1, a rate-limiting enzyme in the biosynthetic pathway of tetrahydrobiopterin, is the most common and well-characterized condition that manifests as DRD⁷. In contrast to the childhood-onset GCH1-related DRD, adult cases often present parkinsonism followed by dystonia, and the movement problems progress slowly without diurnal variation^{8,9}. Furthermore, a number of studies describing atypical or incompatible features of GCH1 deficient-DRD with variable age of onset exist². Theoretically, DRD is considered to be a neurotransmitter disorder that is not accompanied by the nigrostriatal degeneration; however, some patients with adult-onset dystonia-parkinsonism or Parkinson’s disease without any dystonic feature carrying GCH1 mutation have been known to show abnormal DAT imaging².

The most conspicuous feature in this patient’s case is that the dystonic movement which started to present as a guitarist’s cramp. Although infrequent, a few reports of DRD/DYT5a presenting task-specific dystonia in the upper limb have been presented^{10,11}. Among them, the most common phenotype was writer’s cramp, which became obvious during the disease progression. Conversely, there was only one case report which presented adult-onset guitarist’s cramp in the family carrying GCH1 truncating mutation (p. Arg216stop)¹². A genotype-phenotype correlation was unlikely, because even among members of the same family with the same mutation, the movement symptoms were different. While the pathophysiology of task-specific or occupational dystonia still remains elusive, overtraining and

genetic predisposition may contribute to the expression of dystonic symptoms. Indeed, about 20% of patients with musician’s dystonia have a family history of the disorder, and a genome-wide association study demonstrated a possible link between musician’s dystonia and the intronic variant in the arylsulfatase G gene¹³. Furthermore, patients with DYT1 and DYT11 dystonia rarely have writer’s cramp as the cardinal symptom^{14,15}. Although we did not conduct personality and behavioral assessment of the patient, specific personality traits including susceptibility to anxiety and stress, or perfectionism may also increase the risk of developing dystonia¹⁶.

In conclusion, we reported a case of a 37-year-old male who was diagnosed with DRD/DYT5a, which was confirmed through genetic sequencing. The patient presented focal upper limb dystonia which first emerged as task-specific, guitarist’s cramp. The clinical heterogeneity of DRD often makes diagnosis difficult and leads to therapeutic delay. Our experience further underscores the broad clinical presentations of DRD as well as advocating for the diagnostic value of trying levodopa and genetic testing in dystonia.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Extended data

Dryad: Dopa-responsive dystonia patient response before and after levodopa treatment. <https://doi.org/10.5061/dryad.pzgmsbckd3>.

This project contains the following extended data:

- Video S1 (.MOV video of the neurological assessment on admission. Dystonic posturing of the right upper limb with excessive wrist extension and hyperextension of the fingers are seen during the opening of a screw cap bottle. No parkinsonism, pyramidal signs or cerebellar ataxia are observed)
- Video S2 (.MOV video taken on the following day after the oral administration of 300 mg per day of levodopa. The task-specific dystonia in the right upper limb is dramatically improved).

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

Consent

Written informed consent for publication of the clinical details, diagnostic images and videos was obtained from the patient.

Author contributions

Conceptualization: THA

Formal Analysis: THA

Funding Acquisition: THA, IK

Investigation: THA, THO, RH, IK, NS, AK

Methodology: THA, IK

Project Administration: THA

Resources: THA, THO, RH, NS, AK,

Supervision: KH, MA

Validation: THA

Visualization: THA

Writing – Original Draft Preparation: THA

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Current Peer Review Status:   

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Reviewer Report 17 August 2021

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? Juei-Jueng Lin

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Hasegawa T *et al.* report a young adult man with a 10-year history of upper limb dystonia that mimicked as task-specific dystonia. His dystonia responded well to Levodopa treatment and his genetic study revealed a novel heterozygous mutation of GCH1 gene. Therefore, they conclude task-specific dystonia can also be one phenotype of Segawa syndrome or dopa-responsive dystonia (DRD). Meanwhile, a series of neuroimaging studies of this case including CT, MRI and SPECT of the brain were all negative results.

I am interested in this case, but I have three major comments on this paper:

1. The authors emphasized that the patient presented guitarist's cramp in his early stage of disease, three months later after an intensive practice of guitar. Meanwhile, they also described the dystonia can also appear in playing other instruments and in some daily activity. This manifestation is different from the disease course of idiopathic task-specific dystonia. The authors should discuss the differences between idiopathic task-specific dystonia and genetic related task-specific dystonia.
2. The patient responded well to treatment with levodopa and was subsequently diagnosed to be DRD, but did not have a family history. The genetic testing for GCH1 gene revealed a novel heterozygous mutation of c. 542T>G. However, the paper does not mention genetic analysis for GCH1 of his parent or siblings. Therefore, the authors should provide the genetic testing of GCH1 of other families to confirm genetic basis of their reported patient. In addition, they also can discuss the intrafamilial variability of phenotype in DRD family.
3. The authors also reported a normal presynaptic nigrostriatal dopamine function by a normal SPECT study in their DRD case. There have been reports in literature with an abnormal presynaptic nigrostriatal dopamine function in DRD patient presented with either dystonia or Parkinsonism. The author should discuss the relationship of presynaptic dopamine function in patients with DRD presented with variably clinical phenotypes.

Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Parkinson's disease and related disorders

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 09 August 2021

<https://doi.org/10.5256/f1000research.54602.r90523>

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✓ **Taku Hatano** 

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Hasegawa and colleagues reported the case with DYT5, who exhibited the focal dystonia mimicking musician's cramp. They described the patient's medical story and assessed the patient's state by appropriate examinations, including neurological examination, cranial MRI, DAT scan, and genetic analysis. They also mentioned the important learning points. Thus, I am interested in this paper.

But I have a comment on this paper.

Major point:

- The authors pronounced that in the early stage, the patient exhibited the mimicking guitarist's cramp, but his dystonia emerged in not only task-specific but also usual situations. This finding is different from idiopathic task-specific dystonia in the disease course. The authors should discuss the difference between genetic-related and idiopathic task-specific dystonia.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Parkinson's disease, Movement disorders

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 08 June 2021

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Hiroshi Ichinose 

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The authors described an adult male case of DRD/DYT5a who initially developed focal upper limb dystonia and diagnosed as guitarist's dystonia, and found that the dystonic symptoms responded very well to levodopa treatment. They propose that a diagnostic trial with levodopa should be considered in all patients with relatively young-onset dystonia regardless of whether they have typical features of DRD or not.

This paper is worthwhile publishing to report that adult-onset focal limb dystonia can be presented in patients with DRD/DYT5a, suggesting a broad clinical presentation of DRD/DYT5a.

The reviewer would like to ask for the following minor revision to the manuscript;

1. The authors should discuss the benefits and possible adverse effects of levodopa treatment for the patients with dystonia, whereas the authors propose the diagnostic value of levodopa treatment.
2. The biochemical analysis of HVA and neopterin in the CSF is beneficial for a differential

diagnosis of DRD/DYT5a from other types of dystonia/parkinsonism. It should be discussed clearly in the text.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Biochemistry

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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