CASE REPORT

An Indian Family with Tyrosine Hydroxylase Deficiency

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Background: Tyrosine Hydroxylase deficiency is a rare neurotransmitter disorder. **Case Characteristics**: An Indian family with the disorder. **Observation:** Phenotypic variation, elevated serum prolactin, genetic confirmation, and partial treatment-responsiveness. **Messages:** Tyrosine Hydroxylase deficiency is a treatable inborn error of metabolism and serum prolactin assists in diagnosis.

Keywords: *Segawa syndrome, Neurodegeneration, Neurotransmitter disorder.*

Tyrosine hydroxylase (TH) deficiency is an autosomal recessive neurotransmitter disorder that may have a heterogeneous presentation [1]. We report an Indian family with this rare disorder to sensitize pediatricians about the importance of clinical suspicion and serum prolactin in diagnosing this condition. We also wish to highlight its phenotypic variability and treatment-responsiveness.

Case Report

A 10-month-old boy presented with acute onset, rapidly progressive loss of milestones. The child was term born to non–consanguineous, healthy, Indian couple. His birth-weight was 2.8 kgs and perinatal period was uneventful. Pre-morbidly, he was developmentally normal. At nine months, the child had an episode of low-grade fever with rhinorrhea for four days. Subsequently, he became lethargic and rapidly lost abilities to sit, turn-over, reach for objects or babble. He continued to track visually and smile back. He had an episode of generalized seizure for five minutes on second day of illness. On examination he was well built, lethargic with generalized hypotonia and paucity of limb movements. He spontaneously recovered to normalize over three weeks. Two weeks later, he had an acute, unprovoked, rapid recurrence of milestone loss evolving over one week. At the nadir, he could not hold his neck or voluntarily reach out with his hands. He vocalized but could not coo. He recognized parents but lost stranger-anxiety. Parents felt that the child was flaccid and had difficulty swallowing solids. He did not have abnormal breathing, vomiting, abnormal eye/ limb movements, posturing, seizures, unconsciousness or abnormal urine odour.

On repeat examination, the positive findings were significant generalized hypotonia and paucity of spontaneous limb movements.

Child's hematological and biochemical profile, arterial ammonia, serum biotinidase, homocysteine, creatine phosphokinase, anti-TPO antibody titers, cerebrospinal fluid study CSF study, electroencephalogram, nerve conduction study, electromyography, Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) brain, Tandem Mass Spectroscopy (TMS), urinary organic acid profile by Gas Chromatography-Mass Spectroscopy (GC-MS) and serum aminoacidogram were unremarkable. He was managed empirically with carnitine, Coenzyme-Q, thiamine, riboflavin, folic acid besides physiotherapy, multisensory stimulation, and nutritional support. On follow up at two years of age, he had attained partial neck control, voluntary reach, babbling and stranger anxiety . He now was noticed to have intermittent dystonic upper-limb twisting which increased during crying and disappeared during sleep. While this child was being followed up, his younger sister was born and evaluated for being symptomatic.

The younger six-month-old female sibling was term-born with uneventful perinatal period and was pre-morbidly developmentally normal. She was first noticed to have episodes of brief, paroxysmal, non-repetitive, abnormal, multi-directional eye movements at the age of three months. She did not have frothing, sweating, flushing, cyanosis, or pallor. Frequency of these episodes increased from once a day to about ten per day by one month. The child also developed feeding difficulty in the form of abnormal lip and tongue movements when milk was

offered with a spoon or feeding bottle. The child's neck control gradually deteriorated and she stopped gaining new milestones over next three months. On examination, positive findings were truncal and axial hypotonia. Child's home videos suggested paroxysmal non-epileptiform ocular movements, orolingual dyskine-sias and dystonic limb posturing. Her hemogram, serum biochemistry, arterial ammonia, lactate, acyl carnitine profile, urinary organic acid profile, electro-encephalogram, MRI brain and MRS were within normal limits.

Given the above profiles, a neurotransmitter disorder was suspected. Serum prolactin and phenylalanine levels were obtained as the suspicion of TH deficiency and Aromatic L amino acid decarboxylase (AADC) deficiency were entertained. Phenylalanine levels were within normal limits. Prolactin levels of both siblings were significantly elevated [119.4 ng/mL (boy); 132.6 ng/mL (girl)] (reference level:4.79-23.3 ng/mL)] .

The boy's *TH* gene targeted sequencing revealed two heterozygous missense variations in exon 6 and 12. Hence, he was diagnosed to have *TH* deficiency due to a compound heterozygous mutation. The girl was evaluated by targeted Sanger sequencing of exons 6 and 12 for *TH* gene. Both variations were detected in the heterozygous state (***Table* I**). Parents were evaluated for mutations in TH gene. The variation in exon 6 was detected in heterozygous state in the mother and the variation in exon 12 was detected in heterozygous state in the father.

