2년간 뇌성마비로 오진된 *GCH1* 유전자 돌연변이를 동반한 도파 반응성 근긴장이상증 증례

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A Case of Dopa-responsive Dystonia with a Mutation in the *GCH1* Gene Misdiagnosed as Cerebral Palsy for 2 Years

Dopa-responsive dystonia (DRD) is characterized by lower limb-onset, diurnally fluctuating dystonia and dramatic and sustained response to levodopa treatment. Segawa disease, an autosomal dominant deficiency of guanosine triphosphate cyclohydrolase 1 (encoded by *GCH1*) is the most common and well-known condition manifesting as DRD. However, similar clinical manifestations can be seen in individuals with deficiencies of other enzymes that are involved in the biosynthesis of dopamine. We describe the case of an 11-year-old girl who presented with abnormal gait, which had initially begun 2 years back. The patient showed diurnally fluctuating dystonia in both legs. She was able to walk without support in the morning, but was unable to stand without support in the evening. She had been diagnosed as having spastic cerebral palsy and had been managed with physical therapy at a local rehabilitation clinic. The patient had been healthy until the development of dystonia, and did not have a history of perinatal problems or developmental delay. Routine hematologic and biochemical test results were normal. Brain magnetic resonance imaging and electroencephalography showed no abnormalities. When levodopa was administered, the patient's abnormal gait dramatically improved 1 hour after receiving the medication. Genetic testing for the *GCH1* gene revealed a missense mutation (c.293C>T [p.A98V]) that has previously been reported in patients with DRD. This case demonstrated that a levodopa trial is vital for accurate and early diagnosis of DRD in patients with dystonia resulting from an unknown cause.

Key Words: Dopa-responsive dystonia, Levodopa, Cerebral palsy, Diagnostic Errors, *GCH1* gene

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Introduction

Dopa-responsive dystonia (DRD) is characterized by lower limb-onset, diurnally fluctuating dystonia, and dramatic and sustained response to levodopa treatment¹⁾. DRD is an uncommon condition with a prevalence of 0.5 to 1 per 1,000,000, and is more common in females than males (2.5–4:1)^{2,3)}.

Autosomal dominant deficiency of guanosine triphosphate cyclohydrolase 1

(GTP-CH-I), also known as Segawa disease, is the most common and well-researched type of DRD. GTP-CH-I is encoded by the *GCHI* gene on chromosome 14q22.1-14q22.2⁽⁴⁾. It is a rate-limiting enzyme for the biosynthesis of tetrahydrobiopterin (BH4), which is a co-factor for tyrosine hydroxylase, the rate-limiting enzyme for dopamine biosynthesis⁽¹⁾. Deficiency of other rate-limiting enzymes for dopamine biosynthesis can also cause clinical presentation of DRD.

DRD typically presents as action dystonia of the lower limbs in the first decade of life⁽²⁾. The condition progresses to segmental or generalized dystonia associated with marked gait difficulty and postural instability⁽⁵⁾. Some early-onset DRD cases used to be misdiagnosed as cerebral palsy⁽⁶⁾. Although DRD is readily treatable with levodopa, misdiagnosis may cause patients with DRD to live with persistent neurologic deficits. We describe a case of DRD with a mutation in the *GCHI* gene that has been misdiagnosed as spastic cerebral palsy for 2 years.

Case report

An 11-year-old girl was admitted to the Child Neurology Clinic at Ulsan University Hospital due to abnormal gait that had started 2 years prior. The patient presented with diurnally fluctuating dystonia in both legs. She was able to walk on her own in the morning, but could not stand up on her own in the evening. She had a diagnosis of spastic cerebral palsy, which had been managed with physical therapy at a local rehabilitation clinic until recently. The patient had been healthy until the development of dystonia, and did not have a history of perinatal problems or developmental delay. She had no family history of neurological diseases. She entered the clinic in a wheelchair. On neurologic examination, she was fully alert and oriented, and all of her cranial nerves were intact. The patient had normal motor power in the extremities. Muscle tone was spastic in both legs, but normal in the arms, neck, and trunk. She showed a normal sensory response to light touch and pain. Knee and ankle jerks were normoactive, and the Babinski sign was absent. Her cerebellar function was intact. Laboratory results revealed serum total calcium was 9.4 mg/dL, creatinine kinase was 106 IU/L, thyroid stimulating hormone was 1,360 μ U/mL, and free T4 was 0.85 ng/dL. A screening test for Wilson disease (ceruloplasmin 21.4 mg/dL and 24-hour urine copper 18.40 μ g/day) had results within normal limits. Brain magnetic resonance imaging showed no abnormalities. Electroencephalographic findings were normal. A levodopa trial (levodopa 100 mg and carbidopa 25 mg, orally) was initiated the afternoon of the patient's second

