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Case Report

A Compound Heterozygous for Novel Mutations in tyrosine Hydroxylasegene with Hypo kinetic-Rigid Syndrome with Dystonia

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Abstract

Back Ground: Tyrosine hydroxylase deficiency (THD) is the rare cause of recessive dopa-responsive dystonia (DRD) in analogy to dominantly inherited guanosine tri phosphate cyclohydrolase 1(*GCH 1*) deficiency. It always has good response to L-dopa, but it is easily misdiagnosed or missed diagnosed because of atypical symptoms. In order to expend the knowledge of THD, we report the patient with an unusual phenotype and two novel *TH* mutations.

Patient: We describe an 18-year- old girl affected by early-onset hypokinetic-rigid syndrome with dystonia. Apart from diurnal fluctuation, the symptoms aggravated or mitigated irregularly within months could be observed over the past 18 years. She was initially misdiagnosed with cerebral palsy and underwent surgery twice. A therapeutic trial of L-dopa was conducted to the patient. And then, all exons and the intron-exon boundaries of *GCH1* gene and *TH* gene were analyzed with polymerase chain reaction and DNA sequencing in the patient and her parents.

Results: The patient responded completely to L-dopa even with treatment delayed 18 years. Mutation analysis of the *GCH1* was negative .While, a compound heterozygote for novel mutations on *TH* was revealed: c.1451G>A (p.R484H) harbored by the father and c.1559T>A (p.L520H) of maternal origin.

Conclusion: The data expand the genotype and phenotype spectrum of THD. We suggest that L-dopa testand gene analysis (not only *GCH1*, but also *TH*) should be carried out in all patients with a typical, or unexplained movement disorders, especially in children.

Keywords: Tyrosine hydroxylase deficiency (THD); dopa-responsive dystonia (DRD); Segawa Syndrome; genetic analysis; L-dopa test.

Case report

The patient is an 18-year-old girl who was born after an uncomplicated pregnancy and normal delivery from healthy non-consanguineous parents. She developed normally during the first two months of life, but couldn't raise her head at three months. She started walkingat18 months, with dystonic equinovarus feet posture, and sometimes fell down. Upper limbs rigidity and Brady kinesia appeared at the same time. The symptoms fluctuated during the day, worsening in the evening and improving in the morning or after a nap. Apart from diurnal fluctuation, the symptoms aggravated or mitigated irregularly within months could be observed over the past 18 years. The patient could walk about 500 meters on tiptoes in the morning; hardly walk 5 meters in the afternoon during the remission stage. And she could hardly walk all day during the aggravate stage. However, cognitive functions and language development were normal. Other neurological features like tremor, chorea, hyper salivation, oculogyric crises and ptosis, as well as behavioral disturbances were absent. The patient was misdiagnosed as spastic cerebral palsy and underwent selective dorsal rhizotomy (SDR) at 7years old. This treatment resulted in no improvement. She further underwent orthopedics at age 10.There was still no improvement except the equinovarus. She came to our hospital in a wheelchair at age of 18 and could hardly walk for half a year. Neurological examination revealed the patient had Brady kinesia, extremity rigidity, trunk hypotonia, increased muscle tone and brisk tendon reflexes, and was unable to walk or even stand. Cognitive function was normal and pyramidal tract signs were negative. Brain magnetic resonance imaging (MRI) and routine clinical chemistry did not reveal any abnormalities. After taking the L-dopa/benserazide therapy with 75/18.75mg per day in three divided doses, motor functions and hand functions improved impressively, and the neurological examination normalized within 3days.The patient could stand and walk again without any help, and eat by herself. Further examination, Brady kinesia, muscle tone and deep tendon reflexes normalized. However, hyper kinesia was observed when the dosage was increased to 150/37.5 mg per day. Then the medication was reduced to 75mg which have a sustained efficacy, without motor fluctuation over the following 7 months.

Molecular genetic analysis

Both the patient and her parents' genomic DNA were extracted from peripheral leukocytes and followed by polymerase chain

