LEVADOPA THERAPY RESULTED IN SIGNIFICANT MOTOR RECOVERY IN CHILDREN WITH TYROSINE HYDROXYLASE DEFICIENCY: A CASE SERIES (CR 11)

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Introduction

Human tyrosine hydroxylase (TH) deficiency is an autosomal recessive neurometabolic disorder due to mutations in the *TH* gene on chromosome locus 11p15.5. TH deficiency causes impaired synthesis of cerebral catecholamine neurotransmitters including dopamine, adrenaline and noradrenaline. It has a broad continuous clinical spectrum, manifesting from infancy adulthood as progressive encephalopathy, as well as abnormal movements including dystonia and Parkinsonism. TH deficiency is divided into three types based on its severity and responsiveness to L-Dopa.

❑ The TH deficiency Type 1 is the L-Dopa-responsive dystonia, which is also the milder form

❑Type 2 is the more severe form, with infantile Parkinsonism and motor delay

❑Type 3 is the TH-deficient progressive infantile encephalopathy.

We hereby report the cases of three patients with TH deficiency from two families, the challenges in diagnosing this rare genetic condition, and its therapeutic outcomes.

Methods

Analysis of the medical records, laboratory reports, molecular genetics report, MRI brain, clinical photographs, videos and phenotypic data of all 3 patients were obtained by continuous follow up on the patients with parental informed consent. Exemption from Medical Research & Ethics Committee, Ministry of Health has been obtained for this case series study (NMRR ID-22-00483-YRK).

Discussion

- TH deficiency is a rare autosomal recessive neurometabolic disorder cause by mutations in the *TH* gene that is most likely under-diagnosed. Its wide spectrum of disease manifestation ranging from a mild movement disorder at one end to a life-threatening, neurological disorder at the other make it difficult and challenging to be recognized clinically. It took 5 months to 5 years from onset of symptoms and signs for these three patients to obtain a definitive diagnosis. The utilisation of genomic tests may have the potential to end the diagnostic odyssey early, enable accurate diagnosis and management of rare genetic diseases. This is clearly demonstrated in our case series, diagnosis of TH deficiency in all 3 patients have saved them from the devastating effects of this disease.
- Most patients with infantile parkinsonism type of TH deficiency demonstrate early onset of disease, as early as age 3 - 12 months. With regards to our patients, all three of them had an onset of symptoms at 3 months of age. All three patients demonstrated overt motor milestone delay since infancy. The patients in our case series had signs of dopamine deficiency such as hypokinesia, dystonia, oculogyric crises, and diurnal fluctuation. Patient 1 and 2 clinical phenotype fits the description of Type II TH deficiency, whereas Patient 3 has Type III TH deficiency.
- Patients with TH deficiency have a decreased level of dopamine. Dopamine suppresses the release of prolactin, which explains the elevated level of serum prolactin in all our patients. Hyperprolactinemia was found in 50% of the severe cases of TH deficiency and could be a useful biomarker to alert clinicians to consider TH deficiency in patients with unexplained developmental delay and hypotonia.
- L-dopa dosage in TH patients is usually 3 - 10mg/kg/day. The initial dose is usually lower, as tolerated by patient. Some individuals with the severe form of TH deficiency are hypersensitive to L-dopa and are prone to intolerable dyskinesias at initiation of L-dopa therapy; this hypersensitivity necessitates use of very low initial doses of levodopa. Patients who are able to tolerate L-dopa, exhibit drastic improvements, as seen in Patient 2 and 3. Early detection and treatment results in improved outcomes.

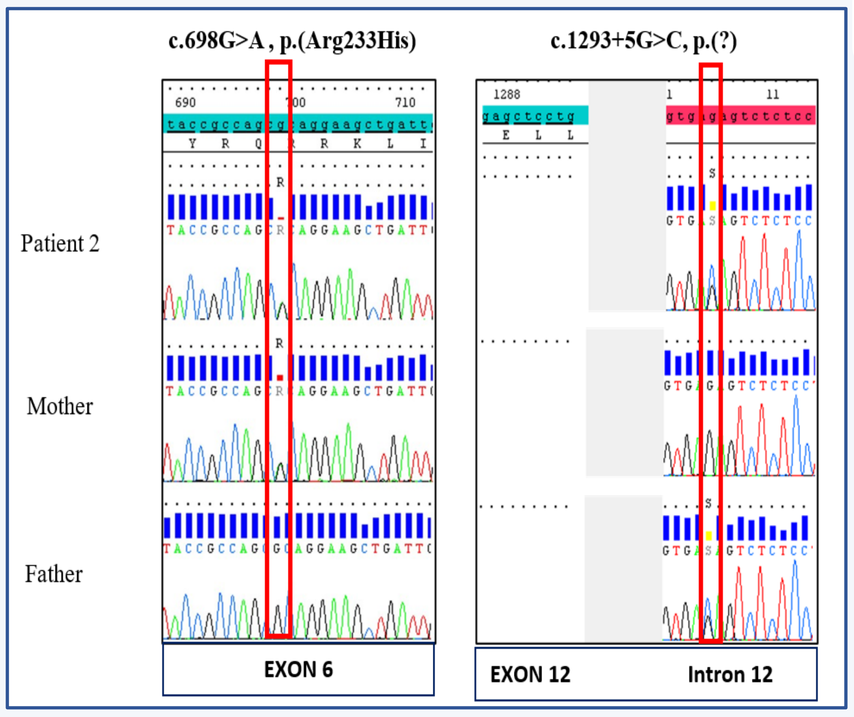

Figure 1: Sequence electropherogram of Patient 2 showed compound heterozygous mutations identified in exon 6 and intron 12 of *TH* gene indicated in red box. Genetic testing carried out on parental samples had detected the variants are in trans phase thus confirmed the autosomal recessive inheritance.

