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Correspondence to
Sung-Rae Cho
Department and Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
E-mail: srcho918@yuhs.ac

HIGHLIGHTS

- We present a case of juvenile parkinsonism with *PARK2* gene mutation.
- This patient was previously misdiagnosed as dopa-responsive dystonia.
- Parkinson's disease was later diagnosed via next-generation sequencing.

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Juvenile Parkinsonism with *PARK2* Gene Mutation Misdiagnosed as Dopa-responsive Dystonia: a Case Report

Seungbeen Hong [1], **Suji Lee** [1], **Sung-Rae Cho** [1,2]

[1]Department and Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine, Seoul, Korea
[2]Brain Korea 21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul, Korea

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Correspondence to
Sung-Rae Cho
Department and Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
E-mail: srcho918@yuhs.ac

ORCID iDs
Seungbeen Hong
https://orcid.org/0000-0002-8222-2920
Suji Lee
https://orcid.org/0000-0002-6376-0125
Sung-Rae Cho
https://orcid.org/0000-0003-1429-2684

Conflict of Interest
The authors have no potential conflicts of interest to disclose.

ABSTRACT

Parkinson's disease is prevalent in elderly patients, usually aged over 50 years. If clinical symptoms of parkinsonism appear before 21 years of age, it is called juvenile parkinsonism (JP). JP may present atypical features such as dystonia, and is often misdiagnosed as other diseases, including dopa-responsive dystonia (DRD). Here, we report a case of JP with *PARK2* mutation misdiagnosed as DRD. A 32-year old female, who presented dystonia of both legs, was initially diagnosed with hereditary spastic paraplegia and showed a dramatic response to low-dose L-dopa, which led to the diagnosis of DRD. However, Parkinson's disease caused by a mutation in the *PARK2* gene was later diagnosed via next-generation sequencing. Accurate understanding of JP is necessary for early diagnosis and comprehensive management of movement disorders at a young age.

Keywords: Juvenile parkinsonism; Genetic disorders; Dystonia

INTRODUCTION

Parkinson's disease is a common degenerative disorder of the nervous system that mainly affects movement. The cardinal symptoms include resting tremor, rigidity, bradykinesia and postural instability; these symptoms are called “parkinsonism” and progress gradually. Many of these symptoms are attributed to the degeneration of dopaminergic neurons in the substantia nigra, a region of the midbrain. Thus, the dopamine production becomes insufficient and movement control is impaired with Parkinson's disease.

Parkinson's disease is usually diagnosed in elderly patients over 50 years of age. However, there are some patients who develop parkinsonian features at younger ages. If parkinsonism starts before age 40, it has been called “Early onset Parkinson's disease (EOPD)” [1] and EOPD can be divided into 2 groups. “Young onset Parkinson's disease” is diagnosed when the parkinsonian symptoms start between 21 and 40 years, while “Juvenile Parkinsonism (JP)” is diagnosed with the onset occurs below age 21 [2]. Unlike late onset idiopathic Parkinson's disease, JP may present atypical features such as dystonia. Thus, JP is often misdiagnosed as other diseases, including dopa-responsive dystonia (DRD).

The aim of this report is to present a case of JP misdiagnosed as DRD. A 32-year old female, who presented dystonia of both legs, was initially diagnosed with hereditary spastic paraplegia. This patient showed diurnal variation of symptoms and dramatic responses to low-dose levodopa-carbidopa, which led to the diagnosis of DRD. However, the next-generation sequencing (NGS) study finally found *PARK2* mutation. Finally, she was diagnosed with JP caused by a mutation in the *PARK2* gene.

CASE REPORT

A 23-year old unmarried woman visited our outpatient clinic with gait disturbance. She had neither past medical history nor family history including genetic disorders (Fig. 1). She was a college student. When she was 19 years old, she visited the Department of Rehabilitation Medicine at another hospital for clawing of bilateral toes. Electromyography (EMG) was performed to evaluate muscle dystrophy or myopathic disease. The EMG findings were not compatible with any types of myopathy involving her legs. Thus, she was considered to have hereditary spastic paraplegia and remained untreated. Clawing of toes and gait disturbance continued and gradually progressed.

