Thyroid Hormone Resistance: Multicentrical Case Series Study

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ABSTRACT

Resistance to thyroid hormone syndrome (RTHS) is defined as increased thyroxine and triiodothyronine associated with normal or increased thyrotropin. This is usually due to a pathogenic variant of the gene coding for thyroid hormone receptor B (THRB). THRB is a rare genetic disorder characterized by an altered response of target tissue to the thyroid hormone action. Retrospective cross-sectional observational study with diagnosis of RTHS evaluated in secondary and tertiary hospitals for 6 years, from 2014 to 2020, in order to describe variables including age, sex, anthropometric data, clinical and biochemical characteristics of patients, who were divided according to age, in a pediatric group from 0 to 14 years (index cases), and an adult group composed of adult relatives of index cases. A molecular analysis of the THRB gene was performed. The total retrospective cohort included 7 pediatric patients and 15 adults. We found 22 cases with a clear male predominance (14/22). Mean age is 24.8 years old (22 days-70 years). Patients were referred because of symptoms 18.2 % (4/22), analysis results 22.7 % (5/22), or familial study 59.1 % (13/22). About 31.8 % (7/22) cases show goiter, 31.8 % (7/22) sympathetic symptoms and 13.6 % (3/22) abnormalities in behavior. In most cases, 77.3 %, (17/22) show familial background of thyroid abnormalities. It is important to remark that 18.2 % (4/22) relatives received previous incorrect treatments such as thyroidectomy, because of wrong diagnosis. In conclusion, a better understanding of RTHS, its prompt molecular diagnosis and genetic counseling, could avoid unnecessary tests and inappropriate treatments.

Introduction

Resistance to thyroid hormone (RTH) [1] is a genetic disorder characterized by an impaired responsiveness of target tissues to the action of the thyroid hormone. There is an abnormal increase of serum thyroxine (T4) levels generally accompanied by elevated serum triiodothyronine (T3), with non-suppressed (normal, or even elevated) serum thyroid-stimulating hormone (TSH) levels.

Resistance to thyroid hormone is rare, with an estimated incidence of 1:40 000 births [2], although accurate data is difficult to obtain. The classic form is, in most cases, due to mutations in the Thyroid Hormone Receptor β (THRB) gene, although there are also alterations in the cellular transport of T4 and T3, and in the conversion from T4 to T3 mediated by deiodinases [3, 4].

The effects of the thyroid hormone are mediated by a receptor encoded by separate genes: THRA (thyroid hormone receptor α) gene, coding for thyroid hormone receptor alpha (TRα), isoforms 1 and 2, located in 17q11.2; and the THRB gene, isoforms 1 and 2, located in 3p24.2 [5].

Currently, according to the THRB gene, 120 mutation sites have been reported, most of which are located in the “hotspot” region. These are carboxyl terminal ligand binding regions of TRB encoded by exon 7 to 10 [6]. Mutated proteins provoke a reduced affinity for T3 and/or an impaired interaction with the cofactors involved in their transcriptional machinery. Thus, dominant negative inhibition of wild-type receptors by the mutant THRB form is the basis of the disorder [7]. Although some cases have been described as being caused by the mutation receptor α1 and α2 [1, 8], the majority of them (80–85 %) are due to heterozygous mutation, although some homozygosis mutations have also been described [9].

RTH-β is an autosomal dominant disease, which has affected individuals who are heterozygous for mutant allele, although recessive heritance and 20–25 % of novo mutations have also been described [10]. On the other hand, gene defects remain unknown in 15 % of subjects with a phenotype similar to RTH-β, called "nonthyroid receptor-resistance to thyroid hormone (TR-RTH)". It is due to mutations in genes, which encode cofactors that interact with receptors [1, 10, 11].

The first description of RTH was made by Refetoff et al. [12] in a family with congenital deafness, stippled epiphyses, goiter, and abnormal high serum protein-bound iodine. The majority of patients maintain an almost normal serum level, although it is variable among people affected. The most common abnormality is the presence of diffuse goiter (66–95 %), followed by tachycardia 35 % [7]. However, patients with RTH-β show very heterogeneous clinical manifestations, being asymptomatic or presenting symptoms from hypothyroidism to hyperthyroidism. Even with the same mutation, due to the distribution of receptor expression, compensatory mechanisms and the effect of previous and/or current treatment, different degrees of peripheral resistance are observed in patients, as well as variable resistance in different tissues of the same individual [9].

