Tyrosine Hydroxylase Deficiency: Report of a Novel Phenotype

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Abstract

Dopamine-responsive dystonia is a rare disorder. The clinical diagnosis is usually made based on the response to levodopa. It is a conglomerate of three enzymatic deficiencies: guanosine triphosphate cyclohydrolase 1, sepiapterin reductase and tyrosine hydroxylase. All of these have some classical presentations and variability in the time of onset and severity, but dystonia and diurnal variation of symptoms have been reported in almost all patients to date. Here, we report the case of a male child, born to consanguineous parents and having symptoms since early infancy, who had only generalized hypotonia with no diurnal variation in symptoms. There was a dramatic response to levodopa therapy. Genetic evaluation revealed a homozygous known pathogenic variant c.698G>A in the *TH* gene (NM_199292.3), confirming the diagnosis of tyrosine hydroxylase deficiency.

Keywords: Neurotransmitter deficiency, dystonia, atypical

Introduction

Dopamine-responsive dystonia (DRD) is a rare disorder. It has a prevalence of 0.5 per million population (Malek et al., 2015). The first case reports were from Segawa et al. in 1976, when it was labelled as hereditary progressive dystonia or Segawa's disease. The term dopamine-responsive dystonia (DRD) was introduced in 1988 by Nygaard. Based on genetic studies, causative variants have been identified in three genes namely *GCH1* (OMIM*600225) encoding guanosine triphosphate cyclohydrolase 1, *SPR* (OMIM*182125) encoding sepiapterin reductase, and *TH* (OMIM*191290) encoding tyrosine hydroxylase. Patients with dopamine-responsive dystonia may have variants in any one of these three genes; however, as majority of them respond to levodopa, they are all labelled as DRD (Randby et al., 2018). Each of these have specific phenotypes although variations are present. Their clinical and genetic heterogeneity makes them a diagnostic challenge, as is highlighted by this case of a child with tyrosine hydroxylase deficiency that is discussed here.

Patient Details

A male child was seen at the age of three years. He was born to first-degree consanguineous parents. The child was delivered per vaginum. There were no perinatal issues. He was the second sib. The elder sib was a four-years-old female child with normal development. On examination, the child was completely hypotonic. There was no head control. The limbs and trunk were totally hypotonic. However, there were no contractures. Deep tendon reflexes were not elicitable. The child was alert, able to understand oral commands and respond with monosyllables. There was no diurnal variation and no dystonic posturing. The parents said that right from the beginning he used to move his limbs less and never achieved any motor milestones. He had been investigated extensively. His metabolic profile including gas chromatography/mass spectrometry (GCMS) of the urine and tandem mass spectrometry (TMS) of the blood were normal. Electroencephalogram (EEG) and magnetic resonance imaging (MRI) of the brain did not show any abnormality. Nerve conduction study (NCS) and electromyography (EMG) were noncontributory. He was empirically started on 25 mg of levodopa. Due to the COVID19 epidemic, he was lost to follow up. After three years he came walking with his father to the outpatient clinic. His father explained that as soon as the medicine was started, he started lifting his head and sitting by the third day. As he had not started walking by the fifth day, he increased the

dose himself to 50 mg and after this the child started walking. There was however now a diurnal pattern. By evening the child would tire out and once the next dose was given, he would again be normal. Now he is eight years old, attends primary school, speaks only bisyllables, and scribbles but has not yet started writing words.

Whole exome sequencing test was done. A homozygous c.698G>A missense variant was detected in exon 5 of the *TH* gene (NM_199292.3), that results in the amino acid substitution of histidine for arginine at codon 233 (p.Arg233His). This variant nests within the biopterin-dependent aromatic amino acid hydroxylase domain of the TH protein coding gene, which is a functional domain. This variant has not been reported in the 1000 genomes databases and has a minor allele frequency (MAF) of 0.01%, 0.01%, and 0.009% in the gnomAD (v3.1), gnomAD (v2.1) and TOPMed databases respectively. Various in-silico prediction tools like MutationTaster2, PolyPhen-2 (HumDiv), SIFT etc. predict this variant to be 'damaging'. This variant has previously been reported in patients affected with tyrosine hydroxylase deficiency and is reported as 'pathogenic' in the ClinVar database [Variation ID:12327; *TH* (NM_000360.4): c.605G>A; p.(Arg202His)]. Homozygous or compound heterozygous pathogenic variants in the *TH* gene result in Segawa disease (OMIM#605407), and the diagnosis of *TH* gene-related autosomal recessive Segawa disease due to tyrosine hydroxylase deficiency was thus established in the child.

Discussion

Tyrosine hydroxylase deficiency has two presentations. In type A, which presents after infancy there is hypotonia, rigidity, and dystonia with diurnal variation. In type B, the onset is in infancy with encephalopathy, hypotonia, hypokinesia, dystonia, tremors, myoclonus, oculogyric crisis, dystonic crisis, and dysautonomia (Goswami et al., 2017; Willemsen et al., 2010). The patient in our case report had an onset in infancy but had no other symptoms other than hypotonia. Absence of wasting and lack of any contractures which develop in all myopathies over a period of time, were absent in this child; this was considered as a pointer for neurotransmitter deficiency. A similar presentation has been reported in some DRD patients with GCH1 deficiency (Eye et al., 2019), but has not been previously reported with TH deficiency.

In addition to genetic testing, analysis of cerebrospinal fluid (CSF) is also important for the diagnosis of TH deficiency. In TH deficiency, homovanillic acid levels (HVA) are low and levels of 5-hydroxyindolic acetic acid (5-HIAA), neopterin and biopterin are normal. The ratio of HVA to 5-HIAA is less than 1 (normal range is 1-3.7). These tests could not be done in our patient.

As per review of literature, various genetic mutations are reported in the *TH* gene, but the commonest are the c.698G>A and c.707T>C variants (Eye et al., 2019; Dong et al., 2020). Our patient also had the homozygous c.698G>A variant but had an atypical presentation of early infantile onset pure hypotonia. This case highlights the variability of phenotypic presentation, in spite of similar mutation, in TH deficiency.

Conflict of interest: None

References

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