



Retrospective analysis and literature review of four cases of thyroid hormone resistance syndrome caused by *THRB* gene mutation

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Background: To summarize the clinical characteristics, genetics and follow-up data of four children with thyroid hormone resistance (RTH) syndrome and review the related literatures.

Methods: The clinical data of the four children diagnosed with RTH syndrome in our hospital from 2018 to 2020 were retrospectively analyzed. Next-generation sequencing of the candidate genes related to thyroid diseases was performed using the blood collected from all the children and their parents who signed an informed consent. Then, relevant cases were retrieved on medical literature databases for analysis and summary.

Results: Among the four cases, three cases of goiter; two cases of tachycardia, palpitations, personality change, hyperactivity, weight loss; one case of academic performance decline, and no hearing and vision loss were observed. Laboratory thyroid function tests indicated a mild increase in free triiodothyronine and with or without increased free thyroxine levels. Thyroid-stimulating hormone (TSH) levels were normal or slightly elevated, but thyrotropin receptor autoantibodies were negative. Octreotide inhibition test showed that the TSH levels of all the children decreased by more than 50% compared with the basal value (the genes of four cases were positive). However, magnetic resonance imaging of the pituitary gland showed no abnormalities. Related gene detection in the children and their families showed that four cases had *THRB* mutations: two proband mutations were from their fathers, and two cases had de novo mutations.

Conclusions: The clinical manifestations of pediatric RTH syndrome vary, and the diagnosis mainly depends on thyroid function tests. Heterozygous mutations in *THRB* are overall rare, even if with the advanced development of next-generation sequencing, not all the children with RTH syndrome have mutations. Furthermore, octreotide inhibition tests cannot be used as a diagnostic criterion to distinguish RTH syndrome from pituitary tumors in children.

Keywords: Thyroid hormone resistance (RTH) syndrome; *THRA*; *THRB* gene; octreotide inhibition test

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Introduction

Thyroid hormone resistance (RTH) syndrome is an inherited endocrine disorder caused by mutations in the thyroid hormone receptor (THR). Clinical manifestations include reduced sensitivity of the central or peripheral target tissue to thyroid hormone (TH). The typical laboratory features are elevated serum levels of free triiodothyronine (FT3) and free thyroxine (FT4) and normal or elevated serum levels of thyroid-stimulating hormone (TSH) due to the loss of negative feedback of TH to the pituitary gland. RTH is an autosomal dominant or recessive disorder, with an incidence of approximately 1/40,000 (1). The first case of RTH was identified and reported in 1967 by Refetoff *et al.* (2). The different expression of THR in various target tissues leads to different clinical manifestations. Only few relevant summaries are available on RTH cases in children in China, raising great challenges to clinical diagnosis. This study aimed to summarize the clinical characteristics and genetic test results of four children diagnosed with RTH in our hospital and provide information for clinical diagnosis and treatment of this disease. We present the following article in accordance with the STROBE reporting checklist (available at <https://tp.amegroups.com/article/view/10.21037/tp-22-59/rc>).

Methods

Patients

The clinical characteristics and genetic test results of four children diagnosed with RTH admitted in Ruijin Hospital, Shanghai Jiao Tong University School of Medicine from 2018 to 2020 were retrospectively analyzed.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ruijin Hospital Ethics Committee, Shanghai Jiao Tong University School of Medicine (No. 2021-370), and informed consent was taken from the patients' parents or legal guardians.

Procedure

The basic information of the children (gender, age, age at diagnosis, and family history), clinical characteristics, physical examination (height, weight, body mass index, thyroid size, heart rate and rhythm), laboratory tests (triiodothyronine, free triiodothyronine, thyroxine, free thyroxine, TSH, anti-thyrotropin receptor antibody, anti-thyroglobulin antibodies, thyroid peroxidase antibody, thyroglobulin), and changes in the thyroid function before and after the octreotide inhibition test were recorded.

For the octreotide inhibition test, rapid inhibition of TSH was examined using a somatostatin analogue. Octreotide acetate (0.1 mg) was injected subcutaneously (every 8 h for three times). Serum FT3, FT4, and TSH levels were measured at 0, 2, 4, 6, 8, and 24 hours after the first injection. Results were evaluated based on the inhibition ratio of TSH.

Peripheral venous blood (2 mL) of the proband and the parents were collected and sent to Shanghai Institution of Endocrine and Metabolic Diseases for thyroid disease-related gene panel detection. Gene panel includes *DUOX2**, *DUOXA2*, *FOXE1*, *GNAS*, *HESX1*, *IGSF1*, *NKX2-1*, *NKX2-5*, *PAX8*, *P0U1F1*, *PROP1*, *SECISBP2*, *SLC16A2*, *SLC26A4*, *SLC5A5*, *TBL1X*, *TG*, *THRA*, *THRB*, *TPO*, *TSHB* and *TSHR* genes.

