



## Resistance to thyroid hormone with a mutation of the thyroid $\beta$ receptor gene in an eight-month-old infant — a case report

Zespół oporności na hormony tarczycy spowodowany mutacją w genie kodującym podjednostkę  $\beta$  receptora hormonów tarczycy u 8-miesięcznego niemowlęcia: opis przypadku

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### Abstract

**Introduction:** Resistance to thyroid hormone (RTH $\beta$ ) is a rare syndrome of impaired tissue responsiveness to thyroid hormones (THs). The disorder has an autosomal dominant or recessive pattern of inheritance. Most of the reported mutations have been detected in the thyroid hormone receptor  $\beta$  gene (*THRB*).

**Case report:** Authors present an eight-month-old infant with poor linear growth, decreased body weight, tachycardia, positive family history, and neonatal features suggestive of RTH $\beta$ . Both our patient and his mother had elevated free thyroxine, free triiodothyronine, and non-suppressed thyrotropin (TSH) concentration. The fluorescent sequencing analysis showed a heterozygous mutation c.728G>A in *TR $\beta$*  gene. This pathogenic variant is known to be associated with THR.

**Conclusions:** The clinical presentation of RTH $\beta$  is variable, ranging from isolated biochemical abnormalities to symptoms of thyrotoxicosis or hypothyroidism. The syndrome should be suspected in patients with increased serum TH level, accompanied by a normal or elevated TSH concentration. The affected patients require individualised management. (*Endokrynol Pol* 2019; 70 (1): 124–130)

**Key words:** resistance to thyroid hormone; thyroid hormone receptor  $\beta$ ; infant

### Streszczenie

**Wstęp:** Zespół oporności na hormony tarczycy to rzadka, uwarunkowana genetycznie choroba, spowodowana zmniejszoną wrażliwością tkanek obwodowych i/lub komórek tyreotropowych przedniego płata przysadki na działanie hormonów tarczycy (HT). Najczęstszą przyczyną zespołu są punktowe mutacje w genie *THR* kodującym podjednostkę  $\beta$  receptora hormonów tarczycy. Dziedziczenie jest autosomalne dominujące lub autosomalne recesywne.

**Opis przypadku:** W pracy przedstawiono opis przypadku 8-miesięcznego niemowlęcia ze słabym przyrostem masy i długości ciała, tachykardią oraz dodatnim wywiadem rodzinnym w kierunku zespołu oporności na hormony tarczycy. Zarówno u probanta, jak u jego matki stwierdzano podwyższone stężenie wolnej tyroksyny i trójjodotyroniny, przy braku supresji sekrecji tyreotropiny (TSH). Przeprowadzono sekwencjonowanie genu *TR $\beta$* , stwierdzając heterozygotyczną mutację c.728G>A, o której wiadomo, że może być przyczyną oporności na hormony tarczycy.

**Wnioski:** Obraz kliniczny zespołu oporności na hormony tarczycy jest zmienny; większość pacjentów znajduje się w stanie eutyreozy, u niektórych obok objawów niedoczynności występują objawy nadczynności gruczołu tarczowego. Zespół należy podejrzewać u pacjentów z brakiem supresji wydzielania TSH mimo podwyższonych stężeń hormonów tarczycy. Leczenie powinno być zindywidualizowane. (*Endokrynol Pol* 2019; 70 (1): 124–130)

**Słowa kluczowe:** zespół oporności na hormony tarczycy; receptor  $\beta$  dla hormonów tarczycy; niemowlę

### Introduction

Resistance to thyroid hormone (RTH $\beta$ ) is a rare syndrome of impaired tissue responsiveness to thyroid hormones (THs) [1, 2]. The incidence of RTH $\beta$  is approximately 1:40,000–1:50,000 per live births, and the inheritance is autosomal dominant or recessive [1, 3]. Nonetheless, approximately 15% of the cases are sporadic [3]. The thyroid hormone receptor (TR) had

two subtypes (TR $\alpha$ , TR $\beta$ ), which are encoded by genes (*THRA*, *THRB*) located on chromosomes 17 and 3, and with three main isoforms (TR $\alpha$ , TR $\beta$ 1, TR $\beta$ 2) with organ-specific distribution [4].

