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Coexistence of Autoimmune Hyper- and Hypothyroidism in a Kindred with Reduced Sensitivity to Thyroid Hormone

Yasmine Abdellaoui[a] Dimitra Magkou[b] Sofia Bakopoulou[b] Ramona Zaharia[b] Marie-Laure Raffin-Sanson[b, c] Laure Cazabat[b, c]

[a]Department of Internal Medicine, Foch Hospital, Suresnes, France; [b]Department of Endocrinology and Nutrition, Ambroise Paré Universitary Hospital, Assistance Publique Hôpitaux de Paris, Boulogne, France; [c]EA 4340, Université Versailles Saint Quentin en Yvelines, UFR Simone Veil Santé, Montigny le Bretonneux, France

What Is Known about This Topic?

- Both Graves' disease and autoimmune hypothyroidism were described in patients with resistance to thyroid hormone beta (RTHβ).
- Undiagnosed RTHβ can lead to misdiagnosis of Graves' disease. The coexistence of these two diseases presents a diagnostic challenge.

What Does This Case Report Add?

- Autoimmune hypo- and hyperthyroidism may coexist in kindred with RTHβ.
- A rapid increase of suppressed thyroid-stimulating hormone contrasting with persistently elevated thyroid hormones during medical treatment of Graves' disease may indicate RTHβ.

Keywords
Reduced sensitivity to thyroid hormone · Resistance to thyroid hormone beta · Autoimmune thyroid disease · Graves' disease

Abstract
Introduction: Resistance to thyroid hormone beta (RTHβ) is a rare disease with an autosomal dominant transmission. Diagnosis may be challenging especially in patients with hyper- or hypothyroidism. ***Case Presentation:*** A 31-year-old male patient with suppressed thyroid-stimulating hormone (TSH), elevated free thyroxine and free triiodothyronine, along with high thyroid receptor antibodies was diagnosed with Graves' disease. Benzylthiouracil was started. One month later, reduced sensitivity to thyroid hormones was suspected because of persistently high thyroid hormone levels contrasting with high TSH level. Molecular analysis highlighted a 10c.1357C>T p.P453S mutation in the thyroid hormone receptor beta gene (*THRB*). RTHβ was diagnosed. Several relatives also had RTHβ (the mother, the young son, and 2 out of 3 siblings). Autoimmune hypothyroidism was present in the mother, whereas 2 out of 3 siblings had asymp-

Y. Abdellaoui and D. Magkou contributed equally to this study.

karger@karger.com
www.karger.com/etj

Marie-Laure Raffin-Sanson
Endocrinology and Nutrition, Université Versailles Saint Quentin en Yvelines
Ambroise Paré Hospital, 9 Avenue Charles de Gaulle
FR–92100 Boulogne (France)
marie-laure.raffin-sanson@aphp.fr

tomatic autoimmunity. ***Discussion/Conclusion:*** Both Graves' disease and autoimmune hypothyroidism were described in patients with RTHβ. We show here for the first time that autoimmune hypo- and hyperthyroidism may coexist in kindred with RTHβ. Seven previously published cases of Graves' disease and RTHβ were retrieved and analyzed. Treatments and thyroid hormone level targets are discussed as well as the possible link between RTHβ and autoimmune thyroid diseases.

Introduction

Reduced sensitivity to thyroid hormone (TH) [1] is a rare disease with a prevalence of 1/40,000 [2]. It is defined by high levels of free thyroxine (FT4) and free triiodothyronine (FT3) with a normal (but inappropriately elevated) level of thyroid-stimulating hormone (TSH) and encompasses all defects that can interfere with the biological activity of a chemically intact TH [1]. The majority of these patients carry a mutation in the β isoform of the thyroid hormone receptor gene (*THRB*), which has an autosomal dominant transmission, a situation defined in the new nomenclature as resistance to thyroid hormone type beta (RTHβ) [1]. Goiter, tachycardia, and nervousness are the most common symptoms. The severity of the disease varies among families with *THRB* mutations [3]. No clear correlation of phenotype with genotype has been found [4]. Autoimmune thyroid diseases (AITD) are relatively common in the general population, frequently showing a familial aggregation. Autoimmune hypothyroidism has been described in families with RTHβ [5]. Graves' disease (GD) has also been described as isolated cases but no familial aggregation has been reported [6]. We describe herein a family with RTHβ and AITD manifesting as both hyper- and hypothyroidism.

