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Case Report

A Case Report of Infantile Dopa-Responsive Dystonia Onset With Sleep Disorder Complicated With Autism Spectrum Disorder

Li Shao[1,*], Jing Zhang[1], Qi Wang[1]

[1]Children's Rehabilitation Center, Jinhua Maternal and Child Health Care Hospital, 321000 Jinhua, Zhejiang, China
*Correspondence: jinhuashaoli@163.com (Li Shao)
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Abstract

Aims/Background: Dopa-responsive dystonia (DRD) is a rare genetic disorder with complex and diverse clinical manifestations, resulting in a high rate of misdiagnosis. This case report describes an infantile case of DRD complicated by autism spectrum disorder (ASD), initially presenting with a sleep disorder. We aim to summarize its clinical manifestations, diagnostic process, treatment, and follow-up outcomes in order to improve clinical understanding of this disease. **Case Presentation:** A retrospective analysis was performed on a male infant who was treated at Jinhua Maternal and Child Health Care Hospital in 2020. The patient presented at one month of age with sleep disturbances, delayed motor development, and intermittent upward deviation of the eyes. Genetic testing identified two heterozygous pathogenic variants in the tyrosine hydroxylase (*TH*) gene. Among them, the c.738-2A>G variant was not recorded in the Exome Aggregation Consortium (ExAC), Genome Aggregation Database (gnomAD), or 1000 Genomes Asian population databases. During follow-up, the patient was also found to have comorbid ASD. **Results:** Genetic testing confirmed biallelic *TH* mutations, establishing the diagnosis of infantile DRD. The patient exhibited marked clinical response to levodopa/benserazide, though dose titration was required with growth. **Conclusion:** For infants with unexplained sleep disorder accompanied by delayed motor development, genetic testing should be performed as early as possible to facilitate the identification of the root cause and implement timely treatment. In addition, close follow-up should be conducted to detect comorbid neurodevelopmental disorders.

Keywords: sleep disorder; infants; dopa-responsive dystonia; autism spectrum disorder; case report

1. Introduction

Dopa-responsive dystonia (DRD), also known as Segawa syndrome, is an autosomal inherited movement disorder. Its incidence rate is estimated at 0.5–1.0 per million population, with a female-to-male ratio ranging from 2:1 to 4:1, and a higher penetrance observed in females [1]. Typical clinical manifestations include progressive postural and gait abnormalities with diurnal fluctuation (milder in the morning and worse in the evening), and a significant and sustained response to levodopa [2]. DRD is associated with multiple pathogenic genes, with three major ones identified thus far. The most common is the guanosine triphosphate cyclohydrolase 1 (*GCH1*) gene, while the tyrosine hydroxylase (*TH*) gene and sepiapterin reductase (*SPR*) gene are considered relatively rare [3,4]. Most cases are diagnosed during childhood due to clinical manifestations of movement disorders. DRD is especially responsive to levodopa treatment. The majority of patients gain weight without the need for dose escalation, which is thought to be related to the reduced demand for dopamine with increasing age [5]. Here, we report a case of DRD in an infant who presented with sleep disturbances as the initial symptom and was found to be complicated by ASD during follow-up. Clinical and genetic characteristics, as well as the follow-up process, are presented in this report, which will serve as a practical reference for early identification of infantile DRD associated with atypical symptoms.

2. Case Report

A male infant, 3 months old, was admitted to Jinhua Maternal and Child Health Care Hospital in 2020 due to relentless episodes of crying and shortened duration of sleep in the preceding 2 months. He was the second child of a gravida 2, para 2 (G2P2) pregnancy, born at full term via vaginal delivery. At birth, he was hospitalized for 7 days due to congenital pneumonia, neonatal hypoglycemia, abnormal levels of myocardial enzymes, scalp hematoma, and neonatal hyperbilirubinemia. He received treatment including nasal catheter oxygen inhalation, cephalosporins and blue light therapy, and all of the above conditions were resolved at the time of admission. There was no family history of neurodevelopmental and neuromuscular disorders. Physical examination results are as follows: weight = 6.8 kg; height = 64.0 cm; head circumference = 40.0 cm; and anterior fontanelle = 1 × 1 cm. The infant was conscious and had a strong cry. His anterior fontanelle was flat and soft. Bilateral upward deviation of the eyes was noted, and no social smile could be elicited. Cardiopulmonary auscultation and abdominal examination were unremarkable. Head control was unstable, and the infant had difficulty lifting his head in the prone position. Lower limb weight-bearing ability was poor when held in a standing position. Decreased muscle strength and hypotonia were present in both extremities. Joint examination revealed shoulder adduction, thumb adduction, and tight