Statistical analysis

Height deviations were calculated using the height Standard Deviation Score (SDS), which is calculated as (child height – normal child height)/normal child height. The method of calculation of TSH inhibition is (basal TSH – minimum TSH)/basal TSH × 100%.

Results

Among the four cases, two were boys and two were girls. The mean age at diagnosis was 7.4 years, and the longest duration of symptoms was three years. Two patients were examined with goiter; one were found with thyroid dysfunction using preoperative examination and short

Table 1 Basic information and clinical symptoms of the four cases

Cases	Sex	Age at onset (year)	Age at diagnosis (year)	Course of disease (year)	Height (cm, SDS)	Family history	Goiter	Hyperactivity	Learning disorder	Proptosis	Weight loss
1	M	7.9	9.9	2	+2.85	+	II	+	+	-	+
2	F	4.3	4.6	0.3	-0.66	-	I	-	-	-	-
3	M	-	4.6	-	-1.29	+	-	-	-	-	-
4	F	7.5	10.5	3	+0.14	-	II	+	-	-	+

M, male; F, female; SDS, Standard Deviation Score.

Table 2 Thyroid function and thyroid-related antibody levels

Cases	T3 (nmol/L)	FT3 (pmol/L)	T4 (nmol/L)	FT4 (pmol/L)	TSH (uIU/mL)	TRAb (IU/L)	TGAb (IU/mL)	TPOAb (IU/mL)	TG (ng/mL)
1	4.44	13.51	226.36	25.64	3.61	0.70	1.48	0.28	208.5
2	3.44	10.06	233.89	32.40	0.85	0.30	19.98	0.35	55.45
3	2.66	6.54	171.04	23.36	1.89	-	0.72	<0.05	39.46
4	2.61	14.84	119.90	15.33	27.03	0.30	2.25	0.15	>500
Ref.	0.8–2.4	2.6–5.7	62.6–150.8	9.0–19.0	0.35–4.94	<1.75	<4.11	<5.61	3.5–77

T3, triiodothyronine; FT3, free triiodothyronine; T4, thyroxine; FT4, free thyroxine; TSH, thyroid stimulating hormone; TRAb, anti-thyrotropin receptor antibody; TGAb, anti-thyroglobulin antibodies; TPOAb, thyroid peroxidase antibody; TG, thyroglobulin.

stature examination, and one patient went to the hospital for routine screening because his father was diagnosed with RTH. Two patients had a family history of thyroid-related diseases, and one patient was misdiagnosed with hyperthyroidism in another hospital. This patient had been treated with methimazole for two years, but the symptoms of palpitations and hand tremors did not improve, and goiter was worse than before. The other three patients were directly admitted to our hospital without treatment.

Furthermore, two cases of tachycardia, palpitations, personality change, and hyperactivity, and one case of academic performance decline were recorded. None of the patients experienced proptosis, hearing, or vision loss. Physical examination indicated thyroid enlargement in three cases and weight loss in two cases (*Table 1*). Ultrasound of the thyroid suggested diffuse changes in bilateral thyroid with swelling or nodular lesions in three cases. Electrocardiogram suggested sinus tachycardia, and magnetic resonance imaging (MRI) of the pituitary showed no abnormalities in four cases.

The FT3 levels were elevated in all cases, FT4 levels were elevated in three patients, while TSH level was increased in one patient. Three cases had TSH levels within the normal range, and thyroid-related autoantibodies were

normal (*Table 2*). Meanwhile, serum FT3, FT4, and TSH levels, as well as the minimum/basal value of TSH, were all lower than 50% in four cases before and after the octreotide inhibition test at 0, 2, 4, 6, 8, and 24 h (*Table 3*).

Genetic test results showed that all cases (100%) had point mutations in *THRB* (*Table 4*). Specifically, C.1012C>T heterozygous variation was found in exon 9 of *THRB* in Case 1, leading to a missense mutation (p.Arg338Trp). Meanwhile, C.1357C>A heterozygous variation was detected in exon 10 of *THRB* in Case 2, leading to a missense mutation (p.Pro453Thr). A C.1378G>A heterozygous variation was observed in exon 10 of *THRB* in Case 3, leading to missense mutation (p.Glu460Lys). Lastly, a C.830C>T heterozygous variation was found in exon 8 of *THRB* in Case 4, leading to missense mutation (p.Thr277Ile). Furthermore, four mutation sites were included in ClinVar and Human Gene Mutation Database, showing pathogenicity. Mutations in Cases 2 and 3 were derived from their fathers. The parents of Cases 1 and 4 did not harbor any mutations in *THRB*.