Case Report/Case Presentation

A 31-year-old male truck driver presented at the emergency room due to palpitations. Eight years previously, he had undergone radiofrequency ablation of a left septal pre-excitation pathway. He was 180 cm tall and weighed 80 kg. Atrial fibrillation (AF) was diagnosed as well as a small goiter without any orbital sign. He received an anti-arrhythmic, a β-blocker, and anticoagulant treatment. The etiological assessment of atrial fibrillation revealed hyperthyroidism related to GD, with nearly suppressed TSH, elevated FT4 and FT3, along with high thyroid receptor antibodies (TRAb) (Table 1). Thyroid ultrasound revealed a vascular goiter with micronodular dystrophy, and technetium 99m scintigraphy showed a diffuse hyperfixation. Benzylthiouracil (BTU) treatment was started at 200 mg/day. Only 4 weeks later, TSH had normalized, while FT4 and FT3 levels remained elevated (Table 1). Four months later, THs were still supranormal, contrasting with an abnormally high TSH level (Table 1). An assay artifact was dismissed as T4 and T3 antibodies were negative and because repeating the assays using different kits produced the same results. Markers of

Table 1. Evolution of thyroid tests of the index case during and after treatment

	TSH, mIU/L (N: 0.27–4.2)	FT4, pmol/L (N: 12–22)	FT3, pmol/L (N: 3.1–6.8)	TRAb, IU/L (N: <1.8)	Treatment decision: BTU, mg
Diagnosis	0.04	54.0	22	8.8	200
1 month	3.4	30.6	8.5		200
2 months	2.29	48.4	9.7	3.52	150
3 months	2.41	31.1	7.3	2.2	150
7 months	4.5	29.9	8.4	0.8	150
16 months	2.5	41.7	6.1	0.75	150
20 months	1.8	43.6	9.1	0.65	100
22 months	1.48	33.5	8		75
2 years	1.16	42.4	5.5	<1	50
30 months	1.59	36.5	10.7		25
32 months	1.35	31.8	8.6		Stop
3 years	0.97	29.6	6.4	<1	0
4 years	0.99	36.6	9.7		0
5 years	<0.01	103	38	11	NMZ 60 mg

TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine; TRAb, thyroid receptor antibody; BTU, benzylthiouracil; NMZ, neomercazole.

TH sensitivity in target tissues (osteocalcin, ferritin, converting enzyme, SHBG, cholesterol) were all normal. Reduced sensitivity to THs was therefore suspected.

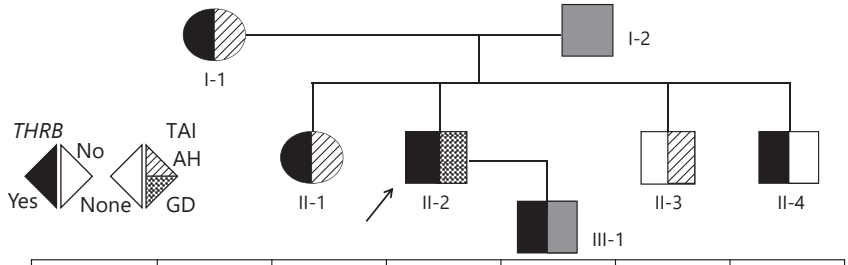
The patient reported that several relatives had abnormal thyroid tests and the diagnosis of RTHβ was confirmed by molecular analysis, which highlighted a 10c.1357C>T p.P453S mutation in the *THRB* gene. The patient's familial history was retrieved. Past medical history, TH levels, and genetic sequencing of *THRB* in the mother and siblings are shown in Figure 1. The P453S *THRB* mutation was present in the mother (I-1), the youngest brother (II-4), and the son (III-1), but not in a second brother II-3 (Fig. 1). The elder sister (II-1) had a typical RTHβ hormonal profile and was positive for thyroperoxidase (TPO) antibodies. She reported hyperthyroidism at age 14 with "eye swelling," treated over 3 years with BTU. No biochemical data from that period was available. She refused genetic testing. Autoimmunity was also found in the brother (II-3), who had a normal *THRB* sequence. The youngest brother (II-4) was diagnosed with RTHβ without thyroid autoimmunity.