Table 1. Genetic testing results.

Gene	Chromosomal location	Gene mutation information	gnomAD MAF (v 3.1.1)	ACMG variant classification	Disease name	Inheritance pattern	Zygosity type (alt/all)		
							Patient	Mother	Father
TH	Chr11: 2167487	NM_199292.3 :exon7: c.738-2 A>G	Not reported	P	Recessive Segawa syndrome (MIM:605407)	AR	Heterozygous (39/98)	Wild-type (0/13)	Heterozygous (68/136)
TH	Chr11: 2167905	NM_199292.3 :exon6: c.698 G>A (p.Arg 233His) ☆	0.0003	P	Recessive Segawa syndrome (MIM:605407)	AR	Heterozygous (67/158)	Heterozygous (77/168)	Wild-type (0/167)

Notes: ☆, The variant locus has been documented in authoritative databases; P, Pathogenic variant; AR, Autosomal recessive inheritance; alt/all, The ratio of the sequencing depth of the variant allele to the total sequencing depth at the locus; *TH*, tyrosine hydroxylase; gnomAD, Genome Aggregation Database; MAF, minor allele frequency; ACMG, American College of Medical Genetics and Genomics; MIM, Mendelian Inheritance in Man.

Achilles tendons. Neurological examination showed bilateral knee-jerk reflexes of (++) and asymmetrical tonic neck reflex (ATNR) of (+). Cranial magnetic resonance imaging, electroencephalogram, hip joint ultrasound, blood routine, blood ammonia, ceruloplasmin, thyroid function and alkaline phosphatase tests showed no obvious abnormalities. Genetic metabolic screening by mass spectrometry revealed increased urinary levels of oxalic acid-2 and glycolic acid-2. However, no additional clinical or biochemical evidence supporting primary hyperoxaluria or related renal or skeletal manifestations was identified in this patient. Developmental assessment using the Peabody Developmental Motor Scales at 3 months of age demonstrated a gross motor developmental quotient of 83, a fine motor developmental quotient of 79, and a total motor developmental quotient of 79. The initial diagnoses were sleep disturbance, motor developmental delay, and dystonia. Initial management included motor training (3 times/week), cognitive training (3 times/week), and sleep guidance for parents. During follow-up, the infant, who was aged 4 months at that time, still could not maintain stable head control, cried excessively during training sessions, and continued to experience poor sleep, while feeding and bowel movements remained unremarkable. Physical examination revealed that the infant was conscious with a loud cry, and the anterior fontanelle was flat and soft. No special facial features were observed, and no social smile could be elicited. Cardiopulmonary and abdominal examinations were unremarkable. Further tests demonstrated decreased muscle tone in all extremities, poor head control, difficulty lifting the head in the prone position, and weak lower limb weight-bearing when supported in a standing position. The genetic testing results were available when the patient was 5 months old. Family exome sequencing identified compound heterozygous variants in the *TH* gene (Table 1): c.738-2A>G and c.698G>A (p.Arg233His). The father was found to carry the heterozygous *TH* variant c.738-2A>G, while the mother carried the heterozygous *TH* variant c.698G>A (p.Arg233His) (Fig. 1).