The most common causes of the syndrome are genetic mutations in *THRB* gene [2, 5]. However, in some cases no mutations have been detected [6]. Recent studies have demonstrated *THRA* mutations, producing defective TR $\alpha$ , as another cause of RTH (termed



RTH $\beta$ ) [7]. The RTH $\beta$  used to be classified into generalised (GRTH) or pituitary (PRTH) [8]. The clinical manifestation is heterogeneous, even between members of the same family harbouring the same mutation. The syndrome can present with variable symptoms, ranging from isolated biochemical abnormalities to symptoms of thyrotoxicosis or hypothyroidism. The biochemical hallmark of RTH $\beta$  is elevated serum TH, along with non-suppressed level of thyrotropin (TSH). The treatment decision should be individualised, depending on the clinical presentation in each patient [2, 9, 10].

## Case report

An eight-month-old boy was referred to the Department of Paediatrics and Paediatric Endocrinology due to abnormal thyroid function test: elevated free thyroxine (FT4) and free triiodothyronine (FT3) concentration, along with TSH level within the normal range, accompanied by poor weight gain and tachycardia.

He was born as the first child of nonconsanguineous parents, by Caesarean section at gestational week 36, due to pregnancy complicated by oligohydramnios, breech presentation, and premature obscuration of placenta. Additionally, during the third trimester of pregnancy growth retardation and acceleration and deceleration of foetal heart rate were observed. The birth weight was 2300 g (3<sup>rd</sup>–10<sup>th</sup> centile, SDS: –1.65) and length was 51 cm (75<sup>th</sup>–90<sup>th</sup> centile, SDS: +2.6). The birth head circumference was 32 cm (3<sup>rd</sup>–10<sup>th</sup> centile), and the size of the anterior fontanelle in the perinatal period was 1 × 1 cm. To evaluate the birth parameters the growth charts by Palczewska and Niedźwiecka for boys born between 32 and 37 week of gestation (Hbd) were used [11, 12]. The postnatal period was complicated by feeding difficulties, due

to weak sucking reflex and retrognathia. Significant failure of thrive was noted, with weight remaining below the 3<sup>rd</sup> centile. Due to his positive family history and suggestive neonatal features of RTH $\beta$ , THs were checked, revealing FT4 and FT3 levels exceeding the upper limit of normal range, accompanied by normal TSH concentration.

On admission to the hospital at age eight months, the patient's length was 67 cm (25<sup>th</sup> centile) and his weight was 5.7 kg (< 3<sup>rd</sup> centile) [12]. Physical examination showed microcephaly (head circumference: 41 cm, < 3<sup>rd</sup> centile), closed anterior fontanelle, facial dysmorphism (almond-shaped, slanted eyes, flat philtrum), dry skin, very scarce subcutaneous fat tissue development, and tachycardia (160 bpm) [12]. Laboratory findings included: FT3 13.11 pg/ml (reference range: 2.15–5.83 pg/ml), FT4 4.00 ng/dL (reference range: 0.65–2.30 ng/dL), TSH 5.390  $\mu$ IU/mL (reference range: 0.730–8.350  $\mu$ IU/mL), antiTG < 20.0 IU/ml (reference range: 0.0–40.0 IU/ml), and antiTPO < 10.0 IU/ml (reference range: 0.0–40.0 IU/ml), TRAb 1.29 IU/l (reference range: < 2 IU/l). To exclude a TSH-secreting pituitary adenoma a thyrotropin-releasing hormone (TRH) stimulation test was performed, and it showed a robust TSH response (time 0' — 4.7  $\mu$ IU/mL, 20' — 59.67  $\mu$ IU/mL, 30' — 57.36  $\mu$ IU/mL, 60' — 32.52  $\mu$ IU/mL, 120' — 23.43  $\mu$ IU/mL). The results of complete blood count, renal and liver function, blood glucose, and routine urinalysis were within normal ranges. The result of biochemical analyses performed at the Institute of Metabolic Science are included in Table I.