The patient's mother (I-1) had been diagnosed with autoimmune hypothyroidism at 40 years of age. At the time of diagnosis, TSH was measured at 11.4 mIU/L (0.35–4.9), anti-TPO and antithyroglobulin antibodies were both positive. A thyroid ultrasound emphasized thyroiditis. Under levothyroxine (LT4) at 100 then 150 μg/day, her TSH remained high, between 8.95 and 12 mIU/L, while her FT4 level increased to 33 pmol/L (9–19) and T3 to 6.15 pmol/L (2.6–5.53). A TRAb test was negative. LT4 was discontinued by the patient 1 year later because of poor clinical tolerance. At the time of genetic testing, in the absence of treatment, TSH had reached 39 mIU/L, FT4 was normal, and FT3 levels were slightly elevated (Fig. 1).

In the absence of prior data for TH values in the propositus, the therapeutic objective was to achieve levels of FT3 and FT4 that were close to those of the youngest brother (II-4), that is, FT4 between 30 and 40 pmol/L and FT3 between 7 and 12 pmol/L. Tests for TRAb became negative after 6 months. BTU was stopped after two and a half years (Table 1). Arrhythmia persisted despite external electric shock and a second radiofrequency ablation. The patient remained in remission for more than 2 years and then presented with a clinical relapse of GD with orbitopathy, confirmed by suppressed TSH and very high TH and TRAb levels. Treatment was resumed, with the same therapeutic targets. With regard to the mother, it was decided, after informing the patient in detail, to reintroduce LT4 treatment at very progressive doses, aimed at maintaining TSH levels slightly above the normal range (5–10 mmol/L) and FT4 between 25 and 30 pmol/L.

Discussion

The association of RTHβ and GD is rare and difficult to diagnose. At presentation, the index patient had typical hyperthyroidism due to GD with suppressed TSH, as expected in the presence of high TH levels, confirming that TSH secretion remains suppressible in RTHβ if exposed to sufficient TH. The usual evolution of thyroid tests under medical treatment of GD consists in prior normalization of THs, whereas TSH usually remains low for a few weeks or months. In the present case, normal TSH before



Age, years	58	37*	31	3	26	13
FT4, pmol/L	17 (N: 12–22)	**32.2** (N: 8–15)	**54** (N: 12–22)	**43** (N: 10–17.6)	16.6 (N: 12–22)	**29.6** (N: 10–18)
FT3, pmol/L	**8.27** (N: 3.8–7.2)	**5.03** (N: 2–4.9)	**22** (N: 3–6.8)	**10** (N: 3–6.8)	5.4 (N: 3–6.8)	**12.98** (N: 4.7–7.2)
TSH, mU/L (N: 0.27–4.2)	**39**	2.22	**0.04**	1.68	4.6	**4.34**
TPO Ab	+	+	–	nd	+	–
TG Ab	+	+	–	nd	–	–
TRAb	–	–	+	nd	–	–
Thyroid size	normal	increased	increased	nd	nd	nd
THRB	P453S/wt	nd	P453S/wt	P453S/wt	wt/wt	P453S/wt