Some common symptoms are described in children: short stature, delayed bone age, deafness, language delay, school delay and even intellectual delay. An amount of 70 % show Attention-Deficit Hyperactivity Disorder (ADHD) [4, 13].

Thyroid antibodies may be present in 20 % of these patients [14, 15]. Clinical presentation needs to be differentiated with TSH secreting adenoma, familial hypertyrosinemia, hypalbuminemia, abnormalities in proteins such as albumin and thyroglobulin [10].

The present review was prepared for the purpose of expanding knowledge of RTH-β in order to reduce the rate of misdiagnosis.

Ethics Approval

All procedures followed in both centers were in accordance with the ethical standards of Virgen del Rocio Hospital´s Ethics committee (code 12011966). Informed consents before the inclusion of patients were not necessary because of the retrospective design.

Patients and Methods

Retrospective cross-sectional observational study with diagnosis of RTH evaluated in secondary and tertiary hospitals for 6 years (Jerez Hospital and Reina Sofia University Hospital) from 2014 to 2020, in order to describe clinical and biochemical characteristics of patients, who were divided according to age, in a pediatric group from 0 to 14 years (index cases), and an adult group composed of adult relatives of index cases. Exclusion criteria were: Alteration of transporter proteins, dysalbuminemia, adenoma, and other genetic etiologies different to RTH-β, RTH-α, or TR-RTH.

In all patients, the diagnosis was based on two biochemical analyses after 12-hour fasting {T4, T3, TSH; autoimmunity, sex hormone-biding globulin (SHBG), thyroglobulin], thyroid ultrasound, echocardiogram, sellar magnetic resonance imaging (MRI), TRH test, and genetics.

Genetic studies were done through peripheral blood samples collected in ethylenediaminetetraacetic acid (EDTA) tubes. DNA was extracted using Qiagen technology. Structural analysis of THRB gene exons 3–10 and intronic regions were studied by polymerase chain reaction (PCR) amplification. Sequences were analyzed by Termofisher Scientific's SeqScape V3 Software.

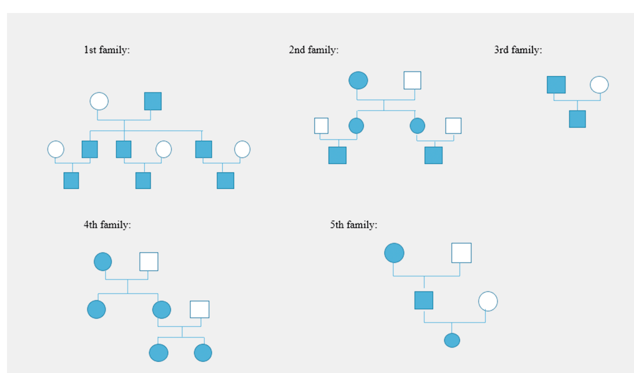
During the study, the following variables were collected: sex, age at diagnosis, anthropometric data at birth and at diagnosis, clinical symptoms, biochemical and imaging results, and genetics. Descriptive analysis was done using statistical package R, version 4.0.3, through percentages, ranges, and means.

Results

In the pediatrics group, we found 7 cases with a clear male predominance (5/7), which represents 71.4 % of the sample. Mean age is 5.58 years old (22 days–14 years). In the adults group, we found 15 patients with a mean age of 44 years old (19–70 years), and male predominance (9/15).

Patients were referred for different reasons: 18.2 % (4/22) were referred because of clinical suspicion of RTH (goiter, tachycardia), 22.7 % (5/22) were referred after abnormal T4 and/or TSH levels in biochemical analysis performed due to clinical symptoms not related to RTH (analytical finding), and 59.1 % (13/22) were studied because they were relatives of a patient with a known mutation in the THRB gene (familial study) (▶ Fig. 1). They showed low TSH/alpha subunit ratio and negative TRH test.

An amount of 31.8 % (7/22) of cases show goiter, 31.8 % (7/22) sympathetic symptoms and 13.6 % (3/22) abnormalities in behavior. Most cases, 77.3 %, (17/22) show familial background of thyroid abnormalities, and some of them, which represents 31.8 % (7/22) of the sample, were diagnosed with thyroid hormone resistance through the study of their children. It is important to remark



▶ **Fig. 1** Pedigree diagrams of studied families.

that 18.2 (4/22) of relatives received previous incorrect treatments such as thyroidectomy, because of a wrong diagnosis.

Around 4.5 % (1/22) of cases show a low weight at birth. At the time of writing, genetic results for one last family were pending, but they were treated with antithyroid with bad response. They have shown lab tests compatible with thyroid hormone resistance, and the index case is having a good evolution with tetraiodothyroacetic acid treatment. So, nowadays they are compatible with TR-RTH (▶ **Table 1** and **2**).