Electrocardiography confirmed sinus tachycardia. Bone age was delayed and assessed as neonatal (Fig. 1). Ultrasound of the thyroid gland revealed no thyroid enlargement and no increased vascular flow pattern on Colour Doppler examination; echogenicity

**Table I.** The result of biochemical analyses performed at Institute of Metabolic Science; Addenbrooke's Hospital; Cambridge  
**Tabela I.** Wyniki analiz biochemicznych przeprowadzonych w Instytucie Nauk Metabolicznych (Addenbrooke's Hospital; Cambridge)

	Proband	Proband's mother
<b>TSH (Delfia)</b>	2.75 [0.40–4.00 mU/L]	1.44 [0.40–4.00 mU/L]
<b>Free T4 (Delfia)</b>	<b>37.3</b> [9.0–20.0 pmol/L]	<b>30.0</b> [9.0–20.0 pmol/L]
<b>Calculated free T4</b>	45.0	29.0
<b>Free T3 (Delfia)</b>	<b>10.9</b> [3.0–7.5 pmol/L]	<b>10.1</b> [3.0–7.5 pmol/L]
<b>Total T4</b>	<b>296.0</b> [69.0–141.0 nmol/L]	<b>241.0</b> [69.0–141.0 nmol/L]
<b>TBG</b>	25.4 [14.0–31.0 ug/ml]	26.7 [14.0–31.0 ug/ml]
<b>TSH (Siemens Centaur)</b>	3.25 [0.35–5.50 mU/L]	1.59 [0.35–5.50 mU/L]
<b>Free T4 (Siemens Centaur)</b>	<b>35.8</b> [10.0–19.8 pmol/L]	<b>26.8</b> [10.0–19.8 pmol/L]
<b>Free T3 (Siemens Centaur)</b>	<b>10.2</b> [4.3–7.6 pmol/L]	<b>9.0</b> [3.5–6.5 pmol/L]

TSH — thyroid-stimulating hormone; T4 — thyroxine; T3 — triiodothyronine; TBG — thyroxine-binding protein



**Figure 1.** Radiograph of the left hand taken at the age of 8 months. Bone maturation was delayed and assessed as neonatal

**Rycina 1.** Badanie RTG lewej ręki przeprowadzone u probanda w wieku 8 miesięcy. Widoczne opóźnione dojrzewanie kości, oceniano je jako noworodkowe

was moderately decreased and heterogeneous. The psychomotor development was assessed as average for the child's age.

The patient's mother also presented abnormal thyroid function. She was born at 41 weeks of gestation with low birth weight (2270 g, < 3<sup>rd</sup> centile) and low length (50 cm, < 3<sup>rd</sup> centile) [13]. Her current weight and height were 50 kg (10<sup>th</sup>–25<sup>th</sup> centile, –1.4 SDS) and 156 cm (3<sup>rd</sup>–10<sup>th</sup> centile, –1.67 SDS), and her BMI was 20.6 kg/m<sup>2</sup>. She had suffered from persistent tachycardia since childhood. Additionally, as a child she exhibited attention deficit, hyperirritability, and learning difficulties. The patient's mother was misdiagnosed for several years. Finally, in adulthood, she was referred to the endocrinologist due to persistent

