Case Report

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R243W Mutation in Thyroid Hormone Resistance Syndrome Beta: A Case Report

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Abstract

A three-year-old girl with a history of recurrent tonsillitis was investigated for failure to thrive and global developmental delay. Clinically, she had a triangular face with low-set ears and intermittent tachycardia. She had growth failure with her weight under the third centile while her height was within normal limits. Other systemic examinations were unremarkable. The presence of an elevated free T4 (FT4) with an inappropriately high thyroid stimulating hormone (TSH) in this patient raised the clinical suspicion of Thyroid Hormone Resistance Syndrome. DNA sequencing confirmed the diagnosis, which showed R243W gene mutation in Thyroid Hormone Receptor-Beta1 (THRB1).

Key words: thyroid hormone receptor, thyroid hormone resistance, goiter

INTRODUCTION

Thyroid Hormone Resistance Syndrome (THR) is a rare condition affecting 1 in 40,000 live births. It is secondary to defects in either of the two thyroid hormone receptors-alpha and beta, leading to tissue unresponsiveness to circulating thyroid hormone.[1] The disorder might be mistaken for congenital hypothyroidism, Graves' disease or other forms of autoimmune thyroiditis. For these reasons, patients will be unnecessarily maintained on thyroxine replacement for hypothyroidism, while some may be subjected to thyroidectomy without considering the primary diagnosis of THR. Careful interpretation of thyroid function tests (TFT) and referral to a paediatric endocrinologist are essential to prevent misdiagnosis. The hypothalamic-pituitary-thyroid axis regulates thyroid hormone. Thyroid hormone exerts negative feedback on the anterior pituitary gland and hypothalamus to suppress TSH and thyroid-releasing hormone (TRH). Typically, patients with hypothyroidism or hyperthyroidism would present with either a low or high FT4 and a high or suppressed TSH, respectively. On the other hand, patients with THR would have a loss of this normal feedback regulation and would present with atypical TFTs characterized by an elevation of both FT4 and TSH. We present a case of a three-year-old girl who was diagnosed with THR.

CASE

A three-year-old girl who had recurrent admissions for acute tonsillitis was investigated due to failure to thrive, global developmental delay and intermittent tachycardia. She was born term, SGA, via spontaneous vaginal delivery, with a birth weight of 1.87 kg. Her neonatal period was uneventful. She had three hospitalizations for acute tonsillitis and was diagnosed with global developmental delay. She could walk independently at age two and could only speak in phrases at three years of age. She could put on socks and shoes but could not feed herself. Her paternal grandfather had goiter and underwent surgery, but the exact diagnosis was not known. He passed away at the age of 50 due to unknown reasons. Physically, she had a triangular face and low-set ears. No goitre or skeletal dysplasia was noted (Figure 1). Although her weight was persistently under the 3rd centile from birth until her current presentation, her height was consistently at the 10th centile. Her baseline heart rate was 110 beats per minute. Other systemic examinations were unremarkable.

A thyroid function test (TFT) was done to investigate the etiology of her failure to thrive and tachycardia. Results showed high FT4 and TSH. Table 1 summarizes her serial TFTs. She had persistently elevated TSH, FT4 and FT3. Other blood investigations are shown in Table 2.

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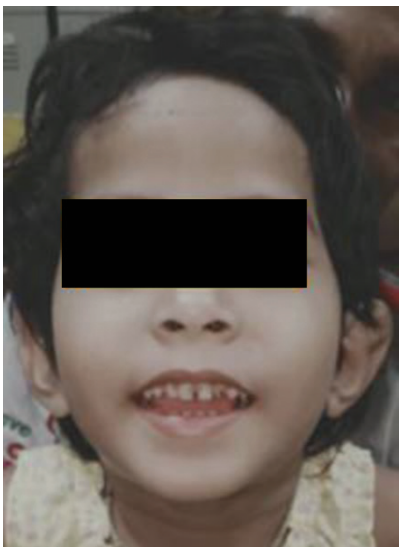

Figure 1. Soft dysmorphism with low-set ears.