Discussion

We found 7 pediatric cases and 15 adults diagnosed with resistance to thyroid hormone, a bigger sample than most publications, especially regarding children [16–18]. In our sample, most reasons for study were in the context of a family study or after obtaining an altered T4 and/or TSH level in a biochemical analysis, as well as in published studies. Although, they referred to biochemical analysis performed due to clinical symptoms unrelated to RTH-β [17], while most cases in our sample were performed for clinical symptoms compatible with thyroid abnormalities.

As we can see in our series, as well as in the literature, depending on the tissue, features of thyroid hormone excess and deficiency may coexist, although most individuals have a euthyroid, normal metabolic state at the expense of high thyroid levels [7]. In fact, the syndrome is often misdiagnosed as hyperthyroidism and unnecessarily treated with antithyroid drugs, as occurred with one of our cases, and some patients receive l-thyroxine treatment for apparent hypothyroidism [19]. So, due to their nonspecific symptomatic presentation, these patients can be misdiagnosed if the physician is not familiar with the condition. This can result in frustration for the patient and sometimes unnecessary invasive treatment, such as radioactive iodine ablation or thyroidectomy [20, 21], as in our familial cases. Routine neonatal screening based on the TSH assay has a limited role in detecting resistance to thyroid hormone, although it could facilitate the early diagnosis of RTH-β in newborns in some cases [16, 17]. Therefore, genetic testing of the candidate genes THRB should be performed for diagnosis of resistance to the thyroid hormone in patients with the suggestive clinical phenotype [16] or familial antecedents, because prompt molecular diagnosis and genetic counseling could prevent unnecessary tests and inappropriate treatments such as iodine or surgery [22].

It is important to highlight that we found some pathogenic variants in our sample, which have not been described before, such as c.1348 C > T; p. (Leu450Phe). These pathogenic variants were defined by experimented geneticians according to known databases and experience.

Fetuses born to RTH-β mothers without diagnosis and treatment have poor intrauterine and postnatal growth due to gestational hypertension and exposure to an excess of the thyroid hormone, with low birth weight and suppressed postnatal thyroid-stimulating hormone (TSH) [21, 23]. Probably, this is the situation with our case 3, who showed low neonatal anthropometry. In fact, adult humans and mice without resistance to the thyroid hormone-β exposed in utero to high maternal thyroid hormone levels have persistent central resistance to the thyroid hormone. This is likely mediated by the increased expression of D3 in the anterior pituitary, enhancing local T3 degradation [24]. So, it is important that maternal fT4 levels are not above 50 % of the upper limit of normal in RTH-β mothers carrying fetuses. This seems to be a prudent approach that prevents the otherwise expected low birth weight and postnatal TSH suppression [23].

On the other hand, we found one case with thyroid hormone resistance and attention deficit hyperactivity disorder. The cognitive phenotype of resistance to thyroid hormone has been reported to be similar to attention deficit hyperactivity disorder. In fact, there were no significant differences with regard to behavior or electrophysiological phenotype, so it is impossible to determine the real cause of that behavior [13].

Regarding the diagnosis, it would be recommendable to conduct a second thyroid function test (TSH, free T4, and free T3) with a different assay, and then screening for a genetic variant by sequencing the genes involved in thyroid hormone regulation, action and transport (THRB,THRA, SECISBP2, SLC16A, ALB, TTR, SERPINA7) [3, 10].

Dieu et al. obtained mutation in THRB in 26 % of cases (15/58), while it is the cause that was evident in all our patients and the most frequent cause in the literature [25, 26]. Furthermore, they found biological interference due to a thyroid hormone serum transport protein variant in 24 % (14/58). On the other hand, biological interference was suspected in 26 % of cases without genetic variant, in which the biological discrepancy was not confirmed by a second analytical technique (15/58). Finally, no etiology for the biological discrepancy could be found in 24 % of cases (14/58) [10], as it occurred in one of our cases. They stated that patients in whom biological discrepancy was due to analytic interference were more often asymptomatic, and patients with no identified etiology tended to be older [10], whilst we show one young patient with this condition.

Xiao et al. also included somatostatin suppression test, electrocardiography (ECG), thyroid ultrasonography, magnet resonance imaging (MRI) of the sellar region, vision and hearing at diagnosis [18]. The reason for this is differential diagnoses with TSH-producing pituitary adenoma (TPA) and Familial Dysalbuminemic Hypertyrosinemia (FDH) [26], and that is why we decided to perform an MRI in some of our cases.

