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Case Report

Thyroid Hormone Resistance Syndrome in an Adolescent Girl: A Case Report

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Abstract

Introduction: Resistance to Thyroid Hormones (RTH) is a rare, hereditary disease characterized by diminished sensitivity of target tissues to thyroid hormones. Most cases (~85%) are caused by mutations in the thyroid hormone receptor beta (*THR*β) gene (RTHβ). The clinical spectrum of RTHβ is quite broad and highly heterogeneous, and the hallmark of the condition is a paucity of signs and symptoms of thyroid dysfunction despite elevated levels of T4 and T3, with a concomitant non-suppressed TSH.

Case Report: Here, we describe a rare case of RTHβ in a female adolescent who was initially misdiagnosed and treated for Graves' disease, but whose unusual evolution motivated her transference to a tertiary center.

The patient exhibited mild manifestations, presenting with a goiter without compressive symptoms and some degree of cognitive impairment with learning disability. Misdiagnosis of RTHβ as Graves' disease can lead to unnecessary treatments such as antithyroid medication, thyroidectomy or radioiodine, but treatment is generally not necessary for most patients with RTHβ.

Discussion and Conclusion: Establishing the diagnosis of RTHβ can be challenging. It must be considered in patients who present with a goiter and increased thyroid hormone levels with an unsuppressed TSH, to potentially avoid an incorrect diagnosis of primary hyperthyroidism and the implementation of unnecessary and harmful treatments. Most patients with RTHβ are asymptomatic, and in children, particular attention must be paid to growth, bone maturation, and mental development.

Keywords: Resistance to thyroid hormones syndrome; Hyperthyroidism; Thyroid hormones; *THR*β

Abbreviations: MRI: Magnetic Resonance Imaging; RR: Reference Range; RTHβ: Thyroid hormone receptor beta (*THR*β) gene; T3: Triiodothyronine; T4: Thyroxine; THR: Thyroid Hormone Receptor; THRα: Thyroid Hormone receptor alfa; THRβ: Thyroid hormone receptor beta; TSH: Thyroid-stimulating hormone

Introduction

Resistance to Thyroid Hormones (RTH) is a rare, hereditary disease characterized by reduced sensitivity of target tissues to thyroid hormones [1-4]. The pattern of inheritance is usually autosomal dominant, and its incidence is equal in both sexes. Most cases (~85%) are caused by mutations in the thyroid hormone receptor beta (*THR*β) gene (RTHβ) [2,5-8]. In ~10% of cases, no mutations are detected, but the phenotype is indistinguishable from RTHβ. The remaining cases are attributed to mutations in the THR alpha gene or in genes related to the cell membrane transport or metabolism of thyroid hormones [2,3,6,8-11].

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Patients with RTHβ present increased levels of circulating thyroxine (T4) and triiodothyronine (T3) without Thyroid-Stimulating Hormone (TSH) suppression [2-4]. Most patients maintain a nearly euthyroid state, but some individuals may present with symptoms of hyperthyroidism, hypothyroidism, and/or non-toxic goiter [3,8,9]. This phenotypic variability makes the diagnosis of RTHβ challenging.

We present the case of a female adolescent with RTHβ, who was initially misdiagnosed with Graves' disease.

Case Report

A 14-years-old female adolescent was admitted to the emergency department with superior respiratory symptoms lasting for five days and a visible goiter. She had no relevant prenatal or neonatal history and had a normal growth pattern for weight and height. However, the patient had previously been referred to Neuropediatrics at the age of 7 due to learning disability, as demonstrated by a low average Intelligence Quotient at the age of 10. Brain Magnetic Resonance Imaging (MRI) scan, electroencephalogram, and array comparative genomic hybridization testing were normal. Upon examination, an enlarged and mildly painful thyroid gland was observed. Thyroid function tests showed TSH levels of 0.905 uUI/mL [Reference Range (RR): 0.450-4.500 uUI/mL] and free T4 levels of 2.40 ng/dL (RR: 0.82-1.77 ng/dL). Ultrasound showed an enlarged thyroid with a homogeneous echotexture and uniformly echogenic relative to the strap muscles, without visible nodules.

