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Guanine Triphosphate–Cyclohydrolase 1–Deficient Dopa-Responsive Dystonia Presenting as Frequent Falling in 2 Children

Chang-Yong Tsao, MD[1]

[1]Department of Pediatrics and Neurology, The Ohio State University, Columbus, OH, USA

Abstract

Guanine triphosphate (GTP)–cyclohydrolase 1 (GCH1)–deficient dopa-responsive dystonia is caused by GCH1 gene mutation. Two children presenting with frequent daily falling are reported with GCH1 gene mutations with persistent response to low-dose levodopa/carbidopa. Typical and atypical clinical features associated with GCH1 mutations are also reviewed.

Keywords

falls; dystonia; dopa-responsive; GTP

Guanine triphosphate (GTP)–cyclohydrolase 1 (GCH1)–deficient dopa-responsive dystonia due to GCH1 gene mutation is characterized by childhood-onset dystonia with dramatic and persistent response to low-dose L-dopa.[1,2] The patients are typically reported as having diurnal fluctuation with more severe dystonia in the evening and may be misdiagnosed with cerebral palsy. We report 2 children with GTP–cyclohydrolase 1–deficient dopa-responsive dystonia and GCH1 gene mutations who presented with frequent daily intermittent falling to the ground and briefly review GTP–cyclohydrolase 1–deficient dopa-responsive dystonia.

Case Reports

Case 1

This 8-year-old previously healthy girl was born at term after normal pregnancy, labor, and delivery with normal milestones. She was in her usual state of health until age 8 years, when she developed frequent daily intermittent tripping and falling to the ground while walking for a few minutes with normal consciousness. Her physical and neurological examinations were normal except brisk deep tendon reflexes in the knees and ankles and her right foot turning inward when walking for a few minutes. Her brain and whole-spine magnetic resonance imaging (MRI) studies were both normal at age 8 years. No brain magnetic

Corresponding Author: Chang-Yong Tsao, MD, Division of Child Neurology E5, The Ohio State, University, 700 Childrens Dr, Columbus, OH 43205, USA, changyong.tsao@nationwidechildrens.org.

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resonance spectroscopy was done. Doparesponsive dystonia was suspected, and carbidopa-levodopa 10/100 mg, ½ tablet twice daily, was started. Two weeks later, her right foot turning inward while walking and her falling completely disappeared, brisk deep tendon reflexes in her knees became normal, and ankle clonus was gone. This patient was tested and had a heterozygous single base pair deletion in exon 1 c.172-175 del C. This mutation has not been described previously but is likely to be pathogenic as it leads to a frame shift changing 56 amino acids in exon 1 (Laboratory of Dr Keith Hyland, Atlanta, Georgia). She has been treated with carbidopa-levodopa and has no more right foot turning inward or falling, and the efficacy has persisted for more than 3 years. Because of her persistent dramatic response to carbidopalevodopa, complete resolution of her dystonia, and the presence of the GCH1 gene mutation, the patient and her mother declined cerebrospinal fluid studies for neurotransmitters. Family history is negative for neurological disorders.

Case 2

This 4-year-old girl was born at term after a normal pregnancy and labor via cesarean section, weighing 6 lbs 4 oz without postnatal problems. She began walking at age 11 months but had toe walking and an abnormal gait (she tended to lean forward and fall to the right side shortly after she began walking). She was diagnosed with spastic diplegic cerebral palsy at age 2 years. Her brain and spine MRI studies as well as serum creatine kinase were normal. No brain magnetic resonance spectroscopy was performed. Despite treatment for spastic cerebral palsy with baclofen and diazepam for 2 years, she continued to have right foot inversion and frequent daily falls when walking. Her neurological examination at age 4 years was normal except for the presence of leg spasticity, worse on the right, and increased deep tendon reflexes at her knees and ankles. Shortly after she walked for a few minutes, her right foot would turn inward and she would fall to the right, which was suspicious of exertion-induced dystonia. She was started on carbidopa-levodopa treatment. She could walk, run, and play normally for hours without the right foot turning inward or falling 1 week after carbidopa-levodopa treatment and has walked normally without exertion-induced dystonia and no more falling for at least 1.5 years. Her neurological examination is now normal. She was tested and had a heterozygous missense mutation in exon 5: c.595 C >T (P199S), leading to substitution of serine for proline. This pathogenic mutation, previously described by Hyland,[3] leads to dopa-responsive dystonia. Her mother also had been suffering from dystonia of her feet since childhood and has improved dramatically with carbidopa-levodopa 25/100 mg, 1 tablet 3 times a day. The patient and the mother declined cerebrospinal fluid studies for neurotransmitters because of the positive mutation of the GCH1 gene in the child's blood and the persistent dramatic response to carbidopa-levodopa treatment in both.