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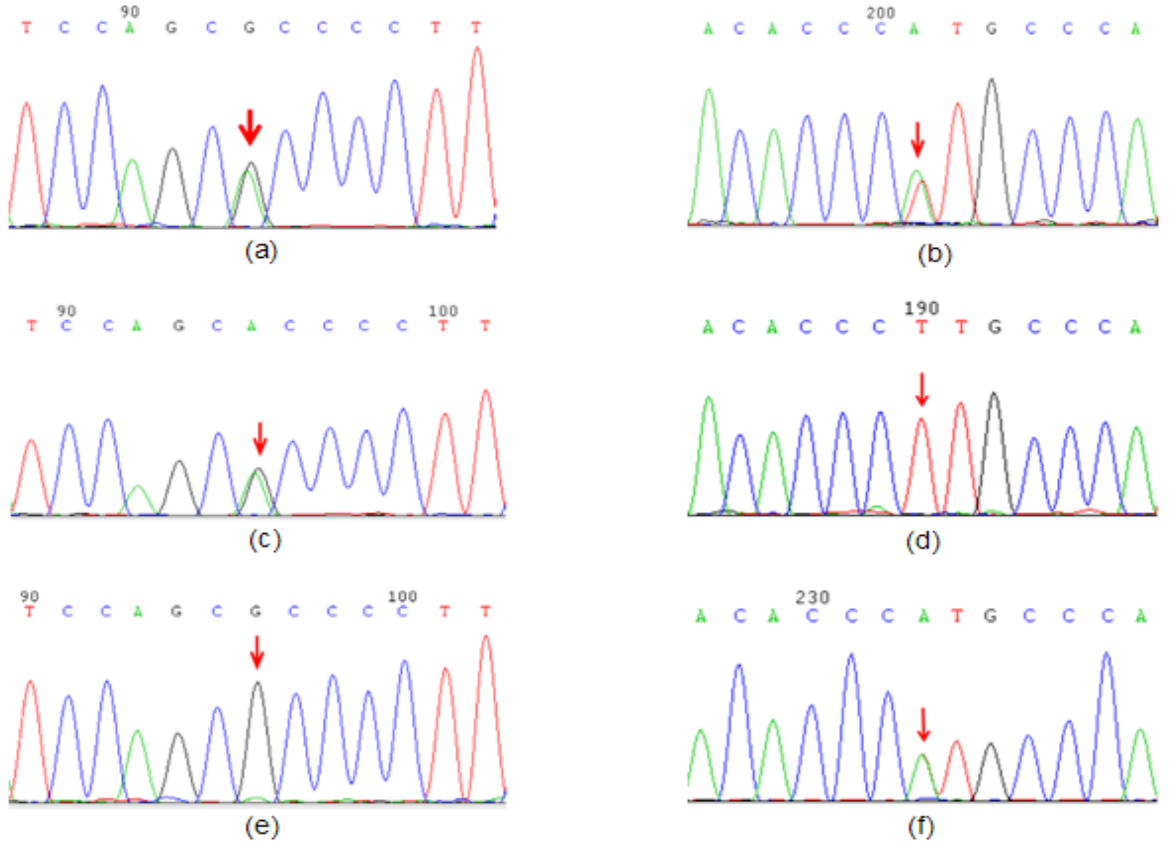
reaction and direct sequencing. All exons and the intron-exon boundaries of *GCH1* gene and *TH* gene were analyzed. Mutation analysis of the *GCH1* was negative. Sequencing of *TH* revealed two novel heterozygous mutations:c. 1451G>A (p.R484H) and c.1559T>A (p.L520H) on exon 14. The patient's healthy parents were shown to be heterozygous for different mutation. Her father is a healthy carrier with the mutation c.1451G>A, and her mother is a healthy carrier with the mutation c.1559T>A. The results of genetic analysis are shown in the figure below.

A heterozygous A-to-G transition at nucleotide position 1451 is indicated by an arrow of the patient (a) and her father(c).A heterozygous A-to-T transition at nucleotide position 1559 is indicated by an arrow of the patient (b) and her mother (f). The nucleotide position 1451of the patient' mother (e) and 1559 of her father (d) are normal.

Informed consent had been obtained from the parents before the blood samples were drawn, and our institutional Ethics Committee approved this case report.



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Discussion

THD was recently identified and incorporated into genetic dystoniaas the cause of recessive DRD or Segawa's syndrome in analogy to dominantly inherited GCH1 deficiency [1]. Moreover, it has been proposed to designate *GCH1*deficiency and THD as 'dystonia 5a' and 'dystonia 5b' [2, 3].Tyrosine hydroxylase deficiency (OMIM191290) is a rare cause of autosomal recessive DRD due to mutations in *TH* on chromosome 11p15.5.The enzyme *tyrosine hydroxylase* (EC 1.14.16.2) catalyzes the conversion of L-tyrosine to L-dopa, which is the rate-limiting step in the biosynthesis of the catecholamine's.

THD causes a broad spectrum of disorders from DRD to progressive infantile encephalopathy. Many different features of THD (hypokinesia, bradykinesia, rigidity, dystonia, tremor, chorea, ptosis, oculogyric crises and hyper salivation, among others) are caused by cerebral dopamine and nor epinephrine deficiency [1, 4]. Based on the presenting neurological features, THD usually be divided in two phenotypes: an infantile onset, progressive, hypo kinetic-rigid syndrome with dystonia (type A), and a complex encephalopathy with neonatal onset (type B)[3]. Obviously, the patient is the former.