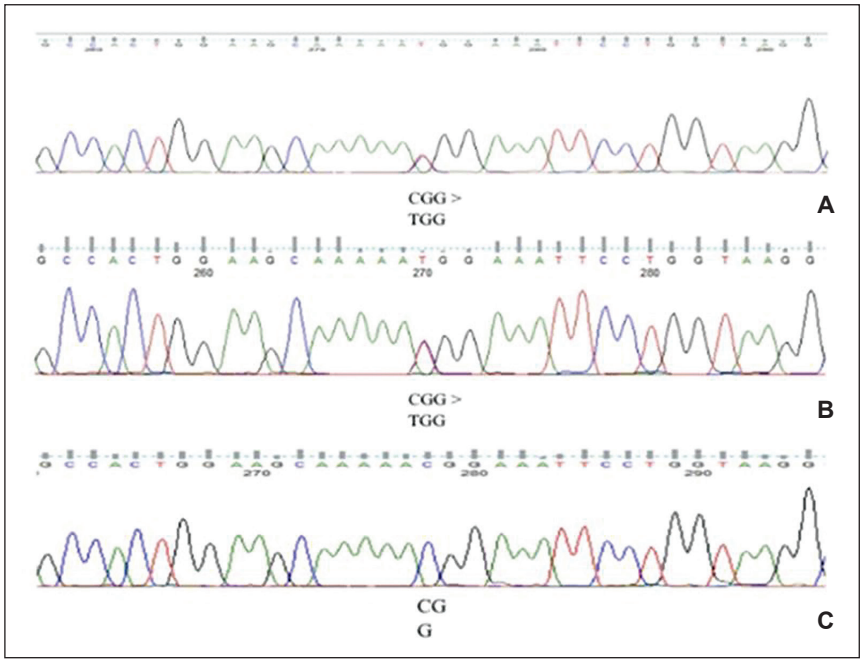

Figure 2. Sanger sequencing results for THRB1 gene. **(A)** and **(B)** represent the patient and her father respectively; **(C)** is the result of the mother.

Table 1. Serial Thyroid Function Test

Age	3 year 5 month old	3 year old 6 month old	5 year 10 month old	7 year old	7 year 11 month old
TSH (mIU/L)	26.48	18.41	4.74	5.97	6.88
FT4 (pmol/L)	42.0	55.74	50.67	51.23	47.10
FT3			16.02		
Ratio FT4/FT3			3.16		

Normal range: TSH: 0.5-4 mIU/L; FT4: 10-24 pmol/L; FT3: 3.1-6.8 pmol/L; FT4/FT3 ratio: 2.2-3.7

Autoimmune testing such as thyroid-stimulating hormone receptor (TRAb), anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies were negative. MRI of the pituitary gland and skeletal survey were normal. Ultrasound of the thyroid gland showed goiter, with the right thyroid gland measuring 0.8 x 1.4 x 3 cm and the left thyroid gland measuring 0.9 x 1.4 x 3.3 cm with generalized increased vascularity within both glands. Due to the expression of thyroid receptors in the muscle and liver, a lipid profile and creatinine kinase were done, which showed normal results.

Family screening with thyroid function tests was done as those who carry the mutations may be asymptomatic and do not require treatment. For this family, the patient is the third of four siblings. Thyroid disease ran in the family as both her paternal grandfather and father showed similar TFT patterns of an elevated FT4 and a non-suppressed TSH. His FT4 was 36.27 pmol/L while TSH was 1.76 mIU/L. DNA sequencing showed that the patient and her father have the same mutation (R243W mutation) in the thyroid hormone receptor-beta gene, as reported in a previous study.[2] On the other hand, her mother was not affected (Figure 2). Other siblings were not screened as they were asymptomatic.

Table 2. Investigations

Calcium (mmol/L)	2.4
Phosphate (mmol/L)	1.78
Hemoglobin (g/dL)	13.7
Cholesterol (mmol/L)	5.3
Triglyceride (mmol/L)	0.44
Creatinine kinase (U/L)	143
TSH receptor antibody	negative
ATG (kIU/L)	14.03 (<115)
TPO (KIU/L)	10.12 (<34)

ATG: Antithyroglobulin antibody
TPO: Thyroid Peroxidase antibody
TSH: Thyroid Stimulating Hormone

DISCUSSION

THR syndrome can be classified into three types: pituitary THR, peripheral THR and generalized THR.[3] In pituitary THR, the pituitary gland cannot sense the circulating thyroid hormone, thus leading to increased secretion of TSH and, subsequently, elevated thyroid hormone.[4] Peripheral THR is caused by tissue insensitivity to thyroid hormone without pituitary gland involvement. They present with normal thyroid hormone and TSH levels but may manifest with symptoms of hypothyroidism. In generalized THR, peripheral tissues and the pituitary gland are resistant to thyroid hormone due to receptor defects causing both elevated TSH and thyroid hormone.[3] This patient is consistent with pituitary THR as both TSH and FT4 were elevated with thyrotoxic symptoms.

