Dopa-responsive Dystonia with a Novel Initiation Codon Mutation in the GCH1 Gene Misdiagnosed as Cerebral Palsy

Jae-Hyeok Lee, Chang-Seok Ki, Dae-Seong Kim, Jae-Wook Cho, Kyung-Phil Park and Seonhye Kim

INTRODUCTION

Dopa-responsive dystonia (DRD) is a progressive primary dystonia that is characterized by onset during childhood, circadian fluctuation of symptoms and a dramatic and sustained response to low doses of oral administration of levodopa (1). DRD is frequently caused by GTP-cyclohydrolase 1 (GTPCH1) deficiency that up to 87% of the DRD is caused by mutations in the GCH1 gene encoding GTPCH1 (2, 3).

Although it is well-known that the clinical features of GTPCH1-deficiency can be extremely variable including benign adult-onset parkinsonism, various types of focal dystonia, DRD simulating cerebral palsy or spastic paraplegia, clinical diagnosis is still a challenge in some instances (4).

In Korea, there has been a few reports on the patients with DRD carrying the GCH1 mutations (5-10). Here, we report a young woman with a novel initiation codon mutation in the GCH1 gene who was severely disabled and misdiagnosed as cerebral palsy over than 10 yr.

CASE DESCRIPTION

She was referred to our clinic when she was 30 on February 22, 2009. She developed well until the age of 8 yr when an abnormal tiptoe gait was observed. It resulted in frequent falls. Her symptoms were mild in the morning and more prominent toward the end of the day. As the disease progressed, she had pes equinovarus posture at rest in both feet. At the age 15 she needed the support of two people to walk a short distance and started to use a wheelchair. At this age she also experienced stiffness and twisting in upper limbs, neck, and trunk. She found it difficult to write and use a chopstick. Her birth and developmental history was unremarkable. She had no prior history of head injury, meningitis, encephalitis, or febrile seizures. There was no known history of motor disorder in her family. She was initially diagnosed as having cerebral palsy. Brain CT was normal. She received physiotherapy and muscle relaxants with no benefit. When she was 20, Madopar® 250 mg was prescribed by neurologist. Her symptoms dramatically improved within days, and she could walk independently. She had been taking levodopa 200 mg/day for 10 yr with sustained benefit without emergence of motor fluctuations or other neurologic manifestations. She felt well and was leading a normal life. The fixed scoliotic deformity of thoracolumbar spine was noted on chest radiography (Fig. 1). Genetic testing using direct sequencing revealed a novel initiation codon mutation (c.1A>T; p.Met1Leu) in GTP cyclohydrolase 1 (GCH1) gene. Although it is known that DRD can be misdiagnosed as cerebral palsy, this case reinforces the importance of differential diagnosis of DRD from cerebral palsy.

Key Words: Dystonia, Dopa-responsive; GCH1 Gene; Mutation; Cerebral Palsy; Diagnostic Errors

© 2011 The Korean Academy of Medical Sciences.
DISCUSSION

DRD-causing mutations in GCH1 include point mutations, small insertions, deletions and whole exon deletions (2, 11). We identified a novel mutation in the initiation codon. We speculate that the GCH1 dysfunction caused by c.1A>T is similar to that caused by the previously reported mutations, c.2T>C (p.M1T) and c.3G>C (p.M1I) (12, 13). The initiation codon mutation abolishes the first start codon AUG, which might interfere the translation of GCH1 gene and cause a decrease in GTPCH1 (enzyme) activity. All three cases with initiation codon mutation presented typical clinical features of DRD, characterized by childhood-onset, started in the legs, and had foot dystonia with equinovarus posture. However, it is difficult to establish a genotype-phenotype correlation because of the limited data.

The classic phenotypic form of DRD presents with childhood-onset foot dystonia, which gradually progresses to other parts of the body, and shows marked diurnal fluctuations with worsening of the symptoms toward the evening and improvement after sleep (1). Many patients have features of parkinsonism, including rigidity, bradykinesia, flexed posture, and loss of postural reflexes. Intellectual, cerebellar, sensory, or autonomic disturbances usually do not occur. However, atypical clinical features may include focal dystonia, spasticity, no dystonia prior to the onset of parkinsonism in mid- or late adulthood, and absence of diurnal fluctuation, making diagnosis difficult (11). Our patient was initially misdiagnosed as having cerebral palsy. In previous series, up to 24% of patients with DRD had been misdiagnosed as cerebral palsy (14). Hyperreflexia, ankle clonus, and other clinical features suggesting spasticity may cause confusion with cerebral palsy. Due to lack of medical records, we were not aware of detailed neurologic findings at pre-treatment state. However, the clinical clues to suggest DRD, such as no developmental abnormalities in early childhood, progressive course, and diurnal fluctuation of symptoms, had been overlooked by her clinicians.