elevation of serum level of FT3 and FT4 with normal TSH concentration. AntiTg, antiTPO, and TRAb autoantibodies were negative. Her thyroid function panels are reviewed and presented in Table II. Oral administration of metizol (thiamazole) did not lead to normalisation of THs or clinical improvement. Anti-thyroid drug therapy was continued during pregnancy. Additionally, she was also treated empirically with a beta-blocker. Ultrasonography of her thyroid showed the gland to be of normal volume with a single nodule in the left lobe (colloid nodule diagnosed in fine needle biopsy). The pituitary MRI was normal, and no adenoma was found. After exclusion of the possibility of TSH-producing pituitary adenoma, the diagnosis of RTH $\beta$  was highly suspected. However, no genetic test was performed at this time. It is noteworthy that also the proband's grandmother had a medical history of thyroidectomy due to goitre in the course of hyperthyroidism. The genetic tests were performed in the proband and his mother. Fluorescent sequencing analysis detected a heterozygous base change, c.728G>A, in exon 7 of *THRB* gene in the child as well as in his mother. This pathogenic variant is predicted to result in abnormal TR $\beta$  protein (p.Arg243Gln) and has been previously associated with RTH $\beta$  [14].

Normalisation of the patient's heart rate and blood pressure were initially obtained by the administration of the  $\beta$ -blocker (propranolol, 2.5 mg twice a day). For the last two years the boy has remained under the care of an endocrine outpatient clinic. During this time his THs concentration stayed elevated with non-suppressed TSH level (Tab. III). Ultrasound of the thyroid gland showed a minor enlargement of the thyroid. The main clinical problem was persistent (mild) tachycardia (100–120 bpm on average), hyperactivity, and failure to thrive. His current weight, at the age of three years and six months, is 9.9 kg (< 3<sup>rd</sup> centile, –4.07 SDS) and his height is 89.7 (< 3<sup>rd</sup> centile, –2.88 SDS) [13] (Fig. 2, 3). Additionally, the bone age,

**Table II.** Thyroid function panel of proband's mother from 2012 to 2015

**Table II.** Wyniki badań czynności tarczycy matki probanda w latach 2012–2015

	Reference value	05/2012	07/2013	01/2014	02/2014	06/2014	09/2014	10/2014	11/2014	12/2014	02/2015
<b>TSH [mU/L]</b>	0.270–4.200	2.200	2.620	1.730	1.540	1.340	1.680	2.88	2.01	1.730	2.240
<b>FT4 [pmol/L]</b>	12.00–22.00	41.33	30.98	40.36	35.48	36.19	36.29	32.56	28.57	23.33	22.98
<b>FT3 [pmol/L]</b>	3.10–6.80	10.88	9.82	10.62	8.87	7.62	10.4	12.78	10.86	9.24	9.16
<b>Dose of tiamazol [mg/d]</b>		–	10	–	–	–	–	–	5	2.5	2.5

TSH — thyroid-stimulating hormone; FT4 — free thyroxine; FT3 — free triiodothyronine