The thyroid receptor (TR) consists of alpha-1, alpha-2, beta-1 and beta-2. TR alpha-1 is expressed specifically in the heart and muscles, while little is known about alpha-2 receptors. TR beta-1 is expressed in the brain, liver and kidneys, while beta-2 is expressed in the hypothalamus and pituitary gland.[5] Different TH receptor tissue expressions result in different clinical manifestations. The majority of THR-beta (THRB) patients have goitre, palpitations, developmental delay, short stature and repeated infections.[6] Dysmorphisms such as bird-like facies and pigeon chest were reported previously but was absent in our patient.[7] Our patient had clinical clues consistent with THRB, such as the failure to thrive, developmental delay, intermittent tachycardia and repeated infection/tonsillitis. Patients with THR-alpha may exhibit dysmorphism, skeletal dysplasia, constipation and intellectual deficits that may mimic features of congenital hypothyroidism.

Concomitant FT4 and FT3 elevation with a non-suppressed TSH are typical findings in THR-beta syndrome. Increased deiodinase activity in THRB results in a high FT4/FT3 ratio.[8] However, THR-alpha syndrome can be differentiated from THRB biochemically with a more significant FT3 elevation than FT4, resulting in a low FT4/FT3 ratio, which was not observed in this patient.[9] Bone profiles, including serum calcium, serum phosphate and alkaline phosphatase, as well as hemoglobin and creatinine kinase levels, can differentiate THR-alpha from THRB. THR-alpha is associated with both skeletal dysplasia, such as macrocephaly and epiphyseal dysgenesis, and normocytic normochromic anemia, which were not seen in this patient.[10] High circulating thyroid hormone results in tachycardia in the case of THRB and may be mistaken for Graves' disease. Although most patients with THRB are clinically euthyroid, some may manifest with goiter and intermittent tachycardia without other peripheral signs of thyrotoxicosis.[11] Moreover, the thyroid hormone antibodies are absent in THRB.

The differential diagnoses for high FT4 and TSH are assay interference, familial dysalbuminemic hyperthyroxinemia (FDH) and TSH-secreting pituitary tumor (TSHoma). Thyroid hormone assay interference can be ruled out by repeating TFT in a different laboratory with a different analysis method. It might be due to the presence of binding antibodies, which results in a falsely high FT4 or TSH. Serial TFT was sent to other laboratories, and the results were similar. FDH is a rare autosomal dominant disease whereby the thyroxine-binding capacity of mutated albumin increases, resulting in an abnormally high thyroid hormone without physical abnormalities.[12] MRI of the pituitary gland was normal, ruling out a TSH-secreting tumor of the pituitary gland.

THR-beta syndrome is inherited in an autosomal dominant, autosomal recessive or sporadic pattern with de novo mutations in 20% of the cases.[13] THR syndrome is caused by a defect in the THRB gene located at chromosome 3. In our patient, genetic testing for both the patient and father showed R243W gene mutation in exon 7, whereby normal arginine-243 has been substituted by tryptophan. This mutation was reported in 1996 (2), with most THRB mutations identified between exons 7 and 10.[14]

Clinical manifestations of THR can be highly variable. Canadas et al.,[15] reported a 4-year-old girl who presented with hyperthyroidism and goiter, causing compressive symptoms. Her TFT showed an elevation of both thyroid hormone and TSH. Genetic testing revealed a mutation of the thyroid beta receptor gene, E445X. A total thyroidectomy was performed. However, her TSH did not decrease despite taking high-dose levothyroxine (175 mcg daily). Triiodothyronine (200 mcg every other day) was added to improve her response. Another case was reported by Tong et al., whereby a 15-year-old girl with attention-deficit hyperactivity disorder (ADHD) presented with oligomenorrhea and a positive family history of hyperthyroidism in her mother and maternal uncle.[16] Her TFT showed high TSH, normal FT4 with positive TPO. She was diagnosed with Hashimoto's thyroiditis and was given levothyroxine. However, the TFT showed persistent derangement. Family screening showed that her mother had similar TFT results. Genetic testing revealed a heterozygous mutation in c8303 C>G in the THRB gene, thus confirming the diagnosis of THRB.

The majority of patients with THR syndrome do not require treatment. Normalization of thyroid hormone levels is not the sole treatment goal. Treatment with conventional antithyroid drugs such as carbimazole may result in drug toxicity, particularly if the attending physician prescribed the dose used for patients with thyrotoxicosis.[17] Beta-blockers can be used for symptomatic treatment of adrenergic symptoms such as palpitation/tachycardia and breathlessness.[11] Thyroid hormone replacement may be initiated for patients with THR-alpha who manifest symptoms of hypothyroidism, especially during infancy.[3] The recommended specific treatment for thyrotoxicosis is triiodothyronine acetate (TRIAC), which inhibits TSH activity, thereby reducing the hypermetabolic state without affecting peripheral tissue activity.[17] However, TRIAC was not available in our country. Surgical removal of the thyroid gland and ablation treatment should not be done as it complicates subsequent management and monitoring.[17] In this patient, we provided symptomatic treatment such as a beta-blocker for palpitations and regular monitoring of her TFT. During subsequent follow-ups, her development milestones had been catching up but were still delayed compared to her peers . She can walk independently, speak in phrases, feed herself and put on clothes. At around 7 to 8 years old, her weight is in the 5th centile while her height is in the 10th centile (Figure 3). Her TFT still showed elevated FT4 and TSH (Table 1).