According to the genetic results, the infant was treated with levodopa and benserazide tablets (each tablet containing 200 mg levodopa and 50 mg benserazide) [5,6]. The initial therapeutic dose of levodopa/benserazide tablets (calculated as levodopa) was 1 mg/kg/day, with a maintenance dose of 4 mg/kg/day, administered orally in two divided doses. Crying was significantly reduced on the second day after treatment, and the infant was able to maintain head control at the 1-month follow-up. Subsequently, the parents requested discontinuation of rehabilitation therapy and opted for home-based intervention instead. Regular follow-up was arranged. The dosage of levodopa/benserazide tablets should be titrated in accordance with body weight; without appropriate dose escalation, the patient may experience symptom recurrence, manifested as hypotonia and unsteady gait. At the most recent follow-up, the patient was 3 years and 10 months old, receiving levodopa/benserazide at a dosage of 12.5 mg/kg/day orally in two divided doses, and the dose has not been increased for one year. Physical and motor development were normal, but cognitive and social impairments, dysarthria, and persistent salivation were observed. Clinical manifestations included emotional instability, poor sitting tolerance, limited eye contact, reduced social interaction, poor compliance with instructions, and impaired attention. The patient was capable of simple verbal communication, but his speech was slurred and largely unintelligible, and persistent sialorrhea was noted. Assessment using the Gesell Developmental Schedules revealed adaptive behavior at 68, gross motor at 89, fine motor at 65, language at 60, and personal-social at 71, indicating mild developmental delay. The Childhood Autism Rating Scale (CARS) score was 31. A diagnosis of autism spectrum disorder (ASD) was established in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

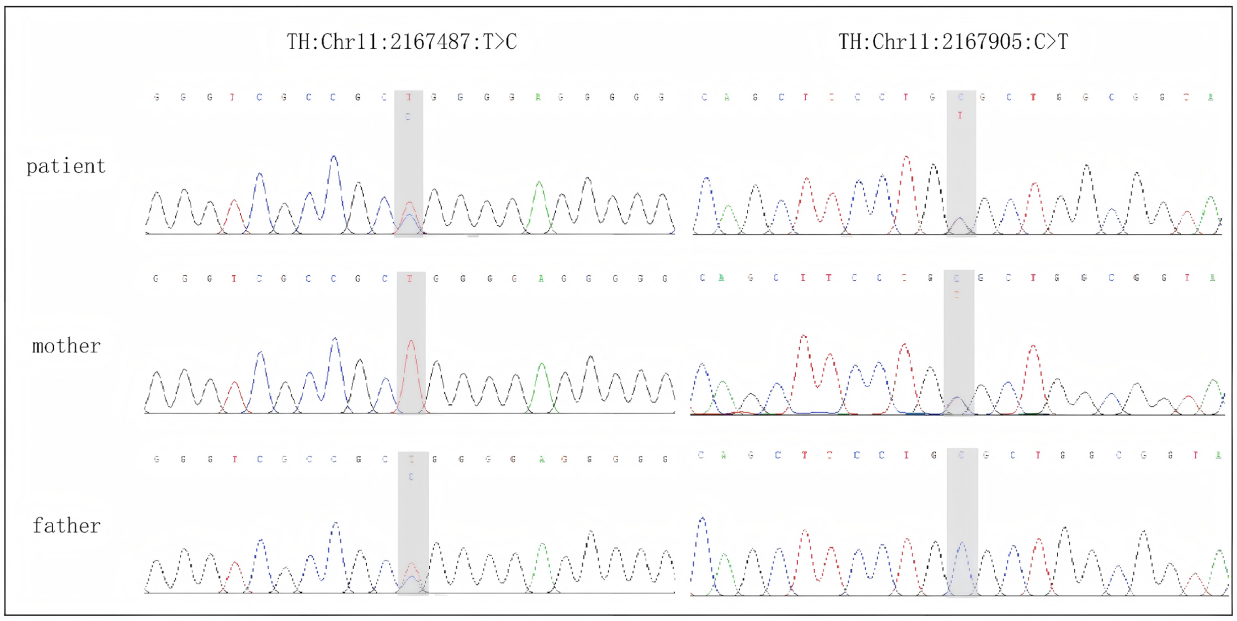

Fig. 1. Sanger sequencing validation of the *TH* gene variants in the family members. Sanger validation was performed using reverse sequencing; the bases displayed in the electropherogram correspond to the reverse complementary sequence of the target region.