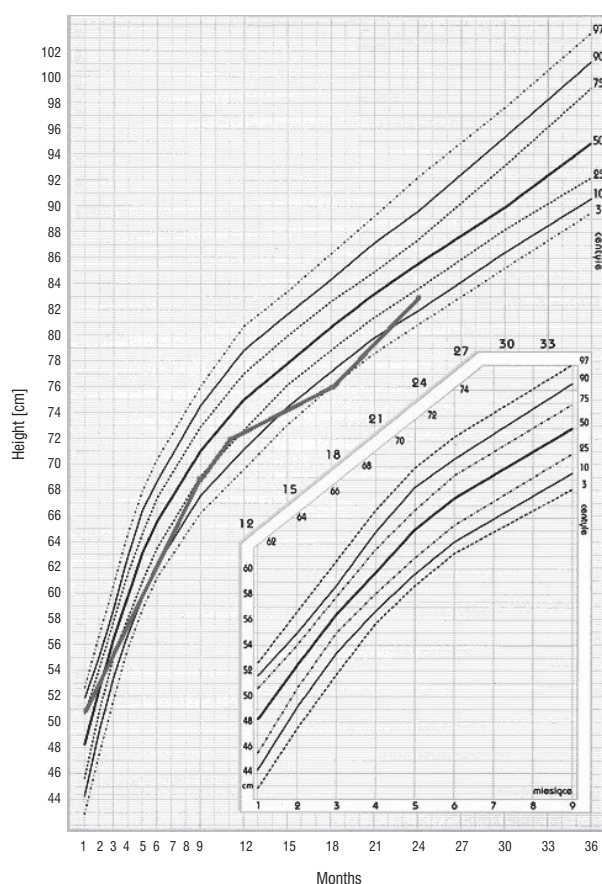


Table III. Thyroid function panel of proband from 2016 to 2017

Table II. Wyniki badań czynności tarczycy probanda w latach 2016–2017

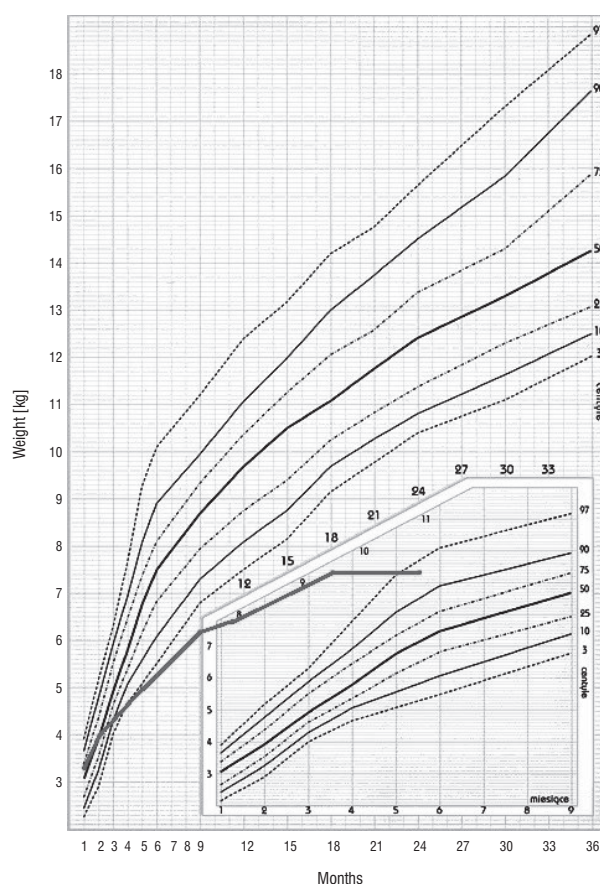
	Reference value	05/2016	01/2016	08/2017	09/2018
TSH [uIU/mL]	0.700–5.970	4.060	2.320	3.63	3.02
FT4 [ng/dL]	0.65–2.3	2.74	3.51	2.75	3.00
FT3 [pg/mL]	2.41–5.50	7.29	8.21		9.68

TSH — thyroid-stimulating hormone; FT4 — free thyroxine; FT3 — free triiodothyronine

**Figure 2.** The growth curve of the proband according to the height growth chart by Palczewska and Niedźwiecka for boys born between 32 and 37 Hbd

**Rycina 2.** Krzywa wzrostu probanda zgodnie z siatką centylową Palczewskiej i Niedźwieckiej dla chłopców urodzonych między 32. i 37. tygodniem ciąży

assessed according to the Greulich and Pyle method, was significantly delayed and asynchronous (wrist bone age and metacarpal bone age: three month, phalanges bone age: one year and six months – two years) (Fig. 4). Treatment with a  $\beta$ -blocker was stopped due to poor drug tolerability (anxiety, nightmares). No anti-thyroid drug treatment was introduced. Due to the relatively mild presentation of the disease, absence of severe tachycardia, stabilisation in growth, and normal development of the child, more aggressive treatment has not been needed so far.

**Figure 3.** The weight curve of the proband according to the weight growth chart by Palczewska and Niedźwiecka for boys born between 32 and 37 Hbd

**Figure 3.** Krzywa masy ciała probanda zgodnie z siatką centylową Palczewskiej i Niedźwieckiej dla chłopców urodzonych między 32. i 37. tygodniem ciąży

## Discussion

Resistance to thyroid hormone is a rare genetic disorder with an autosomal dominant or recessive model of inheritance, characterised by various clinical presentations even within the families with the same mutation [1, 2]. The first case of RTH syndrome was reported by Refetoff et al. in 1967.