The patient was referred to the Pediatric Endocrinology department of her local hospital. During follow-up, successive thyroid function tests showed persistent alterations, with TSH levels ranging from 0.93 to 1.485 uUI/mL, free T4 ranging from 2.17 to 2.8 ng/dL, and free T3 levels from 6.75 to 7.8 pg/mL (RR: 2.31-3.71 pg/mL). Anti-thyroglobulin, anti-peroxidase and anti-TSH-receptor antibodies, as well as erythrocyte sedimentation rate, were negative. A pelvic ultrasound showed no abnormal findings. No drug therapy was initiated.

One year later, the patient maintained elevated free T4 and T3 levels (2.8 ng/dL and 7.43 pg/mL, respectively) and normal TSH (0.948 uUI/mL). A diagnosis of Graves' disease was assumed and she was started on methimazole 0.2mg/kg/day (5mg twice daily), which was increased to 0.3mg/kg/day (7.5mg twice daily) one month later. Six months later, she had TSH levels of 16.48 uUI/mL, free T4 of 1.58 ng/dL, and free T3 of 5.58 pg/mL. Anti-TSH-receptor antibodies remained negative. Thyroid ultrasound was repeated showing no changes. Methimazole was reduced to 2.5mg daily, and TSH levels normalized (1.948 uUI/mL) while free T4 and T3 levels increased (2.31 ng/dL and 5.98 pg/mL, respectively). A Tc-99m pertechnetate thyroid scintigraphy revealed a markedly enlarged thyroid gland with an increased and homogeneous uptake of the radioisotope (34.7%, RR: 1-3.5%), consistent with diffuse toxic goiter (Graves' Disease). During follow-up, the goiter persisted, and the patient remained asymptomatic. Ophthalmology examination was unremarkable.

Due to doubts regarding the diagnosis, the patient was referred to the Pediatric Endocrinology Consultation of our reference center. At her first appointment (at 16 years and 5 months old), the diagnosis of Graves' disease was questioned and methimazole was discontinued. Two months later, a differential diagnosis including TSH-producing pituitary tumor (TSHomas) or RTHβ was considered. Pituitary function profile was within the normal range, and analysis of the THRβ gene by polymerase chain reaction amplification of peripheral blood DNA revealed a missense variant c.Gly344Arg, in heterozygosity, likely pathogenic, with autosomal dominant transmission, consistent with a diagnosis of RTHβ. The patient is now attending adult Endocrinology consultations for further clinical monitoring. At the last follow-up, at 18-years-old, the patient was in the 22nd percentile (z-score -0.78) for final stature, had regular menstrual cycles, and remained asymptomatic, with a stable goiter and without medication.

Discussion

We describe a rare case of RTHβ in a female adolescent initially misdiagnosed and treated as having Graves' disease due to elevated thyroid hormone levels.

RTHβ has an incidence of 1 in 19.000 to 1 in 40.000 live births. Approximately 170 mutations among 805 unrelated families have been identified [2,12,13]. Gene sequencing in our patient revealed a heterozygous point mutation in the THRβ gene (c. 1030G>A p.Gly344Arg). Although described as "likely pathogenic", considering our patient's clinical and laboratory features and the fact that this mutation had been previously described as pathogenic by Yang et al., we consider it can be called as a pathogenic variant [14]. Familial occurrence of RTH has been documented in ~75% of cases and could further support the role of this variant as pathogenic [8]. However, at the last follow-up, only the mother had undergone thyroid function tests that were normal, so we cannot confirm if this genetic variant is *de novo* or inherited.

