A case of dopa responsive dystonia due to compound heterozygous TH gene mutation in a Turkish Girl.

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Dopa responsive dystonia, also known as segawa syndrome, is a rare autosomal inherited genetic disease with an estimated prevalence of approximately 0.5-1 million. Tyrosine hydroxylase deficiency is called autosomal recessive dopa-responsive dystonia. Fewer than 100 cases have been described so far.

An 11-year-old girl with compound heterozygous TH gene mutation-associated dopa-responsive dystonia is presented to raise awareness of this very rare and treatable disease.

We detected two mutations, c.916C>T p. Arg306Cys likely pathogenic and c.1318G>Tp.Ala440Ser variant of unknown significance in TH gene. She was treated with levodopa and benserazide at a dose of 90 mg per day and full recovery was observed in a week.

INTRODUCTION

Dopa responsive dystonia, also known as Segawa Syndrome, is a rare autosomal inherited genetic disease with an estimated prevalence of approximately 0.5-1 million. Typically, between 7-14 years of age, it presents with diurnal fluctuating dystonia in the lower extremities and has an excellent response to low-dose L-dopa. Numerous genes have been identified that cause dopa-responsive dystonia. The most common of these is *GCH1* gene mutation and it shows autosomal dominant inheritance. Except for classical dopa-responsive dystonia, encephalopathy, truncal hypotonicity and generalized dystonia in the neonatal period; focal dystonia or parkinsonism findings in adulthood have also been described. They are named as Type B or DRD-Plus in the literature. Tyrosine hydroxylase deficiency is called autosomal recessive dopa-responsive dystonia. Tyrosine hydroxylase (*TH*) gene is responsible for the this disease. Fewer than 100 cases have been described so far. Tyrosine hydroxylase enzyme deficiency in the metabolic pathway where dopamine is produced from tyrosine, is responsible for the movement disorder that occurs as a result of deficient produce of catecholamine (dopamine, noradrenaline and epinephrine; homovalinic acid, 3-methoxy 4-hydroxyphenylglycol). An 11-year-old girl with compound heterozygous *TH* gene mutation-associated dopa-responsive dystonia is presented to raise awareness of this very rare and treatable disease.

CASE

An 11-year-old girl was admitted to our pediatric neurology outpatient clinic with complaints of gait disturbance and tremor in the hands. She was third child who was born to a first-degree cousin couple at full-term, with a birth weight of 3200 g by cesarean section. Her two elder sister, one younger sister and one younger brother were healthy. Her perinatal history and family history was unremarkable. She was well developed until the age of nine. Her complaints were started two years ago as tiptoe walking, involuntary movements like curling in hands and arms when excited, and her gait deteriorated over time. He was anxious and depressive in general appearance. Her speech was slow and monotonous. She was walking slowly and without waving his hands. There was a gait pattern accompanied by dystonic contraction of the ankles in the form of inward bending and plantar flexion. Muscle strength and sensorial examination was normal. Deep tendon reflexes were normal. Pathological reflex was not detected. Cranial nerve examinations were normal. Cerebellar tests were normal except for tremor. Complete blood count, blood biochemistry and serum creatinine kinase levels were found to be normal. Serum copper and ceruloplasmin were normal. Brain and spinal magnetic resonance imaging were normal. Nerve conduction measurements, repetitive nerve stimulation and acetylcholine receptor antibody for possible myastenia gravis were normal. Acylcarnitine profile, blood amino acids and urinary organic acid excretion were within normal limits. We detected two mutation in next generaiton sequencing; (NM_000360.4: c.916C>T, p.Arg306Cys, chr11:2187924) missense likely pathogenic; This variant has not been seen in the general population (gnomAD Total Allel Frequency (TAF): 0 heterozygotes, 0 homozygotes) and, has not previously been associated with the disease. (NM_000360.4: c.1318G>T, p.Ala440Ser, chr11:2186478 (rs374465917) It is rare in the general population (gnomAD TAF: 0.0082%, 23 heterozygotes, 0 homozygotes) but has not previously been associated with the disease. We studied segragation analysis from mother and father of proband. Ala440Ser missense variant was detected in the father in heterozygous state and p.Arg306Cys missense variant was detected in the mother in heterozygous state. Complete improvement observed in her movements and marked improvement also in mood with levodopa and benserazide treatment at a dose of 90 mg/day.

DISCUSSION

Dopa-responsive dystonia is an autosomal inherited disease that mimics many diseases, often seen in children and adolescents. Distinctive feature of the disease is its excellent response to low-dose L-dopa therapy. As far as we know, our case is the first case with a diagnosis of Segawa Syndrome reported with these variants.

As mentioned above, we identified compound heterozygous variants of TH gene in our patient. It was observed that these two variants were not found to be homozygous in healthy population screenings. Of these, c.916C>T p.Arg306Cys is not previously reported and likely pathogenic variant, while c.1318G>T p.Ala440Ser was reported in one research paper as heterozygous Although this variant is reported as variant of unknown significance, it is considered close to likely pathogenic classification according to variant classification platforms. When we evaluate variants with clinical findings together, we think that c.1318G>T p.Ala440Ser variant may be likely pathogenic and cause Segawa Syndrome together with the other variant. However, for a certain pathogenicity classification, adequate variants should be reported together with clinical findings in literature .

Previously, three brother in a family with segawa syndrome due to TH gene mutation in homozygous state reported from Türkiye. Our patient well responded to levodopa an benserazide at a dose of 90 mg/day. In addition to motor findings, our patient also had nonmotor symptoms such as introversion and depressive mood. The interesting aspect of our case is that this mood disorder was also responsive to treatment. In the literature, psychological disorders other than movement disorders have been described in patients with dopa-responsive dystonia. We think that these non-motor findings are related to the defect in catecholamine synthesis.

CONCULSIONS

Mild clinical findings in some DRD cases may cause the diagnosis to be overlooked, and in some, severe findings starting in the neonatal period cause patients to be mistakenly diagnosed with cerebral palsy. In such cases, dopa responsive dystonia should be kept in mind and genetic testing should be performed.

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