day in the hospital. Her abnormal gait dramatically improved 1 hour after receiving the medication, and she was then able to walk on her own (Fig. 1). Genetic testing for the *GCHI* gene revealed a missense mutation (c.293C>T [p.A98V]) that has previously been reported in patients with DRD (Fig. 2)⁽⁷⁾. Genetic testing for the Torsin family 1, member A (*TOR1A*) gene showed negative result. She complained of intermittent myoclonus in the legs a week following commencement of the levodopa treatment (levodopa 100 mg and carbidopa 25 mg, orally three times a day), but this completely disappeared several months later without modification of the medication dosage. Fourteen months after beginning levodopa treatment, the patient had no issues performing her usual activities and was even able to participate in physical education classes without any difficulty.

Discussion

In 1976, Segawa first described a condition in 9 patients from 6 families, characterized by dystonia that developed as the day progressed and responded to treatment with levodopa⁽⁸⁾. This condition, called DRD, has symptom onset at a mean age of 6–11 years^(9,10), and typically presents with action dystonia in both lower limbs. Patients with DRD show equinovarus foot posturing and impaired walking and balance⁽⁵⁾. A gradual progression to segmental or generalized dystonia follows. Diurnal fluctuation of dystonia appears in 56–80% of the

Fig. 1. Gait features of patients with dopa-responsive dystonia before and 2 hours after levodopa administration. (A) The patient shows equinovarus foot posturing and required the support of a banister to walk before levodopa administration. (B) The patient was able to walk on her own, without apparent equinovarus foot posturing, after levodopa administration.

Fig. 2. Genetic testing for the *GCH1* gene. Note a missense mutation, c.293C>T (p.A98V).

patients¹⁰⁾. The degree of diurnal fluctuation diminishes with age, and usually little or no fluctuation remains by the third decade of life⁴⁾. Disappearance of the characteristic diurnal fluctuation makes it difficult to accurately diagnose DRD. In this current case, the patient showed childhood onset dystonia in the lower limbs with obvious diurnal fluctuation, and no history of perinatal problems or developmental delay. Based on her typical clinical presentation and medical history, we were able to diagnose DRD without difficulty.

The first step in the diagnosis of DRD is to establish responsiveness of the dystonia to levodopa by means of a levodopa trial^{1,10)}. Levodopa is administered in combination with a peripheral decarboxylase inhibitor, such as carbidopa or benserazide, to block conversion of levodopa to dopamine in the periphery¹⁾. DRD is a readily treatable condition, and the effect of levodopa is rapid, dramatic, and sustained. If no response is seen after 1 month, the trial should be aborted¹⁾. Once the responsiveness of dystonia to levodopa has been established, a genetic test for *GCH1* gene is the simplest means of confirming a diagnosis of DRD^{1,10)}. However, some patients with DRD may have mutations in other genes, such as the *TH* and *SPR* genes, and others may have no identifiable mutation¹⁾. Furthermore, the *GCH1* gene mutation does not necessarily result in DRD. In addition to autosomal dominant deficiency of GTP-CH-I (Segawa disease), deficiency in the other rate-limiting enzymes for dopamine biosynthesis, such as tyrosine hydroxylase, sepiapterin reductase, and 6-pyruvoyltetrahydropterin synthase can also cause clinical presentation of DRD¹⁾.

If genetic tests are negative or inconclusive, but the patient's phenotype suggests DRD, cerebrospinal fluid (CSF) analysis can be useful to determine which rate-limiting step of the dopamine biosynthesis is deficient, based on neurotransmitter profiles¹⁾.

Low CSF concentrations of homovanillic acid and 5-hydroxyindoleacetic acid, metabolites of dopamine and serotonin, respectively, are found in all BH4 deficiency variants¹¹⁾. If CSF analysis in patients with DRD reveals low concentrations of homovanillic acid, 5-hydroxyindoleacetic acid, neopterin, and BH4, a GTP-CH-I deficiency is indicated^{1,11)}. Meanwhile, when neopterin is high and BH4 is low, a 6-pyruvoyltetrahydropterin synthase deficiency is indicated, and when BH4 concentrations are very high, a dihydropteridine reductase deficiency is indicated. A DRD case diagnosed on the basis of the typical clinical features and decreased neopterin level in CSF was reported in Korea in 2004¹²⁾.

