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CASE REPORT

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Thyroid hormone resistance syndrome caused by a novel mutation in the thyroid hormone receptor-beta gene (*THRB*, GLU457LYS) treated with methimazole

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Abstract

A 15-year-old girl presented with hyperactivity and behavior disorders. She had tachycardia and no goiter. Thyroid hormones were high and TSH normal. A novel mutation GLU457LYS in *THRB* gene was observed. Methimazole and propranolol improved clinical symptoms but increased TSH level.

KEYWORDS

anti-thyroid drug, hyperthyroidism, *THRB*, GLU457LYS, thyroid hormone receptor gene, thyroid hormone resistance

1 | INTRODUCTION

Thyroid hormone resistance (RTH) is a rare syndrome characterized by reduced tissue sensitivity to thyroid hormones (TH). It is mainly caused by mutations of the β-isoform of the thyroid hormone receptor gene (*THRB*). The partial tissue resistance to TH is compensated by an increase in the production of TH by a non-suppressed thyroid stimulating hormone (TSH).[1,2] The clinical presentation is variable with the possible coexistence of symptoms of cell-specific TH deprivation and excess. The main differential diagnosis is TSH-secreting pituitary adenomas (TSHoma). Anti-thyroid medications have been rarely used to treat thyrotoxic symptoms in reported cases with RTH. We report a patient with RTH caused by a novel *THRB* gene mutation treated with methimazole.

2 | CASE REPORT

A 15-year-old Tunisian girl was investigated for agitation, behavior disorders, and insomnia. Her medical history was unremarkable except for hyperactivity disorder and learning disability since childhood. She dropped out of school 2 years earlier. She was not taking any regular medication. She had a first-degree parental consanguinity. There was no negative family history of thyroid disease, in particular in her parents, her three sisters and two brothers. The results of blood tests indicated inappropriate secretion of TSH; TSH: 2.05 μUI/ml (normal range: 0.12–3.4), high FT3: 11.67 pmol/L (normal range: 2.2–5.34), and high FT4: 28.2 pmoL/L (normal range: 9.0–19.3). Based on these findings, the patient was referred to our department for further investigations and management.

On admission, it was difficult to deal with her as she was restless and had difficulties in concentration and fits of laughter. She seemed to be intellectually normal. She left school because of difficulties in attending classes. Her mother reported polyphagia, weight gain, insomnia, no diarrhea, and no thermophobia. On physical examination, the weight was 48 Kg, the height was 141 cm, body mass index was 24.1 Kg/m^2, there was no dysmorphia, pulse rate was regular, and varied between 92 and 120 beats per minute, blood pressure was 100/60 mmHg, there was no moist skin, no tremor, no thyroid enlargement, no ophthalmopathy, puberty was normal, and she had regular menses since the age of 13 years.

Further examinations showed the persistence of inappropriate secretion of TSH (Table 1). On ultrasound, thyroid had a normal size without any nodule. Thyroid scintigraphy revealed diffuse heterogeneous uptake much higher in the left lobe. Pituitary magnetic resonance imaging (MRI) was performed twice and did not show a pituitary adenoma. The TSH-α subunit concentration was normal. The other pituitary parameters were within normal limits (Table 1). So, a TSH secreting adenoma was ruled out and the diagnosis of RTH was highly suspected. The analysis of the TRHB gene was performed. Genomic DNA was extracted from peripheral blood leucocytes and amplified by polymerase chain reaction. The sequencing of *THRB* gene identified a heterozygous nucleotide substitution (c.1369 G > A) resulting in the substitution of the normal glutamic acid at position 457 in exon 10 with lysine (GLU457LYS). Genetic analysis of her family members was unfortunately not performed.