CONCLUSION

Clinical manifestations of THR syndrome are nonspecific and diverse. Early diagnosis is challenging. However, with

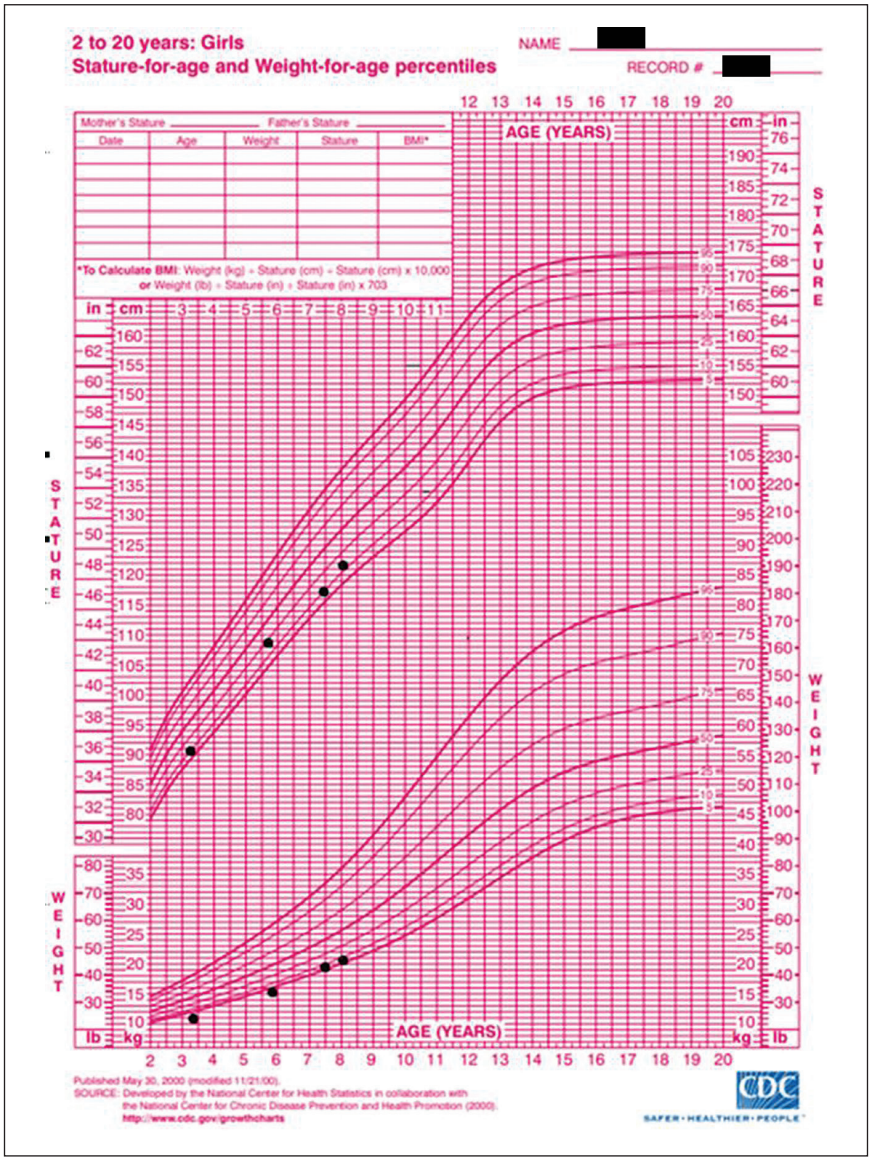

Figure 3. Growth chart. Centers for Disease Control Prevention. National Center for Health Statistics. Downloadable charts.

https://www.cdc.gov/growthcharts/data/set1clinical/cj41c022.pdf.

proper biochemical or hormonal tests and genetic testing, diagnosis can be made earlier to institute appropriate treatment.

Ethical Consideration

Patient consent was obtained before submission of the manuscript.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement

JCO: Writing – original draft preparation, Writing – review and editing; **WMHWO:** Resources; **TSTI:** Investigation; **KC:** Investigation; **SH:** Writing – review and editing, Supervision.

Author Disclosure

The authors declared no conflict of interest.

Data Availability Statement

Datasets generated and analyzed are included in the published article.

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