The Care Checklist has been attached as **Supplementary Material** associated with this article.

3. Discussion

Most Chinese patients with Segawa syndrome are carriers of *GCH1* gene mutations [7]. The disease typically presents between infancy and 12 years of age, with a mean onset at approximately 6 years of age. A small proportion of cases begin in adulthood. It accounts for 5%–10% of primary dystonias in children and adolescents [5]. However, in the early stage, particularly in infancy, its atypical symptoms often result in misdiagnosis as cerebral palsy, early-onset Parkinson's disease, motor developmental delay, and other types of dystonias. This frequently leads to delayed treatment or overtreatment, and some patients may exhibit obvious sequelae by the time of confirmed diagnosis [8].

The inheritance patterns of DRD include autosomal dominant, autosomal recessive, and sporadic. To date, three pathogenic genes have been identified: *GCH1*, *TH*, and *SPR*. According to the literature, autosomal dominant DRD caused by *GCH1* mutations accounts for an average of 65% of cases [9], while autosomal recessive forms due to *TH* and *SPR* mutations account for 10%–15%. In the present case, the patient harbored compound heterozygous mutations in the *TH* gene, with two heterozygous pathogenic variants identified. To date, no reports of c.738-2A>G variant detected in the Asian populations have been recorded in the Exome Aggregation Consortium (ExAC), Genome Aggregation Database (gnomAD), and 1000 Genomes Project databases. More than 60 types of *TH* mutations have been reported thus far. In a study on TH deficiency involving a sample of 36 subjects, the patients were classified based on the disease types: hypokinetic-rigid syndrome (type A) and complex encephalopathy (type B) [10]. In this case, the patient presented with oculogyric crisis (bilateral upward deviation of the eyes), autonomic dysfunction (sleep disorder), motor developmental delay, and decreased muscle tone shortly after full-term birth, which were consistently characteristic of the manifestations noted in type B disease. Levodopa is the first-line treatment for DRD [5,6]. Treatment using levodopa is initiated at a low dose and gradually titrated up to a therapeutic dose of 2–5 mg/kg/day, with a maximum dose not exceeding 1000 mg/day (20 mg/kg/day for children). The treatment should be continued for at least 4 weeks, but can be discontinued if no response is observed. The patient initially received routine rehabilitation therapy for motor developmental delay upon presentation, with unsatisfactory clinical improvement. After a definitive genetic diagnosis was established at 5 months of age, treatment with levodopa/benserazide hydrochloride tablets was initiated. Subsequent follow-up demonstrated that both physical growth and motor development of the patient were consistent with those of age-matched peers. Given that levodopa significantly improves the motor prognosis of TH-related DRD and that untreated patients are at risk of eventual disability, clinicians should consider this diagnosis in all patients presenting with dystonia or Parkinsonism. A trial of low-dose levodopa may be warranted when necessary.

The *TH* gene is located at 11p15.5, containing 14 exons and encoding 497 amino acids. Tyrosine hydroxylase (TH) serves as the rate-limiting enzyme in the biosynthesis of catecholamines, including dopamine, norepinephrine, and epinephrine [7]. This enzyme catalyzes the conversion of tyrosine to L-dopa, representing the most critical step

in dopamine biosynthesis. Diminished dopamine synthesis directly gives rise to a spectrum of clinical abnormalities, including impaired regulation of muscle tone and coordinated movements, emotional and behavioral disturbances, cognitive developmental deficits, and suppressed secretion of gonadotropins [11]. Dopamine also plays a pivotal regulatory role in early brain development, encompassing neuronal migration, differentiation, and synaptic plasticity. TH deficiency should therefore be regarded as a complex neurodevelopmental disorder, in which ASD-like behavioral features may represent a prominent behavioral manifestation of its underlying neurodevelopmental impairment. For families of children harboring *TH* mutations, preparation is required to address more complex medical and rehabilitative needs.