TABLE 1 Biological parameters of the patient in favor of thyroid hormone resistance

Parameter (unit)	Patient's results	Normal range
Fasting glucose (mmol/L)	5.2	3.88–5.55
Creatinine (μmol/L)	53	53–97
Sodium (mmol/L)	136	136–145
Potassium (mmol/L)	3.9	3.5–5.1
Calcium (mmol/L)	2.4	2.15–2.65
Phosphorus (mmol/L)	1.4	0.74–1.53
Total cholesterol (mmol/L)	5.65	3.2–5.5
Triglycerides (mmol/L)	2.71	0.56–1.92
HDL cholesterol (mmol/L)	1.16	>1.04
ALT (IU/L)	17	<55
AST (IU/L)	13	5–34
γ-GT (IU/L)	20	12–64
Total bilirubin (μmol/L)	10	<20
Alkaline phosphatase (IU/L)	125	<150
FT4 (pmol/L)	27.15	9.0–19.30
TSH (μIU/ml)	2.86	0.12–3.4
TSH α-subunit (IU/L)	0.54	0.05–0.9
Cortisol (nmol/L)	322	110.36–551.8
Prolactin (μg/L)	31	<25
Thyroperoxydase antibody (IU/ml)	Negative	<75
Thyroid receptor antibody (IU/ml)	Negative	<5
Sex hormone binding globulin (nmol/L)	45	14.5–48.8

Further tests were performed to evaluate the degree of RTH and showed normal bone turnover and normal hepatic sensitivity to TH as demonstrated by normal cholesterol and sex hormone binding globulin (SHBG) levels (Table 1). The audiogram could not be performed as the patient was not cooperating.

The patient was treated with methimazole 20 mg per day and propranolol 10 mg three times a day. There was an improvement in hyperactivity, tremor, and tachycardia. Three months later, thyroid tests showed a decrease of FT4 to 21.75 pmol/L and an increase of TSH to 19 μIU/ml. The dose of methimazole was then decreased to 10 mg leading to a re increase of FT4 to 24.9 pmol/L and a decrease of TSH to 11.5 μIU/ml. Anti-thyroid drug was discontinued after 2 years of treatment and propranolol was continued to control heart rate.

3 | DISCUSSION

We reported the case of a 15-year-old girl with RTH due to a novel mutation in the *THRB* gene, c.1369 G > A in exon 10, due to the substitution of glutamic acid with lysine at the position 457. This variant was not reported previously.[1,3–5] The clinical presentation was behavior disorders, hyperactivity, tachycardia, and short stature with no goiter. Clinical symptoms improved with treatment with methimazole.

The prevalence of RTH is about 1 in 40,000–19,000 new-borns.[1] *THRB* gene is located at 3p24.2 (short arm of chromosome 3) and consists of 10 exons. It is identified with the number 190160 according to the "online Mendelian Inheritance in Man".[5] Up to 236 different mutations have been reported.[1] The mutation found in our patient has not been reported to date. The inheritance of *THRB* gene can be either autosomal recessive or dominant.[5] Unfortunately, family genetic testing could not be performed in our case. So, the transmission of the mutation was not studied. This loss of function mutation on *THRB* gene is responsible of RTH.

On a clinical basis, RTH has been classified into three subtypes: generalized, pituitary, and peripheral resistance

to TH.[3] However, the clinical presentation is not correlated to the genetic mutation et varies between patients having the same mutation.[3] Hence, patients may present with the symptoms of both increased and decreased thyroid hormone action, depending on the tissue's predominant receptor isoform expression (alpha or beta) and the degree of hormonal resistance.

The most common clinical signs of RTH are goiter (66%–95%), tachycardia (33%–75%) and different neurological manifestations such as attention deficit, hyperactivity disorder (40%–60%), emotional disturbances (60%), hyperkinetic behavior (33%–68%), and learning disability (30%).[4,6] Recurrent ear infections in childhood and hearing impairment have been reported. The majority of the patients have a normal metabolic state.[6] A goiter can be detected on ultrasound if not clinically obvious. It is a diffuse goiter that is secondary to the stimulating effect of TSH. In our case, RTH is rather pituitary as the patient had clinical signs of hyperthyroidism such as insomnia, tachycardia, hyperkinesia, and emotional disturbances. However, the patient had a short stature that has been related to tissue hypothyroidism signing bone resistance to TH.[7]