In December 2009, she visited our outpatient clinic for a comprehensive evaluation. During the physical examination, bilateral lower extremities remained normal except for left hip flexor (grade 4) with the manual muscle test. Muscle tone was increased in both her legs and hyperactive patellar tendon reflexes were noted. There was no clasp-knife response or cogwheel rigidity. While walking, in-toeing gait pattern in both legs, genu recurvatum in left knee and toe walking in right foot were observed. These patterns showed diurnal variation and worsened in the afternoon.

In January 2010, we conducted direct sequencing after polymerase chain reaction to test for *SPG4* (spastin) gene mutation underlying familial spastic paraplegia. No *SPG4* mutation was detected. Thus, we conducted a trial to compare pre- and post-administration of low-dose levodopa-carbidopa (3.5 mg/kg/day for levodopa; 100 mg at once for levodopa, twice a day) considering the possibility of DRD. Clinically, toe-clawing and toe-in gait improved after low-

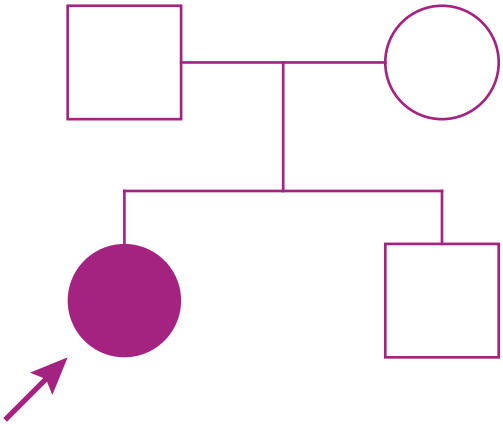

Fig. 1. Pedigree structure of the patient's family. The patient is indicated by an arrow. The major symptoms of the patient including dystonia were not expressed among other family members. Genetic evaluation for the family was unavailable.

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dose levodopa-carbidopa administration. Temporospatial gait analysis was compared before and after administration and the parameters of cadence, walking speed, step length, and step time improved (Table 1). Before low-dose levodopa-carbidopa administration, the movement score of the dystonia rating scale (DRS) was 10 out of 120 points and the disability score of the DRS was 5 out of 30 points. After the treatment, the movement and disability scores of the DRS were improved by 2 and 1 scores respectively (Table 2). Most of the patient's symptoms and patterns of diurnal variation were improved after levodopa-carbidopa administration.

In September 2012, direct sequencing of the *GCH1* gene, which is known to be a cause of DRD, was performed. However, there was no mutation in the coding region of the *GCH1* gene. We still regarded her diagnosis as DRD and continued the levodopa-carbidopa treatment because *GCH1* gene mutation is not positive in all patients diagnosed with DRD and the patient's clinical symptoms were consistent with DRD. Initially, low-dose levodopa-carbidopa was effective for the patient. However, the demand for medication increased due to progressive gait disturbance. In December 2013, the dosage was increased to 7 mg/kg/day for levodopa.

In February 2018, NGS was conducted to identify other possible genetic factors via NGS panel including 193 genes related to dystonia. Massive parallel sequencing was performed using the MiSeq System (Illumina, San Diego, CA, USA). BaseSpace (Illumina) and NextGENE (SoftGenetics, State College, PA, USA) software programs were used for quality control and sequence analysis. Surprisingly, the NGS results showed *PARK2* exon 4 deletion indicating Parkinson's disease (Fig. 2). In addition, brain fluorine-18 fluoro-propyl-carbomethoxy iodophenyl-tropane positron emission tomography (FP-CIT PET), dopamine transporter PET imaging showed that decreased fluorine-18 FP-CIT uptake was detected in the bilateral putamina and posterior caudate nuclei (Fig. 3). Finally, she was diagnosed with JP with *PARK2* gene mutation.