The thyroid hormone receptor belongs to the nuclear receptor superfamily and has four functional domains: transcription activation domain, DNA-bind-



**Figure 4.** Radiograph of the left hand taken at the age of 3 years and 6 months. Bone maturation was delayed and asynchronous (wrist bone age and metacarpal bone age: 3 months, phalanges bone age: 1 year and 6 months – 2 years)

**Rycina 4.** Badanie RTG lewej ręki przeprowadzone u probanda w wieku 3 lat i 6 miesięcy. Widoczne opóźnione i niesynchroniczne dojrzewanie kości (kość nadgarstka i kość śródręcza: wiek oceniono na 3 miesiące, paliczki palców: wiek oceniono na 1,5–2 lata)

ing domain, hinge region, and ligand binding domain. Each of the thyroid hormone receptors ( $TR\alpha$ ,  $TR\beta$ ) has two different isoforms. Only  $TR\alpha1$ ,  $TR\beta1$ , and  $TR\beta2$  are able to bind THs. The receptors have specific organ distribution.  $TR\alpha1$  is widely expressed, especially in cardiac and skeletal muscles, gastrointestinal tract, and central nervous system (CNS).  $TR\beta1$  is mainly expressed in brain, liver, and kidney;  $TR\beta2$  expression is primarily limited to the hypothalamus and pituitary [4].  $TR\alpha2$  is also widely expressed but unable to bind hormones; its function is not fully understood.

Approximately 85% of individuals with RTH $\beta$  have a *THRB* mutation [2, 5]. Approximately 170 different mutations of the *THRB* gene have been described. Most of the mutations are single-nucleotide substitutions [5, 15]. The majority of them are located in three hotspot regions between exon 7 and 10 [16]. Mutations may result in reduced or absent T3 binding to the mutant receptor; some mutant  $TR\beta$  have an abnormal interaction with coactivators and corepressors involved in mediating TH action via the receptor. Additionally, mutant receptors are characterised by dominant negative activity and are capable of interfering with the function of the wild-type receptor [16]. The mutation identified in our proband and his mother was first described by Onigata et al. in 1995. This single nucleotide substitution, guanine

for adenine, was identified at the second position of 243 codon located in the hinge domain between the ligand binding and DNA binding domains, resulting in the substitution of arginine with glutamine. This leads to reduced ligand affinity but also to inhibition of wild-type  $TR\beta$  action in a dominant negative manner. Reversal of the inhibition is possible with the higher T3 concentration [14].

The clinical presentation of RTH $\beta$  is variable, from completely asymptomatic to hyper- or hypothyroid signs and symptoms or a combination of them [9]. The variability seen in the clinical presentation could be explained by different tissue distribution of TR isoforms, individual tolerance to elevated THs levels, or varying mutant TR tissue expression [17]. The RTH syndrome has been classified into generalised (GRTH) or pituitary (PRTH) [2,8]. Approximately 80% of cases belong to GRTH type. The majority of patients with GRTH are clinically euthyroid. Patients with PRTH exhibit symptoms of tissue-specific mild to moderate hyperthyroidism. However, in some cases, differentiating selective PRTH from GRTH may be difficult. [2, 9].

Early goitre development is one of the most common clinical findings, and it is observed in 66–95% of RTH $\beta$  patients. Enlargement of the thyroid is related to the continuously high level of TSH that stimulates the thyroid to overgrow. Some individuals present symptoms of TH insufficiency, such as growth retardation with delayed bone age, intellectual impairment, or hypercholesterolaemia. Recent studies showed that approximately 50% of patients have learning disabilities, such as Attention Deficient Hyperactivity Disorder (ADHD) and lower intellectual quotients. However, mental retardation (IQ < 60) occurs exclusively in 3% of cases. Many individuals manifest signs of TH excess, such as sinus tachycardia (80–90%), advanced bone maturation, or hyperactivity. Some patients may also present combination of symptoms of TH deficiency and excess [9]. It has been observed that the symptoms become milder with age. Patients with homozygous mutations in *THRB* exhibit a more severe phenotype. Other common complaints include recurrent ear infection and sensorineural deafness. The individuals also present dysmorphic features such as bird-like facies with prominent nasal bridge, pigeon chest, or winged scapulae. This severe phenotype is probably due to the dominant negative effect of the mutant protein and the lack of functional  $TR\beta$  [18, 19]. In our patient a combination of hypo- and hyperthyroidism symptoms was observed. He is a carrier of heterozygous mutation in *THRB*, and some symptoms of TH excess are present (tachycardia, hyperactivity, poor weight gain); however, they are not severe. Moreover, some features suggesting hypothyroidism (delayed bone age) were also observed.