Comorbidities such as intellectual disability, anxiety, and depression are common in DRD; however, only one case of DRD complicated with ASD has been reported so far. When the child in this case was admitted at 3 months of age, no social smile could be elicited. During follow-up, the child gradually developed sialorrhea, dysarthria, language developmental delay and social impairment accompanied by hyperactivity. The diagnosis of ASD was confirmed by a developmental and behavioral specialist based on clinical evaluation and the Childhood Autism Rating Scale (CARS).

The relationship between DRD and sleep disorders has received increasing attention in recent years. Although DRD is mainly characterized by dystonia and motor symptoms, a study has shown that children with this disease may also experience various sleep-related problems [12]. The possible cause is related to dopamine dysfunction. Dopamine plays an important role in regulating the sleep-wake cycle. In children with DRD, dysregulated or impaired dopamine biosynthesis leads to reduced dopamine levels, which may adversely affect their sleep quality and architecture. In addition, due to dystonia, they may suffer from frequent nocturnal awakenings, which lead to sleep fragmentation and difficulty in continuous deep sleep.

Autism spectrum disorder (ASD) is a common neurodevelopmental disorder in children with an unknown etiology, and its reported incidence has shown an upward trajectory in recent years. The 2023 report from the US. Centers for Disease Control and Prevention (CDC) estimated an incidence of 1 in 36 individuals, while in China, it is approximately 0.7% [13,14]. Several factors may contribute to the upward trend of ASD incidence among children. First, increased awareness of ASD among society, families, and medical institutions has facilitated earlier identification and reporting of ASD symptoms. Second, the diagnostic criteria for ASD outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) are broader and more inclusive, covering a wider spectrum of mild and high-functioning autism. Finally, environmental factors, such as maternal infection and drug exposure, may contribute to an elevated risk of ASD.

In the present case, the patient presented with autonomic dysfunction, oculogyric crisis, motor developmental delay, and social impairment. After implementing a range of assessments, a final diagnosis of DRD complicated with ASD was made. Genetic testing results identified both c.738-2A>G and c.698G>A (p.Arg233His) variants, thereby confirming the diagnosis. To date, no reports have described the coexistence of DRD and ASD in association with these specific variants. This case underscores the importance of close follow-up in children with DRD to facilitate the detection of potential comorbid ASD.

4. Conclusion

For infants and young children, particularly those with symptom onset within the first year of life and presenting with delayed motor development, hypotonia of the trunk and extremities, and decreased voluntary movements, dopa-responsive dystonia (DRD) should be considered, irrespective of the presence of dystonia. Clinicians should maintain a high index of suspicion of this disorder to facilitate early identification and subsequently prescribe timely treatment with levodopa/benserazide therapy, which most patients show a favorable response. Families of children with *TH* gene mutations should be prepared for more complex medical and rehabilitation needs. Meanwhile, intensive follow-up is warranted to monitor for potential comorbid neurodevelopmental disorders.

Learning Points

• Clinicians must prioritize DRD screening for pediatric patients with early-onset motor delay, generalized hypotonia and diminished spontaneous movements, even in the absence of typical dystonic manifestations.

• This case demonstrates that genetic testing enables the definitive diagnosis of infantile-onset DRD characterized by motor developmental delay and truncal and extremity hypotonia with a favorable response to levodopa/benserazide treatment, highlighting the importance of early genetic diagnosis and intervention for infants with dystonia accompanied by decreased muscle strength and tone.

• TH deficiency represents a complex neurodevelopmental disorder with motor, cognitive, behavioral and autonomic phenotypic spectrums, as evidenced by this patient's comorbid ASD.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

LS, QW and JZ designed the research study. JZ and QW performed the research. LS and QW analyzed the data. LS and JZ drafted this article. All authors contributed to the

important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Jinhua Maternal and Child Health Care Hospital (approval number: 2026QT007), and all procedures followed the principles of the Declaration of Helsinki. Written informed consent was obtained from the patient's legal guardian.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/BJHM49819.

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