Discussion

THR consists of two subtypes: TR- α and TR- β , and their

Table 3 Results of the octreotide inhibition test

Cases	Hormone	0 hour	2 hours	4 hours	6 hours	8 hours	24 hours	IR (%)
Case 1	FT3 (pmol/L)	13.51	11.86	10.35	10.14	11.67	8.72	60
	FT4 (pmol/L)	25.64	26.57	24.04	26.05	26.00	22.45	
	TSH (uIU/mL)	3.61	3.39	2.14	1.95	1.75	1.44	
Case 2	FT3 (pmol/L)	10.06	9.60	8.65	7.78	7.23	6.46	62
	FT4 (pmol/L)	32.40	39.00	29.10	27.35	27.25	27.27	
	TSH (uIU/mL)	0.86	0.49	0.39	0.46	0.39	0.33	
Case 3	FT3 (pmol/L)	7.28	6.70	6.13	6.45	5.90	4.42	67
	FT4 (pmol/L)	23.41	20.19	18.86	18.96	18.07	18.68	
	TSH (uIU/mL)	0.97	0.67	0.54	0.49	0.45	0.32	
Case 4	FT3 (pmol/L)	21.80	15.68	14.81	13.38	13.05	11.05	83
	FT4 (pmol/L)	21.01	22.26	24.05	20.48	22.55	22.41	
	TSH (uIU/mL)	17.95	5.03	4.85	3.75	4.88	2.98	

IR, inhibition ratio: (basal TSH – minimum TSH/basal TSH ×100%); FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone.

Table 4 Next-generation sequencing test results of *THRB*

Results	Case 1	Case 2	Case 3	Case 4
Exon	Ex9	Ex10	Ex10	Ex8
Base	c.1012C>T	c.1357C>A	c.1378G>A	c.830C>T
Amino acids	R338W	P453T	E460K	T277I
Origin of mutation	<i>De novo</i>	Father	Father	<i>De novo</i>

abnormal function is an important cause of RTH (3). *THRA* (OMIM:190120), which encodes for TR- α , is located in 17q21.1 and contains 10 exons with a total length of 27 kb. Meanwhile, *THRB* (OMIM:190160), encoding for TR- β , is located in 3p24.2 and contains 10 exons with a total length of 378 kb. Dominant-negative mutations leading to loss of functions of *THRA* and *THRB* can cause RTH. At present, approximately 80% of RTH are caused by *THRB* mutation, and approximately 10–15% of the cases are not attributed to *THRB* mutation (4–6). Furthermore, *THRB* heterozygous mutations are the most common genetic causes of RTH. Because of the different expression patterns of the two receptors in different tissues (7), pituitary or systemic resistance may occur; therefore, the clinical manifestations in children may vary, with hyperthyroidism or hypothyroidism.

There are three main T3 binding splicing products of

TR- β (8). TR- β 1 is ubiquitously expressed; TR- β 2 is mainly expressed in the brain, retina, and inner ear; and TR- β 3 is expressed in the kidney, liver, and lung tissue (9). Since the mutation in *THRB* has a dominant-negative effect, point mutation is often autosomal dominant, and deletion of the both copies of the *THRB* is often autosomal recessive. Exons 7–10 of *THRB* mainly encode the T3 ligand-binding region. Currently, the reported mutation hotspots mainly focus on the partial hinge region of the carboxyl-terminal and T3 ligand-binding region (10); in this study, the mutation sites of all children were all located in this hotspot region. The patients with TR- β mutations can manifest as goiter or can cause hearing defects, hyperactivity, learning disabilities, growth retardation, and tachycardia; and in severe cases, growth retardation, intellectual disability, and hearing loss. Serum T4 and T3 levels of the *THRB* mutation were elevated, and TSH levels were normal or slightly elevated.

Moreover, the clinical manifestations listed above were observed in most of the cases, indicating *THRB* mutation.