Case Series

Patient 1

- Male, first child of a non-consanguineous couple
- Onset: 3 months
- Presenting clinical features: psychomotor delay, limb dystonia, truncal hypotonia, feeding difficulties and oculogyric crises
- Investigations: routine biochemistry, karyotype, MRI brain, EMG were all normal
- Initial diagnosis: cerebral palsy
- First genetic clinic visit: 5 years old
- Additional test: serum prolactin - 2,146 mU/L (Normal range: 102 - 496 mU/L)
- Whole exome sequencing: 2 pathogenic variants of *TH* gene were detected: c.698G>A [p.(Arg233His)]; c.1293+5G>C
- Treatment: L-dopa (+decarboxylase inhibitor), initiated at 0.08 mg/kg/day and gradually titrated to 5 mg/kg/day over 12 months
- Adverse effect: minimal
- Outcome (last reviewed at 9 years old): He was able to stand and walk a few steps without support, able to form multisyllable words, able to grip better although mild hypotonia and hyperreflexia were still present.

Patient 3

- Female, first child of a non-consanguineous couple
- Onset: 3 months
- Presenting clinical features: presented with encephalopathy and paroxysmal periods of lethargy alternated with irritability; significant delay in motor milestones and intermittent blank stare with jerky movements of the lower limbs with diurnal fluctuation
- Investigations: routine biochemistry and MRI brain were normal
- Initial diagnosis: Primary mitochondrial disorder
- First genetic clinic visit: 7 months old
- Additional test: serum prolactin – 1,003 mU/L (Normal range: 102 - 496 mU/L)
- Whole genome sequencing: 2 pathogenic variants of *TH* gene were detected: c.943G>A [p.(Gly315Ser)]; c.1196C>T [p.(Thr399Met)]
- Treatment: L-dopa (+decarboxylase inhibitor), initiated at 0.1 mg/kg/day and gradually titrated to 11.5 mg/kg/day over 6 months
- Adverse effect: minimal
- Outcome (last reviewed at 2.3 years old): She could walk, run, and climb the staircase independently.

Patient 1 **Patient 2** **Patient 3**

Scan the QR code for respective patient to view the progress of the patient. Before and after commencement of treatment.

WE HAVE OBTAINED PARENTAL WRITTEN CONSENT FOR ALL THE ILLUSTRATIVE MATERIALS FOR MEDICAL EDUCATIONAL USE

Patient 2

- Female, sibling of Patient 1
- Onset: 3 months
- Presenting clinical features: she developed hypotonia after an episode of fever, subsequently had psychomotor delay, limb dystonia, truncal hypotonia, feeding difficulties and oculogyric crises
- Investigations: routine biochemistry was normal
- Initial diagnosis: global developmental delay of unknown cause
- First genetic clinic visit: 3 years old (as part of sibling screening)
- Additional test: serum prolactin – 1,800 mU/L (Normal range: 102 - 496 mU/L)
- Targeted *TH* gene sequencing: 2 pathogenic variants of *TH* gene were detected: c.698G>A [p.(Arg233His)]; c.1293+5G>C
- Treatment: L-dopa (+decarboxylase inhibitor), initiated at 0.1 mg/kg/day and gradually titrated to 5.8 mg/kg/day over 12 months
- Adverse effect: minimal
- Outcome (last reviewed at 7 years old): She was able to speak a few monosyllables, meaningful words. She was able to walk independently, able to use fork and spoon, but still required assistance to climb up stairs. She only has mild hypotonic and mildly increased deep tendon reflexes


A


B


C

Fig. A, B and C show Patient 1, Patient 2 and Patient 3 before the treatment. Lack of facial expression was noticeable.


D


E


F


H

Fig. D, E and F show Patient 1, Patient 2 and Patient 3 after commencement of treatment. More facial expression noticed.

Conclusion and Learning Points

1. Our case series has demonstrated that TH deficiency is a treatable disorder if recognized early.
2. TH deficiency should be considered in any children with unexplained neurological symptoms especially if oculogyric crises and diurnal fluctuation are present.
3. Hyperprolactinemia is a biomarker of dopamine deficiency.
4. Genomic testing is recommended in undiagnosed patients to end their diagnostic odyssey.
5. L-dopa dose needs to be titrated carefully to minimize side effects due to dopamine receptor hypersensitivity.


G


I


J

Fig. G (pre-treatment) and H (post-treatment) showed marked motor recovery of Patient 1 and 2

Fig. I (pre-treatment) and J (post-treatment) showed marked motor recovery of Patient 3.

Scan the QR code to give us feedback.

References:

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