L-dopa response is variable, ranging from complete remission

to lack of responsiveness in THD [5, 6]. Treatment with L-dopa results in an excellent response in almost all patients with type A, but does not improve all signs equally, and it may take months before all effects become clear in type B [7].The good news is that, most patients are belong to type A and can be successfully treated with L-dopa [3]. While, untreated THD may causes gradually progress to dystonia-parkinsonism, even lead to immobilization and contractures [1, 8] .Therefore, early diagnosis would be vital to the treatable disease.

The diagnosis of THD often treatable rare condition needs to be made from a large spectrum of early onset movement disorders. Diurnal fluctuations of trunk hypotonia and dysautonomic symptoms are clinical suspicion of the diagnosis [9]. Genetic analysis of DRD genes can usually confirm the diagnosis. We recommend conducting sequence analysis not only of *GCH1* but also of *TH*, and conducting a therapeutic trial of L-dopain those patients. Besides, sepiapter in reeducates (SR)-deficient DRD have been recently reported in literatures, which suggest the SR gene should be included in the genetic analysis [10, 11].

It was considered that diurnal fluctuation is usually not present, and a markedly delayed and incomplete dopa-response might be shown in THD compared with *GCH1* deficiency [1]. Nevertheless, in our patient, diurnal fluctuation was prominent, and the response of L-dopa was completely.

In the presence of delayed developmental mile stones, and brisk tendon reflexes, the patient was misdiagnosed with cerebral palsy and underwent surgery twice. Besides, the symptoms paroxysmal aggravated irregularly could be confusing, which is apt to missed diagnose. However, the patient still showed good response to L-dopa even after 18 years delayed of treatment from the onset of neurological symptoms. In this case, genetic analysis and L-dopa test are very necessary. According to the literature, THD can best be treated with an initial L-dopa dose of 0.5–1 (for type B patients) to 3 (for type A patients) mg/kg bodyweight per day, divided over three or four doses [3]. Following slow titration, response to L-dopa can usually be observed within a few days to few weeks. And the trials may be stopped after 6 weeks upon the dose of 450–600 mg/day, if no improvement can be observed [12]. It was reported that selegiline could be added to the treatment to increase the effection some cases [1, 4, 13].Besides, there is literature mentions that anticholinergics and dopamine agonists may also be effective in the disease [12]. The patient had a complete response to a very low dose of L-dopa within 3 days, so the other medicines were not added.

Until now, approximately 70 THD patients with a total of 40 different disease-related missense mutations of the *TH* gene have been reported [14]. Genetic analysis revealed a compound heterozygote for novel mutations on *TH* gene: c.1451G>A (p.R484H) harbored by the father and a gene mutation c.1559T>A (p.L520H) of maternal origin. Neither of the two mutations has been so far reported in the literature. The Single Nucleotide Polymorphism Database (dbSNP), human gene mutation database (HGMD), exone sequencing project 6500(ESP6500) and 1000 Genomes haven't been yet reported. In addition, the bioinformatics analysis showed that the two missense mutations are both predicted to be probably damaging by PolyPhen-2 (Polymorphism Phenotyping V2).

According to the literatures, decreased cerebrospinal fluid (CSF) concentrations of homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylethylene (MHPG), with decreased HVA/5HIAA(5-hydroxyindoleacetic acid) ratios were demonstrated in most patients with THD[1, 3]. Regrettably, the patient couldn't conduct the lumbar puncture.

Willemsen etc summarized 29 patients' cerebral MRI, and never observed gross structural abnormalities of the brain or signal changes in the basal ganglia [3].The patient's brain MRI is also normal.

Conclusion

As a rare cause of recessive DRD, THD is a severe but often very treatable neuro metabolic disorder. It's very vital for early diagnosis and adequate treatment to this movement disorders. The diagnosis of THD relies on clinical suspicion, L-dopa test and the analysis of genes. Patients with THD may be misdiagnosed or missed diagnosed because of atypical symptoms. Diurnal fluctuation of the symptoms should take the L-dopa test into account. Then, the lack of abnormalities on cerebral imaging studies, and a marked responsiveness to L-dopa are clues to this disease. Final confirmation diagnostic approach to THD is by genetic analysis.

We report a THD patient's clinical features in detail and found two novel mutations in *TH* gene. The data expand the genotype and phenotype spectrum of THD. Last but not least, we suggest that gene analysis and L-dopa test should be carried out in all patients with a typical, or unexplained movement disorders, especially in children.

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