The diagnosis of RTH is suspected on clinical findings and laboratory tests and is, when possible, confirmed by genetic studies. After excluding assay errors, by confirming the hormonal data by another measurement in another laboratory, the other condition to be considered in the differential diagnosis of RTH is a TSHoma. As the RTH is familial in 90% of cases, TSHoma may be excluded when other members of the family, and especially the first-degree relatives of the patient, exhibit similar thyroid function abnormalities.[6] One investigation of particular value is serum SHBG, that reflects TH activity. SHBG is often elevated in TSHoma but is invariably normal in RTH. The measurement of the α-subunit may also be useful for the diagnosis. Its level is often elevated in TSHoma due to its co secretion by the adenoma.[2,6] Dynamic tests of the pituitary-thyroid axis can also be helpful. Indeed, TSH increases after TSH-releasing hormone stimulation and is suppressed after T3 administration in patients with RTH, whereas TSH secretion from autonomous tumors is classically unresponsive. Somatostatin suppression test can also be useful showing a decrease of TSH in TSHoma.[6] The normal levels of SHBG and α-subunit as well as normal MRI excluded TSHoma in our patient.

To date, there is no therapy to correct the defect in thyroid hormone receptor function. So, the aim of the treatment is to relieve the symptoms of hypo- or hyperthyroidism. Patients with symptoms of hypothyroidism should be treated with thyroid hormones. Those with symptoms of hyperthyroidism are much more difficult to manage as there is no efficient therapeutic options. Beta-blockers are indicated for tachycardia and tremor. Propranolol that is generally used in hyperthyroidism is actually not the best choice in this pattern as it inhibits the conversion of T4 to T3 and therefore reduces T3-mediated feedback inhibition on TSH.[6] Anxiolytics can be needed for behavioral and attention disorders.[8] The use of anti-thyroid medications is controversial. A low dose of methimazole (10 mg/day) has been used in 37-year-old women with an improvement of her condition 5 months later and a decrease in FT4 with however a small increase in TSH that remained within normal limits.[9] Two other reported cases described two children who were treated with methimazole. They had a good response to treatment with especially an improvement in intelligence quotient scores, verbal skills, hyperactivity, and a weight gain.[7,10] On methimazole, our patient had also an improvement of hyperactivity, tremor, and tachycardia. Treatment with anti-thyroid drug may, however, lead to an enlargement of the thyroid gland associated with compressive symptoms if TSH increases significantly.[11] According to the pathophysiology of RTH, it is suggested that TH levels should not be normalized but rather maintained above or at the upper limit of the normal range depending on symptomatology and other biochemical markers such as SHBG, cholesterol, ferritin, and urinary hydroxyproline, and osteodensitometry.[7]

Other drugs such as liothyronine (LT3), dextrothyroxine, triiodothyroacetic acid (TRIAC), bromocriptine, somatostatin analogues, glucocorticoids, and retinoid-X receptor agonists have been used with success in some patients.[6,8] Overall, no efficient treatment has been found. It is, however, to emphasize that invasive treatment such as thyroidectomy or radioactive iodine ablation are not indicated.[12]

4 | CONCLUSION

We have reported the case of a Tunisian 15-year-old girl with RTH syndrome related to a novel mutation GLU457LYS of the *THRB* gene. The management of RTH is challenging. Methimazole was clinically efficient in our patient but increased TSH level.

AUTHOR CONTRIBUTIONS

Imen Rezgani and Melika Chihaoui performed the acquisition and interpretation of data, and the conception and design of the manuscript. Ibtissem Oueslati, Fatma Chaker, Sonia Nagi, and Meriem Yazidi were involved in the management of this patient and the revision of the manuscript and approved the final version. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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CONFLICT OF INTEREST

There is no conflict of interest.

DATA AVAILABILITY STATEMENT

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

ETHICAL APPROVAL

The legal representative of the patient gave the consent for the publication of the data.

CONSENT

Written informed consent was obtained from the patient's parents to publish this report in accordance with the journal's patient consent policy.

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