The father's 20-year-old paternal first cousin has history of episodic generalized weakness and involuntary twisting of wrists from thirteen years of age. These episodes were triggered by tension and fatigue. She was advised tablet L-dopa empirically to which she responded. As these episodes were infrequent and non-impairing, she was not on regular medication or follow-up. She was interviewed telephonically.Clinical examination could not be organized as she resided in a distant city.Her genetic testing revealed the variation in exon 12 in heterozygous state.

The children were started on gradually increasing dosage of L-Dopa (0.6 mg/kg/day), carbidopa (1mg/kg/day), selegiline (3 mg/kg/day) and trihexyphenidyl and were kept on follow-up. They have been followed up for one more year.The boy has minimal decrease in dystonia while the girl has demonstrated a significant decrease in oro-lingual, ocular and limb dyskinesias. Both are gaining new milestones.

DISCUSSION

Tyrosine Hydroxylase (TH) deficiency (MIM No: 191290) is also called 'autosomal recessive Segawa Syndrome' [1]. TH catalyzes conversion of L-tyrosine to L-dihydroxyphenylalanine (L-dopa). This is a rate-limiting step in the formation of dopamine, norepinephrine and epinephrine [2].

Our index case (boy) presented with neuroregression with trivial illness while his younger sibling (girl) had more prominent extrapyramidal movements. In such clinical scenarios a host of differentials including amino-acidopathies, organic acidurias, urea cycle disorders, respiratory chain disorders and rarely neurotransmitter disorders need to be considered. Normal biochemical investigations including arterial ammonia, lactate, acyl carnitine and urinary organic acid profile, and unremarkable MRI brain and MRS made the diagnosis of inborn errors of metabolism and respiratory chain disorders seem less likely. These laboratory findings in addition to the core symptom of extrapyramidal movements made the possibility of neurotransmitter disorder more likely.

Investigations for neurotransmitter disorders begin with CSF analysis of neurotransmitter level. CSF analysis in TH deficiency reveals low homovanillic Acid (HVA) and normal levels of 5-hydroxyindole acetic acid (5-HIAA),neopterin, and biopterin [3]. The HVA: 5-HIAA ratio is less than 1 (normal 1.0-3.7) [4].CSF analysis could not be performed in our cases due to non-availability. Hyperprolactinemia is noted in about 50% of severely affected patients [5]. This surrogate marker was helpful in both of our children.This serum marker is widely available and useful for evaluation of neurotransmitter disorders.

Type A TH deficiency manifests after infancy with hypokinesia, rigidity , dystonia with diurnal fluctuation [1]. Symptoms respond to L-Dopa [1]. Type B TH deficiency manifests in early infancy with encephalopathy, hypotonia, hypokinesia, dystonia, tremor, myoclonus and oculogyric crises, dystonic crises and dysautonomia [4]. Our cases had features of Type B TH deficiency of varying severity. A remarkable feature seen in the family we report is the phenotypic variability, as has also been reported previously [6]. Heterozygous carriers of *TH gene* mutation may have intermittent symptoms of mild severity [1].This was seen in one of the heterozygous carriers in the family while other carriers were asymptomatic. Diagnosis of TH deficiency is established by demonstrating *TH gene* mutations. The gene mutation at exon 6 of *TH gene* was first reported in three unrelated Dutch families [5]. However, the gene mutation at exon 12 seen in this family is novel.

TH deficiency is a treatable neurotransmitter disorder. L-Dopa is the key drug for treatment of this condition. Low dose L-dopa/carbidopa with selegiline

and trihexyphenidyl are more effective than plain L-dopa/ carbidopa [3,7]. Folinic acid supplementation reverses secondary folate deficiency [8]. The affected and unaffected family members need long term followup as rapid dose-escalation, fever and stress may paradoxically increase dyskinesias. Dose reduction and amantadine combats this adverse effect [8].

To conclude, the report highlights the clinical heterogeneity of this newly described group of neurotransmitter disorder. With a clue from widely available investigation like prolactin, this potentially treatable condition may be suspected and proven in the correct clinical context.

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WEB TABLE I MUTATIONS DETECTED BY NEXT-GENERATION SEQUENCING IN *TYROSINE HYDROXYLASE* GENE

Patient	*Genomic Position*	*Gene Strand*	*Sequence Depth*	*cDNA Position*	*Change in amino acid*	*Exon No*
Patient 1 and Patient 2	chr11:2189135; C>C/T (HET)	*TH (-)*	39x	c.698G>G/A (ENST00000381178)	p.R233H	6
	chr11:2186909; C>C/T (HET)	*TH (-)*	66x	c.1282G>G/A (ENST00000381178)	p.G428R	12
Father of Patient 1,2	chr11:2186909; C>C/T (HET)	*TH (-)*	66x	c.1282G>G/A (ENST00000381178)	p.G428R	12
Mother of Patient 1,2	chr11:2189135; C>C/T (HET)	*TH (-)*	39x	c.698G>G/A (ENST00000381178)	p.R233H	6
Patient 3	chr11:2186909; C>C/T (HET)	*TH (-)*	66x	c.1282G>G/A (ENST00000381178)	p.G428R	12