Another method of diagnosing DRD is by using abnormalities in phenylalanine metabolism as indicators^{1,13)}. BH4 is required as a cofactor in the breakdown of phenylalanine to tyrosine. The autosomal recessive mutation in GTP-CH-I not only reduces monoamine synthesis in the brain, but also interferes with phenylalanine metabolism in the liver, which can lead to hyperphenylalaninaemia¹³⁾. However, the autosomal dominant mutation in this gene selectively affects the brain and not the liver; hence, it does not cause baseline hyperphenylalaninaemia. The phenylalanine loading test is conducted by administering 100 mg/kg phenylalanine and subsequently measuring the phenylalanine:tyrosine ratio in the blood at different time intervals^{1,3)}. Patients with mutations in *GCH1* or *SPR* have an increased phenylalanine:tyrosine ratio in the blood, 1–2 h after phenylalanine administration. However, false-negative and false-positive results have also been reported¹³⁾.

DRD should be considered in the differential diagnosis of disease in children or adolescents presenting with a dystonic gait, diplegic cerebral palsy, sporadic spastic paraplegia, ataxic syndrome, and juvenile parkinsonism^{8,14)}. In this case, the patient

had been misdiagnosed with spastic cerebral palsy for 2 years, and managed with physical therapy before admission to our hospital. A previous study has reported that 24% of the patients with DRD are misdiagnosed with cerebral palsy¹⁾. Cases of DRD misdiagnosed as cerebral palsy have been reported in Korea. One report described a young woman with DRD misdiagnosed as cerebral palsy for over 10 years¹⁵⁾. The patient began to show an abnormal tiptoe gait at the age of 8 years. She was initially diagnosed as having cerebral palsy and received physical therapy and muscle relaxants, as in the present case. Levodopa treatment was finally commenced when she was 20 years old. Her symptoms dramatically improved within days. However, the thoracolumbar scoliosis persisted as a sequela, due to late identification of DRD. She revealed the same *GCH1* gene mutation observed in the present case. As shown in this and previous reports, due to the prevalence of misdiagnoses, a levodopa trial should be considered for all infants or children with dystonia of unknown cause.

The dosage and regimen of levodopa used for treatment of DRD depends on the precise nature and severity of the condition. A low dose of levodopa (50–200 mg) daily, combined with a peripheral decarboxylase inhibitor, is often sufficient for almost complete resolution of neurologic deficits¹⁾. Even though levodopa therapy is delayed for many years, most patients respond well to this low dose regimen. Some patients may have residual symptoms, and others can develop levodopa-induced dyskinesia⁹⁾. Fortunately, the patient in this case had no residual symptoms, and the levodopa-induced myoclonus during the initial treatment spontaneously subsided without specific management.

In conclusion, this case demonstrated that as DRD is a readily treatable neurological condition, a levodopa trial is vital for accurate and early diagnosis of DRD in patients with dystonia, particularly children or adolescents with dystonia resulting from an unknown cause.

요약

도파 반응성 근긴장이상증은 근긴장이상 증상이 하지부터 시작되고, 일간 변동성을 보이며, 레보도파 치료에 극적이고 지속적인 반응을 나타내는 특징을 갖는다. Segawa 병이라고도 불리는 상염색체 우성 GTP cyclohydrolase 1 결핍은 도파 반응성 근긴장이상증 중에 가장 흔하고 잘 알려진 질환이다. 하지만, 도파민의 생합성에 관련되는 다른 효소의 결핍이 있는 환자들에서도 유사한 임상 증상이 나타날 수 있다. 저자들은 이상 보행으로 발현된 도파 반응성 근긴장이상증 환자를 경험하였기에 보고하는 바이다. 11세 여자 환자는 2년 전

부터 양측 하지에 일간 변동성을 보이는 근긴장이상 증상이 나타났다. 아침에는 도움 없이 걸을 수 있었으나 저녁에는 혼자 서지도 못하였다. 환자는 본원 내원 전에 인근 재활의학과 의원에서 강직성 뇌성마비로 진단받고 물리치료를 받아 왔다. 환자는 근긴장이상증이 발생하기 전까지 건강했고, 출생력에 문제가 없었으며 발달 지연도 없었다. 일상적 혈액검사 및 생화학적 검사 결과는 정상이었으며, 뇌 자기공명 영상과 뇌파검사도 정상 소견이었다. 입원 2일째 레보도파를 시험적으로 투여하였는데, 투여한 후 1시간 만에 환자의 이상 보행이 극적으로 호전되었다. *GCH1* 유전자 검사에서 과거에 도파 반응성 근긴장이상증 환자에서 보고되었던 과오돌연변이(c.293C>T [p.A98V])가 확인되었다. 본 증례는 원인불명의 근긴장이상증 환자에서 도파 반응성 근긴장이상증을 정확하고 빠르게 진단하기 위하여 레보도파 시험을 해보는 것이 중요함을 보여주었다.

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