In July 2018, 7 mg/kg/day of levodopa-carbidopa was administered, which showed improvement of gait disturbance. Both movement and disability scores of the DRS were improved to 1, respectively (Table 2). We checked the DRS after stopping the medication for one day, and the scores of the movement and disability scores worsened to scores of 12 and 3, respectively, similar to pre-levodopa-carbidopa score (Table 2). After the diagnosis of JP, we started new medicines such as levodopa/benserazide, rasagiline, and ropinirole under consultation with the Department of Neurology. Follow-up evaluations showed improvement in both movement and disability scores of the DRS which were 1, respectively (Table 2).

Table 1. Temporospatial parameters of gait analysis before and after levodopa-carbidopa administration

Temporospatial parameters	Before levodopa-carbidopa administration		After levodopa-carbidopa administration		Improvement (%)	
	Right	Left	Right	Left	Right	Left
Cadence (steps/min)	87.80	91.28	112.00	114.00	27.56	24.89
Walking speed (m/sec)	0.80	0.78	1.20	1.18	50.00	51.28
Step length (m)	0.55	0.54	0.66	0.63	20.00	14.55
Step time (sec)	0.66	0.70	0.54	0.53	19.40	24.29

Table 2. Dystonia rating scale scores before and after levodopa administration

Dystonia rating scale	Before levodopa-carbidopa administration	Levodopa-carbidopa (3.5 mg/kg/day)	Levodopa-carbidopa (7.0 mg/kg/day)	Medication (stop at 2018.07.24)	Levodopa-benserazide, rasagiline, ropinirole
Date	2009.12.08	2010.04.15	2018.07.23	2018.07.25	2018.07.31
Movement score	10	2	1	12	1
Disability score	5	1	1	3	1

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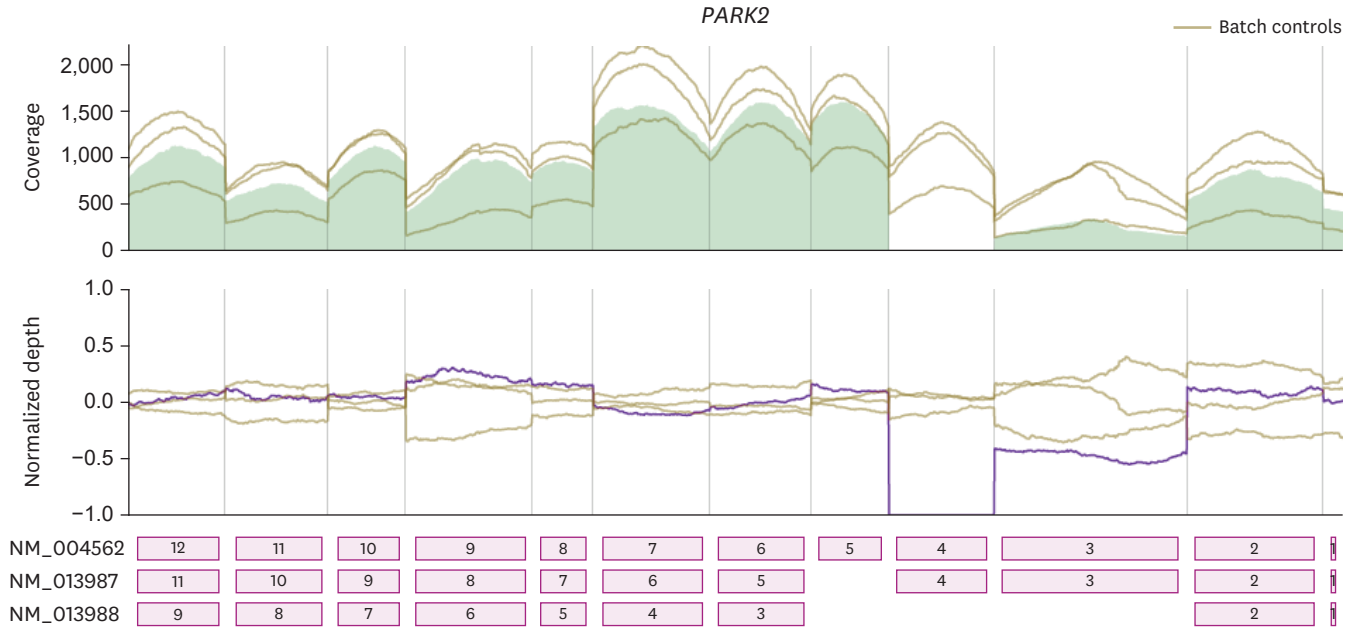

Fig. 2. Result of NGS using a panel including 193 genes related to dystonia. NGS result shows homozygous deletion of exon 4 detected in *PARK2* gene.
NGS, next-generation sequencing.