The severity of hormonal resistance varies among different tissues within the same individual. This variation is likely due to distinct relative expression of THRβ and THRα in different target tissues. Consequently, manifestations of hypothyroidism and hyperthyroidism can coexist in the same individual, including sinus tachycardia, hyperkinetic behavior, attention deficit hyperactivity disorder, learning disabilities, mental retardation, hearing loss, short stature, delayed bone age, and recurrent ear and throat infections [2-3,8]. There is also distinct impaired sensitivity between patients with the same gene mutation, even within the same family. This discrepancy is not fully understood but may be partially explained by interindividual differences in the setpoint of the hypothalamic-pituitary-thyroid axis, which is also observed in healthy individuals [11,16,17].

Most patients with RTHβ maintain a nearly euthyroid state, as increased secretion of thyroid hormones may partially compensate for the thyroid hormone resistance. This was the case for our patient, who exhibited mild manifestations such as a goiter without compressive symptoms and mild cognitive impairment with learning disability. In fact, the hallmark of RTHβ is a paucity of signs and symptoms of thyroid dysfunction despite the increased levels of thyroid hormones [2-4]. Goiter is common, occurring in 66-95% of cases. In our case, it was the goiter that motivated an evaluation of thyroid function [2,3,16]. These findings can frequently result in an erroneous diagnosis of Graves' disease, as in our patient. Non-suppressed TSH levels with elevated thyroid hormone levels should raise suspicion for central hyperthyroidism and contest a diagnosis of Graves' disease. The main differential diagnoses to be considered are the TSHomas. Differentiating RTHβ from TSHomas may be difficult, but, in general, patients with TSHomas are more symptomatic. Measurement of the alpha glycoprotein subunit of the TSH (α-GSU/TSH), a T3 suppression test, and a TRH stimulation test can help differentiate these two entities [2-4]. We believe

that the diagnostic procedures performed were sufficient to establish a diagnosis of RTHβ, as the patient showed no evident symptoms of hyperthyroidism, the MRI was normal, and a mutation in the THRβ gene was detected [4,6,7]. Up to 10% of RTHβ cases do not have a genetic mutation, and genetic testing may not be widely available at all healthcare centers. Elevated thyroid hormone levels in conjunction with non-suppressed TSH, with exclusion of TSHomas, is sufficient to establish the diagnosis of RTHβ.

Prompt diagnosis of RTHβ is important because its management differs from central or primary hyperthyroidism. There is no medication to correct the THRβ defect, so treatment should be tailored to address symptoms of hypothyroidism or hyperthyroidism. However, treatment is unnecessary for most patients, as the majority are asymptomatic. In children, particular attention must be paid to growth, bone maturation and mental development [1-4,8]. Misdiagnosis as Graves'disease can lead to unnecessary treatments with anti-thyroid medication, thyroidectomy or radioiodine I-131. According to Amor et al. [18], approximately 20% of patients with TRHβ had undergone some form of thyroidal ablative therapy before correct diagnosis. Our patient was referred to our center due to an unusual clinical course of a supposed Graves' disease. If a patient has no manifestations consistent with thyrotoxicosis, they should not be treated with antithyroid medications, as this can reduce available thyroid hormones, worsen symptoms, compromise growth, and increase goiter size [2-4,19]. However, beta-adrenergic blockers may be used to relieve tachycardia; thyroid hormone or thyroid hormone analogues can be prescribed to treat hypothyroidism; and supra-physiological doses of liothyronine are effective in reducing goiter without side effects [4,19,20]. Determining the optimal thyroid hormone dose and the target TSH level can be challenging, as these cases are rare [2-4,21]. Lifelong follow-up is necessary, with a focus on goiter size and symptoms.

Conclusion

Our case highlights the challenge of diagnosing RTHβ. This diagnosis should be considered in patients with goiter and increased thyroid hormone levels with an unsuppressed TSH to avoid misdiagnosis as primary hyperthyroidism. This can prevent unnecessary and potentially harmful treatments, such as anti-thyroid drugs or ablative therapies. Additionally, treatment should be personalized to control symptoms rather than normalizing elevated thyroid hormone levels.

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