Fig. 1. Pedigree of the family and results of thyroid function tests. The arrow indicates the index case. Thyroid function test results are presented under each symbol representing a family member. Abnormal values are in bold. Symbols filled in black on the left indicate subjects with thyroid hormone resistance beta. Symbols filled in white on the left indicate subjects with no thyroid hormone resistance. Symbols hatched on the right indicate subjects with autoimmune hypothyroidism (AH). Symbols checkered on the right indicate subjects with Graves' disease (GD). Symbols filled in white on the right indicate subjects with no thyroid autoimmunity (TAI). Symbols filled in gray indicate the individual was not tested for thyroid function. *THRB*, thyroid hormone receptor beta; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyrotropin; TG, thyroglobulin; TPO, thyroperoxidase; Ab, autoantibodies; TRAb, TSH receptor antibodies; wt, wild-type sequence; N, normal range; nd, not done. * II-1 was tested at 37 years of age, after resolution of a possible GD treated between 14 and 16 years of age.

Table 2. Published cases with Graves' disease and thyroid hormone resistance beta

	Gender	Age at diagnosis	Medical treatment duration	Radical treatment	Relapse	*THRB* mutation	TRAb	Status at last evaluation
Sato, 2010 [9]	F	34	22 months	No	No	*THRB* (P453T)	TRAb 78% (N: <10) TPO Ab +	Remission
Sivakumar, 2010 [13]	M	53	No	Radio-iodine	No	*THRB* (G347W)	TSI 143% (N: <130)	Hypothyroidism under levothyroxine
Ogawa, 2011 [10]	M	17	12 months	No	No	*THRB* (A234T)	TRAb >30 IU/L (N: <1)	Under medical treatment
Shiwa, 2011 [11]	F	33	3 years	No	No	*THRB* (G251R)	TRAb 80.7% (N: <10)	Remission
González Cabrera, 2012 [7]	F	39	6 months (stopped due to abnormal liver tests)	Radio-iodine	No	*THRB* (P453S)	TRAb: 21 IU/L (N: <1.5) TPO+	Hypothyroidism under levothyroxine
Ramos-Leví, 2016 [8]	F	46	1 year	Radio-iodine	No	*THRB* (P453R)	TRAb: negative TPO +	Hypothyroidism under levothyroxine
Sun, 2017 [12]	F	11	7 years	No	No	*THRB* (C95T)	TRAb >40 IU/L (N: <1.5) TPO Ab +	Remission
Current case (II-2)	M	31	2.5 years Stop 2.5 years and resume	No	Yes	*THRB* (P453S)	TRAb: 8.8 (N: <1.8)	Under medical treatment by ATD

NA, not available; ATD, antithyroid drug; *THRB*, thyroid hormone receptor beta gene; TRAb, TSH autoantibodies; TPO Ab, anti-thyroid peroxidase autoantibodies.

complete FT4 and FT3 control prompted the endocrinologist to search for an assay artefact, then for RTHβ. Treatment of GD in the context of RTHβ is difficult. At present, the optimal therapy is unknown. Medical treatment with antithyroid drugs is the first choice, but determining the therapeutic target range for TH may be difficult when the level of TH before the onset of GD is unknown, as was the case in this patient. Attempts to normalize TH level with antithyroid drugs would likely lead to hormonal failure in peripheral hormone-resistant tissues. It was thus decided to take the FT3 and FT4 levels of his younger brother, with RTHβ and no thyroid autoimmunity, as a reference and target. Although the same mutation may lead to slightly different thyroid profiles within the same family, this approximation has proven helpful for the patient who has reported clinical wellbeing. Radioiodine therapy or surgery are not usually used as a first therapeutic choice for GD in RTHβ patients, since they lead to hypothyroidism, while appropriate hormone replacement therapy is also difficult to achieve in these patients. The patient's mother, with RTHβ and autoimmune thyroiditis, illustrates this difficulty. Although true hypothyroidism is very likely because of the significant elevation of TSH, substitution was not tolerated, probably because of the use of an excessive dose of TH in an attempt to normalize TSH. RTHβ diagnosis in this patient led to prescription of lower L-thyroxin substitution and an adapted TSH target.