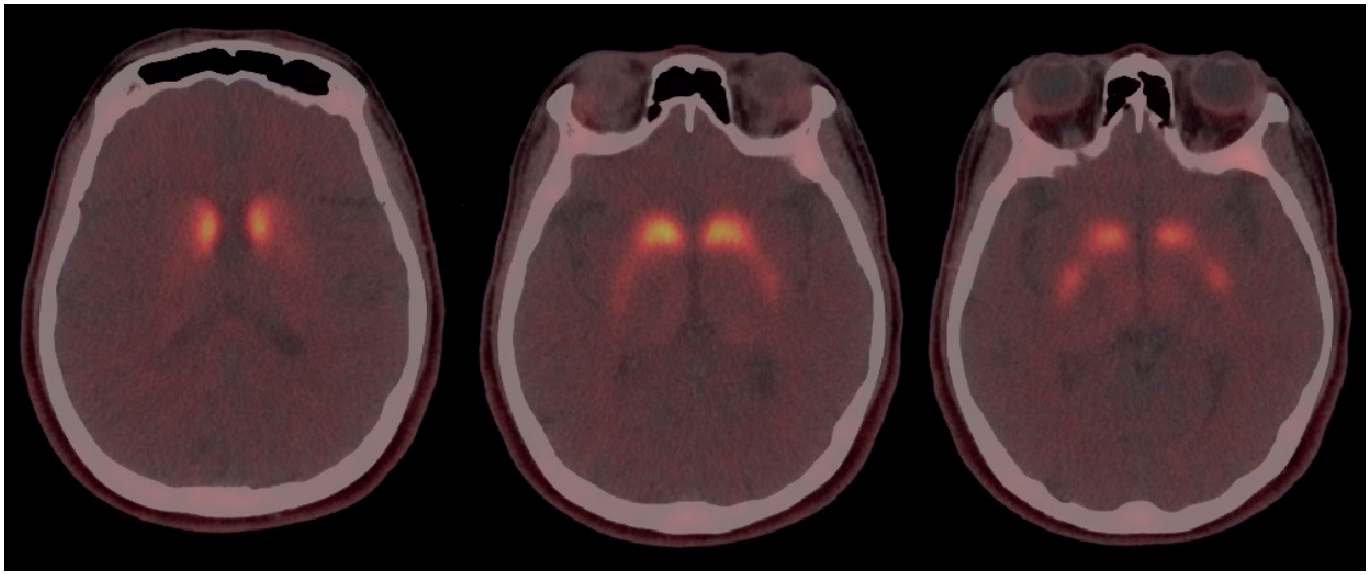

Fig. 3. Finding of brain dopamine transporter PET imaging. Hypometabolism in the bilateral putamina and posterior caudate nuclei was noted in fluorine-18-FP-CIT PET-CT images.
FP-CIT PET-CT, fluoro-propyl-carbomethoxy iodophenyl-tropane positron emission tomography-computed tomography.

In addition to pharmacological treatment, we prescribed comprehensive rehabilitation program including strengthening and endurance training for lower extremities and gait pattern correction. Berg balance scale of this patient scored 56 out of 56; however, she showed poor standing balance even after a short exercise. We trained how to exercise to improve muscular strength and endurance, and corrected her toe walking pattern. After short-term rehabilitation program focusing on patient education, she felt comfortable while walking and climbing stairs in her daily life.

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DISCUSSION

JP is a term describing parkinsonian syndromes occurring before 21 years of age. Parkinsonian syndrome includes resting tremor, bradykinesia or akinesia, rigidity, loss of postural reflexes and other atypical conditions such as dysautonomia, and dystonia. This concept was first introduced about a century ago, but it is still a rare disease [3]. Quinn et al. [2] described 4 cases and Cardoso et al. [4] introduced 6 patients diagnosed with JP.