In further investigation of family history, the patient's mother, the maternal grandmother, and a maternal aunt and her daughter all suffered from muscle tightness and the foot turning inward when walking or running for several minutes since childhood. Another maternal aunt and her 2 daughters did not have similar muscle tightness or foot dystonia. However, other affected and unaffected maternal family members live in other states and have not agreed to get medical attention or treatment for muscle tightness.

Discussion

Dopa-responsive dystonia, a childhood-onset dystonia initially described by Segawa et al,[2] is characterized by dramatic and sustained response to low-dose levodopa and diurnal fluctuation. Dystonia fluctuates during the day, often worsens in the evening, and improves in the morning after sleep. Recently, dopa-responsive dystonia has been reported with deficiencies of GTP–cyclohydrolase 1, tyrosine hydroxylase, and sepiapterin reductase, as well as autosomal recessive juvenile parkin-sonism.[4] Among dopa-responsive dystonia patients, GCH1 point mutations are shown in 50% to 62.5% and GCH1 deletions in 8% to 11% in reported series.[4-6] No correlations are seen between types of GCH1 gene mutations (nonsense mutations; missense mutations, including exon 5 mutations; splicing mutations; small deletions and large deletions) and clinical phenotypes.[4,7] In patients with GCH1 gene mutations, the percentage of exercise-induced dystonia is unknown, but some patients develop dystonia only after exercise or exertion.[7,8] Patients with the GCH1 mutation typically present with pure dystonia affecting the lower extremities, with onset most frequently in the first decade of life, but onset between ages 11 and 27 years also has been described.[4] Over time, dystonia in the lower limbs often becomes generalized. Brisk deep tendon reflexes, ankle clonus, and spasticity are seen in many patients, and patients may be misdiagnosed as having cerebral palsy.[7,9] These patients often are unresponsive to a variety of treatment modalities for cerebral palsy. However, when treated with levodopa, these patients improve dramatically with resolution of ankle clonus, spasticity, and dystonia.[1,2,4-7,9] No dopainduced dyskinesia, wearing off, or on-off phenomena were seen. There is a female predominance in GTP–cyclohydrolase 1 deficient dopa-responsive dystonia, with a female to male ratio of 2:1 to 6:1.[4,7,9] GTP–cyclohydrolase 1 catalyzes the conversion of GTP to dihydroneopterin triphosphate, the first and rate-limiting step in the biosynthesis of tetrahydrobiopterin, which is the cofactor for the activities of tyrosine hydroxylase, tryptophan hydroxylase, and phenylalanine hydroxylase. Tetrahydrobiopterin serves as a cofactor for phenylalanine hydroxylase to convert phenylalanine to tyrosine, for tyrosine to convert to L-dopa and eventually to dopamine, and for tryptophan to convert to serotonin. As shown in Figure 1, the concentrations of total biopterin and total neopterin in the cerebrospinal fluid are reduced in individuals with GTP–cyclohydrolase 1 deficiency. Reduction of both biopterin and neopterin is not seen in deficiencies of sepiapterin reductase, tyrosine hydroxylase, or other tetrahydrobiopterin-deficient states.[3,7] Brain and spine MRI studies are normal in patients with GCH1 mutations.[7]

In typical patients with GCH1 mutations, no cognitive, cerebellar, sensory, and autonomic abnormalities are seen.[7,9] However, atypical clinical features in dopa-responsive dystonia with GCH1 gene mutations, including mental retardation, depression, obsessive-compulsive disorder, anxiety, sleep disorders (including difficulty in sleep onset and maintenance), excessive sleepiness and frequent nightmares, and deafness, have been reported in some patients.[4,10,11] Medications have been useful to treat these clinical features.[10,11] Most recently, a family was reported with autosomal dominant paroxysmal exercise-induced dystonia and a nonsense mutation in exon 1 of the GTP–cyclohydrolase 1 gene, which dramatically and persistently stopped on low-dose levodopa.[8] The family members also suffered restless leg syndrome, depression, and adult-onset parkinsonism.[8]

In conclusion, we report 2 children with dopa-responsive dystonia with GTP–cyclohydrolase 1 mutations and briefly review typical and atypical clinical features and treatments.