Seven cases of GD in patients with RTHβ have been published to date, and data from these reports are summarized in Table 2. In three cases, GD was diagnosed in patients with known RTHβ [7–9]. In 4 cases, RTHβ was discovered after several years of medical treatment for GD [10–12] or because of the difficulty in equilibrating medical treatment of iatrogenic hypothyroidism after radioiodine treatment [13]. This is the first time, to our knowledge, that RTHβ was suspected soon after initiating the medical treatment of GD. Among the seven patients with GD in a context of RTHβ, three received radical treatment with radioiodine, all resulting in hypothyroidism, whereas 4 obtained remission with medical treatment only. Patients with RTHβ and hypothyroidism require TH supplementation at doses much higher than the usual replacement doses. Reaching thyroid equilibrium in these patients may be difficult to achieve [13]. Interestingly, the mother reported poor clinical tolerance of LT4 substitution in spite of frank hypothyroidism. She described rapid heart rate and palpitations as LT4 was in-

creased. Two assumptions can be made here. Since RTHβ was not yet diagnosed when the treatment was initiated, we hypothesized that she had been given too much LT4, in an attempt to normalize TSH, whereas basal TSH is mildly elevated in this RTHβ family. She would have experienced clinical hyperthyroidism due to excessive LT4 stimulation in TR-α-dependent tissues. Alternatively, unpleasant symptoms frequently present in patients with RTHβ (tachycardia, palpitation, hyperactivity) due to TR-α excessive stimulation could have been relieved when the patient developed hypothyroidism. Introducing LT4 substitution would have induced a relapse of these symptoms. At the same time, we must assume that in this patient, the lack of TH in tissues in which *THRB* is predominantly expressed had few noticeable consequences, as is sometimes observed in patients diagnosed with frank biological hypothyroidism in the absence of obvious clinical symptoms.

This family is remarkable in showing the aggregation of thyroid autoimmune diseases, including at least one patient with GD, as the diagnosis could not be firmly established in the sister (II-1). Barkoff et al [14] searched for a possible link between RTHβ and AITD in 130 families (330 subjects) with RTHβ, confirmed by the presence of *THRB* gene mutations, and in 92 unaffected first-degree relatives. They concluded that patients with RTHβ have an increased likelihood of AITD (defined by the presence of anti-TPO and/or anti-thyroglobulin antibodies) compared to healthy first-degree relatives.

The reason for this link is unknown. It has been proposed that chronic TSH stimulation in RTHβ could activate intrathyroidal lymphocytes [15] leading to autoimmune hypothyroidism. A parallel decrease of serum TSH and titers of antithyroid autoantibodies is observed in patients with hypothyroidism treated with levothyroxine, as well as coincidence of GD and thyrotropic adenomas [16]. Stimulation of autoimmunity by TH-α receptors present in epithelial cells of the thymus has also been proposed [17], but only autoimmunity against thyroid has been linked to RTHβ. Thus, the exact nature of the association of RTHβ and AITD remains to be further investigated.

Conclusion

The concurrent presence of RTHβ and AITD in a patient can render both the diagnosis and treatment challenging. TSH is suppressed in GD, even in a context of RTHβ. When RTHβ is undiagnosed, a rapid increase in TSH after the beginning of the treatment of GD contrasting with persistently high TH levels should raise the diagnosis.

For GD in a setting of RTHβ, medical treatment should be the first line of therapy, the goal of treatment being to obtain TH levels close to those observed before the onset of GD. In the absence of any prior reference, the TH levels of relatives with RTHβ but unaffected by AITD can be used as a target.

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Statement of Ethics

Patients provided written informed consent for the anonymous publication of their medical data.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Y. Abdellaoui, S. Bakopoulou, R. Zaharia, and L. Cazabat cared for the patient and collected the medical data. Y. Abdellaoui, D. Magkou, and M.L. Raffin-Sanson wrote the manuscript. All authors approved the manuscript.

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