There are various illnesses showing similar initial presentations, such as DRD. Therefore, the differential diagnosis of JP must include genetic, degenerative, infectious, metabolic or immune-mediated causes [5]. Genetic causes involving *PARK2* (parkin), *PINK1* (PTEN-induced putative kinase 1) and *PARK7* mutation are known to be associated with autosomal recessive JP. *PARK2* mutation is a major cause of JP. Parkin is a component of an E3 ubiquitin ligase complex that involves targeting of proteins for degradation, including alpha-synuclein [6]. The exact mechanism of *PARK2* mutation in JP remains unclear; however, a decreased dopaminergic uptake was detected in functional imaging [7].

Symptoms of JP associated with *PARK2* mutation encompass typical parkinsonian syndrome, and especially dystonia involving bilateral lower extremities usually occurs at onset. Patients with JP are more likely to manifest dystonia at onset, hyperreflexia, symmetric involvement of symptoms and responsiveness to levodopa; however, the side effects induced by levodopa treatment such as levodopa-induced dyskinesia occur earlier [8]. Diurnal fluctuations may occur in JP associated with *PARK2* mutation [9]. In the present case, dystonia of bilateral lower extremities was present at onset and hyperreflexia in bilateral knee jerks, diurnal fluctuation, and levodopa effects were noted. The temporospatial data of gait analysis and DRS scores improved with levodopa-carbidopa administration.

DRD is a group of genetic diseases characterized by dystonia in childhood. Segawa disease, the most common cause of DRD, is attributed to an autosomal dominant *GCH1* deficiency [10]. Similar dystonia can be seen in autosomal recessive GCH, tyrosine hydroxylase (TH) or sepiapterin reductase (SPR) deficiency [10]. Initially, dystonia begins with lower extremities and gradually progresses to disability involving all 4 limbs within 4 to 5 years. Similar to JP, gait disturbances associated with diurnal variation and response to low-dose levodopa can present in patients with DRD. However, complications related to levodopa treatment are uncommon in DRD with *GCH1* deficiency. In this case, *GCH1*, *TH*, *SPR* genes are included in our NGS panel, we could find no deletions or duplications of these genes.

Additional potential causes may include Wilson's disease, Juvenile-onset Huntington's disease, spinocerebellar ataxias, immune-mediated or infectious causes, toxins, and drugs. No exposure to medications or toxins and no abnormal laboratory findings of liver enzymes or evidence of infection were found in this patient. Clinical symptoms were not compatible with Wilson's disease, Huntington's disease, or spinocerebellar ataxia.

The differential diagnosis of JP and DRD has been reviewed by Wijemanne and Jankovic [10]. For imaging methods, dopamine transporter PET and single-photon emission CT (SPECT) could be used to distinguish between DRD and JP. The dopamine transporter density and fluorodopa uptake decreased in JP, while in DRD these parameters are mostly known to be normal [10]. As above, decreased fluorine-18 FP-CIT uptake was observed in this patient.

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Similar to our case, Tassin et al. [11] showed some patients presenting dystonia at onset, progressive parkinsonism and low-dose levodopa effect, later diagnosed with *PARK2* mutation. A patient reported by Eggers et al. [12] presented late onset parkinsonian symptoms without signs of dystonia, and showed heterozygous *GCH1* deletion with definite reduction of dopamine transporter density, implying that imaging studies, such as dopamine transporter PET or SPECT, are not sufficient for discriminating JP from DRD supporting the necessity of an early complementary genetic confirmation test.

In conclusion, we present a JP patient previously misdiagnosed as DRD. The differential diagnosis of JP and DRD is complex since both are heterogenous neurological disorders associated with similar symptoms in adolescence. It is necessary to consider other conditions that cause abnormal movement. Although genetic testing is not common, further investigations including genetic studies or imaging studies can facilitate the diagnosis and predict patient's prognosis accurately.

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