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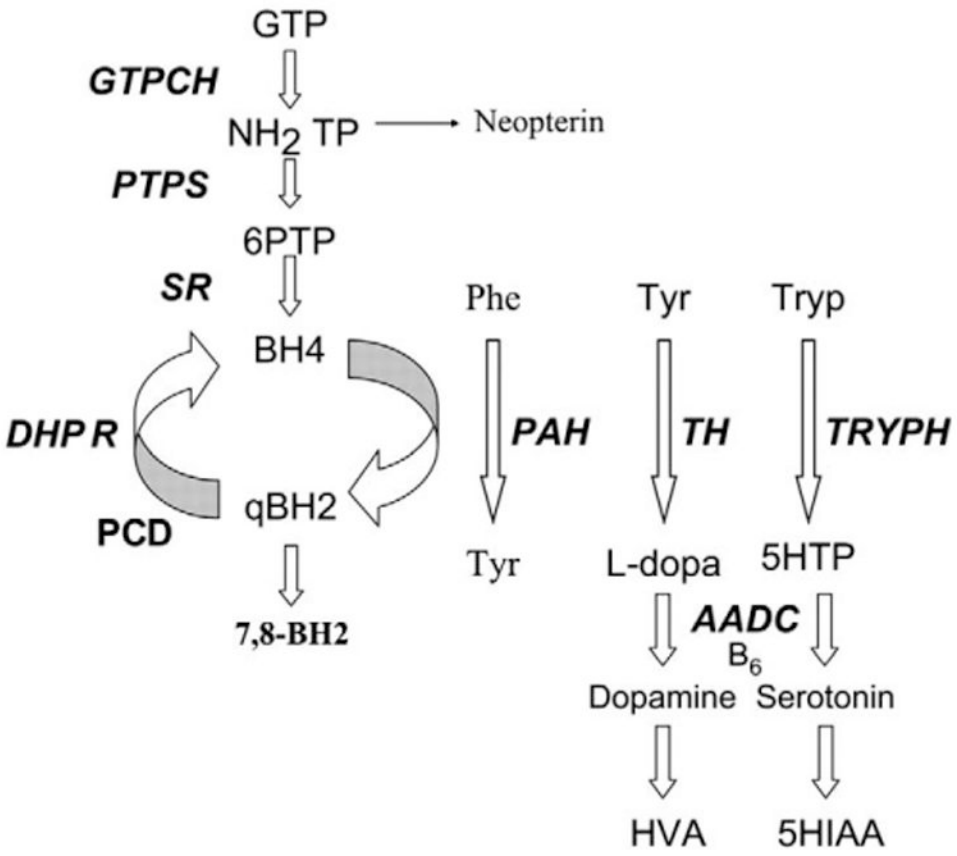

Figure 1.

Synthesis and catabolism of dopamine and serotonin. Dopamine and serotonin are formed from the amino acids tyrosine and tryptophan, respectively. Their synthesis also requires 2 cofactors. Tetrahydrobiopterin (BH4) is formed in a 3-step pathway from guanine triphosphate (GTP) and is the cofactor for tyrosine hydroxylase and tryptophan hydroxylase. It is also required for the activity of PAH. The second cofactor is pyridoxal 5′-phosphate, which is required for aromatic L–amino acid decarboxylase activity. Following release of dopamine and serotonin, they are rapidly metabolized to form HVA and 5HIAA, respectively, and these metabolites are measured in spinal fluid and provide an indication of the overall turnover of these neurotransmitters. GTPCH, GTP cyclohydrolase; 6PTPS, 6-pyruvoyltetrahydropterin synthase; SR, sepiapterin reductase; PCD, pterin α-carbinolamine dehydratase; DHPR, dihydropteridine reductase; PAH, phenylalanine hydroxylase; TH, tyrosine hydroxylase; NH2TP, dihydroneopterin triphosphate; 6PTP, 6-pyruvoyltetrahydropterin; qBH2, quinonoid dihydrobiopterin; 7,8-BH2, 7,8-dihydrobiopterin; Phe, phenylalanine; Tyr, tyrosine; Tryp, tryptophan; TH, tyrosine hydroxylase; TRYPH, tryptophan hydroxylase; 5HTP, 5-hydroxytryptophan; B6, pyridoxal 5′-phosphate; HVA, Homovanillic acid; 5HIAA, 5-hydroxyindoleacetic acid. Figure reprinted with permission from Hyland K, *J Nutr* (2007;137:1568S-1572S), American Society for Nutrition.