On the other hand, TR- α can be divided into three types: $\alpha 1$, $\alpha 2$, and $\alpha 3$. TR- $\alpha 1$, specific to T3 binding, is mainly expressed in the central nervous system, skeletal muscle, myocardium, and digestive tract, while TR $\alpha 2$ and TR $\alpha 3$ are non-T3 binding splice products (9). A study (11) has shown that THs stimulate neural development in the brain during childhood and adulthood and play an essential role in learning, memory, and mood. TR- $\alpha 1$ levels in the bone are at least 10 times higher than TR- $\beta 1$. This suggests that TR- $\alpha 1$ is the primary mediator of T3 in the bone and can mediate T3 to stimulate osteoblast proliferation and differentiation, as well as the synthesis, modification, and mineralization of the bone matrix. TR- $\alpha 1$ also participates in bone growth and maturation and regulates intestinal peristalsis. When *THRA* is mutated, clinical manifestations include transient delayed motor development, mild cognitive development disorder, short stature, bone retardation, sinus bradycardia, chronic constipation, and so on (12). In our study, none of the four patients had any clinical manifestations such as constipation, bradycardia, cognitive dysplasia, severe short stature, skeletal deformity, and thyroid function examination results did not conform to the characteristics of RTH α laboratory, so this *THRA* mutation can be excluded in our study.

Clinical manifestations can be divided into generalized TH resistance (GRTH) and pituitary TH resistance (PRTH) (13). The clinical manifestations are heterogeneous and may coexist with different degrees of hyperthyroidism, hypothyroidism, or hyperthyroidism without apparent symptoms. In GRTH, both pituitary and peripheral tissues are resistant to THs, and clinical manifestations vary according to different levels of resistance and compensatory differences. PRTH is a selective pituitary resistance wherein TSH secretion increases. Peripheral tissues may show mild hyperthyroidism due to the increase in THs (14). In this study, two of the four patients had obvious symptoms of hyperthyroidism (palpitations, personality change, hyperactivity, and weight loss), but no eye protrusion or anterior tibial mucinous edema were observed, and the possibility of pituitary resistance was relatively high. The other two patients had no obvious clinical symptoms and could be classified as GRTH.

It was found that the TRH stimulation test combined with cranial MRI can be used to differentiate TSH-oma from RTH. Since TRH stimulation test is not available in the Chinese mainland, the octreotide inhibition test was used as

an alternative. Somatostatin can negatively regulate TSH, and somatostatin receptor is expressed on the cell surface of pituitary TSH tumor. Octreotide, a somatostatin analogue, can inhibit TSH secretion and even shrink tumors (15). It can be used for preoperative preparation and postoperative recurrence or treatment of TSH tumor. RTH patients have low response to somatostatin, and the mechanism is unclear. A study conducted by the Department of Endocrine and Metabolism in our hospital in 2013 showed that TSH levels in patients with TSH-omas were inhibited to below 36% of the baseline value, while TSH levels in patients with RTH were above 36% (16). In our study, the 24-h TSH inhibition rate of four patients who underwent the octreotide inhibition test was below 50%, specifically two cases were below 36%, but no TSH-omas was detected on the head MRI. Mannavola *et al.* have demonstrated that acute administration of somatostatin analogues leads to a similar reduction in TSH in patients with TSH-omas or PRTH (17). Another study in our hospital showed that the TSH trough value of adult TSH-omas decreased by 77.02% \pm 13.43% 24-h after injection of somatostatin, while that of RTH group decreased by 52.33% \pm 15.02% after injection (18). Although the inhibition rates of the two groups were statistically different, the inhibition rates of some patients were similar. Furthermore, somatic mutations in *THRB* have been identified in some TSH-secreting pituitary adenomas in foreign studies (19) and knockout mutant mice (mutant TR- β) spontaneously developed TSH-omas, suggesting the role of TR- β in pituitary tumorigenesis (20). More interestingly, patients with RTH have been reported to have TSH-omas (21). In this study, four children were diagnosed with *THRB* mutation, the TSH inhibition rate of all children was below 50% after the octreotide inhibition test, but no TSH-omas was found on the head MRI. These results were inconsistent with the molecular diagnosis. Whether these changes are related to the distribution and expression of TRH receptors in the tissues at different stages of the disease require further studies. Moreover, based on our results, the octreotide inhibition test cannot be used as a reference standard for differentiating TSH-omas from RTH in children, thus confirming previously reported data (22). Further studies are needed to confirm these hypotheses.

In conclusion, the clinical manifestations of RTH caused by *THRB* mutations are diverse and can be easily confused with other diseases. The current octreotide inhibition test cannot clearly distinguish TSH-omas from RTH in children. It is recommended that relevant genetic testing

be improved as soon as possible to confirm the diagnosis of children with elevated FT3 and FT4 levels, accompanied by normal or uninhibited TSH levels.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ruijin Hospital Ethics Committee, Shanghai Jiao Tong University School of Medicine (No. 2021-370), and informed consent was taken from the patients' parents or legal guardians.

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