The syndrome should be suspected in patients with increased serum TH level accompanied by a normal or elevated TSH concentration. Due to lack of pathognomonic symptoms associated with RTH $\beta$ , the diagnosis of this disorder should be confirmed by the clinical examination, laboratory findings, and gene mutation analysis. Because of variability of the clinical presentation of RTH $\beta$  syndrome, affected patients require individualised management. Avoidance of inappropriate treatment is especially important when managing infants and children.

At present, specific treatments for RTH $\beta$  are not available. The majority of affected patients compensate for tissue resistance by increased endogenous supply of TH and do not require therapy [10]. The administration of TH is reserved for individuals with insufficient tissue hyposensitivity compensation, especially in cases of autoimmune thyroiditis coincidence. The aim of the therapy is to diminish symptoms of hypothyroidism and to reduce serum TSH concentration to a normal level. The optimal dose of exogenous TH is variable and highly individual. Patients with RTH $\beta$  with evidence of hypothyroidism (elevated TSH, symptoms of hypothyroidism, positive anti-TPO antibodies) require the administration of supraphysiological, incremental doses of levothyroxine (LT4). This therapy requires careful monitoring of markers of TH action, such as SHBG, cholesterol profile, basal metabolic rate (if possible), and bone density. Thyroidectomy is been reserved for individuals with pronounced hyperthyroid symptoms and compressive goitre, which cannot be controlled medically [20].

Patients with RTH $\beta$  with symptoms of hyperthyroidism should be treated symptomatically. Administration of  $\beta$ -blockers improves tachycardia and tremor. Treatment with dopaminergic drugs and somatostatin analogues, due to only transient benefits, have limited use. The thyroid hormone analogue triiodothyroacetic acid (TRIAC) is used in cases of individuals with PRTH with selective resistance accompanied by symptoms of hyperthyroidism. However, whether TRIAC has beneficial effects on all markers of TH action is not known [21].

Treatment of affected infants still remains controversial. It is proposed that TH therapy (usually LT4) should be reserved for children with elevated serum TSH levels and developmental failure that cannot be explained by other illness or defect, or family history of growth or mental retardation [10]. Some authors have suggested short-term treatment with methimazole and iodine in hyperthyroid RTH $\beta$  neonates [22]. Interestingly, liothyronine therapy may alleviate the symptoms of ADHD in a significant number of RTH $\beta$  children [23]. In our patient, due to relatively mild

symptoms, we decided against the use of anti-thyroid drugs and used beta-blockers to control tachycardia. Unfortunately, we had to discontinue therapy due to the side effects. The patient is now carefully followed by endocrinology and cardiology, and his thyroid function is regularly checked.

## Conclusion

We describe a case of RTH $\beta$  caused by a common germline mutation located at *THRB* exon 7 hot spot. In our study, both the patient and his mother had elevated FT3, FT4, and non-suppressed TSH concentration. They presented symptoms of hyperthyroidism, such as tachycardia, hyperactivity, and poor weight gain. It can be concluded that despite the rarity and atypical clinical presentation of the RTH $\beta$ , primary care physicians, paediatricians, and endocrinologists should consider this diagnosis when evaluating individuals with hyperthyroxinaemia and non-suppressed TSH levels. The treatment should be individualised, but no therapy is fully effective.

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