The hallmark of DRD in most cases is a dramatic and persistent response to levodopa (14). Long-term treatment with low dose levodopa is not associated with the motor fluctuations that are seen with levodopa therapy in juvenile (and adult) Parkinson’s disease. A small dose restored a wheelchair bound disabled our patient to normality. However, thoracolumbar scoliosis has remained as a sequela due to late detection of DRD. The prognosis of secondary orthopedic deformities has directly related to the timing of diagnosis and the initiation of levodopa therapy (15). Some patients have shown remarkable responsiveness to levodopa with spontaneous resolution of the abnormal spinal curvatures. Therefore, a diagnostic levodopa trial is warranted as soon as possible in patients with early onset dystonia or atypical cerebral palsy of unknown etiology.

Fig. 1. Chest X-ray show fixed scoliotic deformity. The major scoliosis is concentrated in the thoracic region and curves to the right.

Fig. 2. Sequence analysis of the GCH1 gene identified a heterozygous mutation of the first nucleotide (arrow) in the ATG translation initiation site (c.1A>T; p.Met1Leu).
REFERENCES

1. Segawa M, Hosaka A, Miyagawa F, Nomura Y, Imai H. Hereditary progressive dystonia with marked diurnal fluctuation. Adv Neurol 1976; 14: 215-33.

2. Hagenah J, Saunders-Pullman R, Hedrich K, Kabakci K, Habermann K, Wiegers K, Mohrmann K, Loh nau T, Raymond D, Vieregge P, Nygaard T, Ozelius LJ, Bressman SB, Klein C. High mutation rate in dopa-responsive dystonia: detection with comprehensive GCHI screening. Neurology 2005; 64: 908-11.

3. Ichinose H, Ohye T, Takahashi E, Seki N, Hori T, Segawa M, Nomura Y, Endo K, Tanaka H, Tsuji S, Fujita K, Nagatsu T. Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene. Nat Genet 1994; 8: 236-42.

4. Furukawa Y. GTP cyclohydrolase 1-deficient dopa-responsive dystonia. In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. GeneReviews. Seattle: University of Washington, Seattle, 1993.

5. Hong KM, Kim YS, Paik MK. A novel nonsense mutation of the GTP cyclohydrolase I gene in a family with dopa-responsive dystonia. Hum Hered 2001; 52: 59-60.

6. Kang JH, Kang SY, Kang HK, Koh YS, Im JH, Lee MC. A novel missense mutation of the GTP cyclohydrolase I gene in a Korean family with hereditary progressive dystonia/dopa-responsive dystonia. Brain Dev 2004; 26: 287-91.

7. Kim YS, Choi YB, Lee JH, Yang SH, Cho JH, Shin CH, Lee SD, Paik MK, Hong KM. Predisposition of genetic disease by modestly decreased expression of GCH1 mutant allele. Exp Mol Med 2008; 40: 271-5.

8. Yum MS, Ko TS, Yoo HW, Chung SJ. Autosomal-dominant guanosine triphosphate cyclohydrolase I deficiency with novel mutations. Pediatr Neuro 2008; 38: 367-9.

9. Jeon BS. Dopa-responsive dystonia: a syndrome of selective nigrostriatal dopaminergic deficiency. J Korean Med Sci 1997; 12: 269-79.

10. Jeon BS, Jeong JM, Park SS, Kim JM, Chang YS, Song HC, Kim KM, Yoon KY, Lee MC, Lee SB. Dopamine transporter density measured by [123I] beta-CIT single photon emission computed tomography is normal in dopa-responsive dystonia. Ann Neurol 1998; 43: 792-800.

11. Segawa M, Nomura Y, Nishiyama N. Autosomal dominant guanosine triphosphate cyclohydrolase I deficiency (Segawa disease). Ann Neurol 2003; 54(Suppl 6): S32-45.

12. Tamaru Y, Hirano M, Ito H, Kawamura J, Matsumoto S, Imai T, Ueno S. Clinical similarities of hereditary progressive/dopa responsive dystonia caused by different types of mutations in the GTP cyclohydrolase I gene. J Neurol Neurosurg Psychiatry 1998; 64: 469-73.

13. Cao L, Zheng L, Tang WG, Xiao Q, Zhang T, Tang HD, He SB, Wang XI, Ding IQ, Chen SD. Four novel mutations in the GCH1 gene of Chinese patients with dopa-responsive dystonia. Mov Disord 2010; 25: 755-60.

14. Nygaard TG, Marsden CD, Fahn S. Dopa-responsive dystonia: long-term treatment response and prognosis. Neurology 1991; 41: 174-81.

15. Tsirikos AI, Carr LJ, Noordeen HH. Variability of clinical expression and evolution of spinal deformity in a family with late detection of dopa-responsive dystonia. Dev Med Child Neurol 2004; 46: 128-37.