RTH should be suspected in both adults and children with elevated thyroid hormone and not suppressed TSH [27], so we could diagnose adults due to diagnostic in children, as it occurred in our family cases. It is interesting that higher serum TSH levels in RTHβ patients have been described when compared to those without mutations in beta isoform of the thyroid hormone receptor, but this difference did not extend to free T4 level [26].

According to treatment, compounds with thyromimetic potency but with different biochemical properties compared to T3 may hold therapeutic potential in these syndromes by bypassing defective transporters or binding to mutant T3-receptors. Such thyroid hormone analogues have the potential to rescue thyroid hormone signaling. So, the application of 3,3′,5-triiodothyroacetic acid (Triac) in resistance to thyroid hormone due to defective TRβ and the role of 3,5-diiodothyropropionic acid (DITPA), 3,3′,5,5′-tetraiodothyroacetic acid (Tetrac) and Triac in MCT8 deficiency are really useful [3, 28], as we have shown in our cases.

▸ **Table 1** Pediatric patients with Thyroid Hormone Resistance in our sample.

Family	Age	Relation	Sex	Background	Symptoms	Labs	Imaging	Genetics	Treatment
1	14 years	index	M	No interest	ADHD	TSH 6.33 mUI/l	Ultrasound: Enlarged thyroid, heterogeneous echogenicity, and increased vascularity	c.1348 > T; p.(Leu450Phe) in heterozygosity in exon 10 of THRB gene	No
					Goiter II	T4 2.2 ng/ml	Scintigraphy: Diffuse hyper-uptake goiter		
						T3 6 pg/ml	MRI and EKG normal		
						Tg 18 ng/ml			
						Autoimmunity against Tg: 405 ng/ml			
						α Subunit < 0.3 mUI/ml			
						SHBG 28 nmol/l			
						Prealbumin 28 mg/l			
						Albumin 4.4 g/dl			
	6 years	Cousin	M	No interest	No	TSH 2.16 mUI/l	Ultrasound, MRI and EKG normal.		No
						T4 1.5 ng/ml			
						T3 5 pg/ml			
						Autoimmunity against Tg: 64 ng/ml			
						α Subunit < 0.3 mUI/ml			
						SHBG 29 nmol/l			
						Prealbumin 22 mg/l			
2	10 months	index	M	No interest	No	TSH 6 mUI/l	Ultrasound, MRI and EKG normal.	c.1348 > T; p.(Leu450Phe) in heterozygosity in exon 10 of THRB gene	No
						T4 2.3 ng/ml			
						T3 5 pg/ml			
						Autoimmunity against Tg: 29 ng/ml			
						α Subunit 0.1 mUI/ml			
						SHBG 29 nmol/l			
						Prealbumin 22 mg/l			

Table 1 continued.

Family	Age	Relation	Sex	Background	Symptoms	Labs	Imaging	Genetics	Treatment
3	2 years	index	M	Low birth weight	No	TSH 3.7 mUI/l	Ultrasound, MRI and EKG normal.	C1313 > A (pArg438His) in exon 7 of THRB gene	No
						T4 2.44 ng/ml			
						T3 8.2 pg/ml			
						Autoimmunity against Tg: 42 ng/ml			
						α Subunit 0.2 mUI/ml			
						Prealbumin 27 mg/l			
4	5 years	index	M	Learning difficulties	Learning difficulties	TSH 2.84 mU/l	Ultrasound, MRI and EKG normal.	c.1357 C > T (p.Pro452Ser) in THRB gene	No
						T4 2.34 ng/dl			
						T3 10.36 pg/ml			
						Autoimmunity negative			
	22 days	Sister	F	No interest	Nervousness, insomnia	TSH 3.67 mU/l	Ultrasound, MRI and EKG normal.		Propranolol
						T4 2.97 ng/dl			
						T3 9.14 pg/ml			
						Tg 68.24 ng/ml			
						Autoimmunity negative			
5	11 years	index	F	No interest	Nervousness, insomnia, palpitations, behavior changes, weight stagnation, concentration problems, goiter II	TSH 12.17 mU/l	Ultrasound: Thyroid enlarged at the right lobe. Diffuse increased vascularization. Nonspecific lymphadenopathy.	THRB and THRA normal	Propranolol
						T4 1.44 ng/ml	Cranial MRI: Plagiocephaly, ventricular asymmetry.	Cofactor pending	Melatonin
						T3 5.41 pg/ml			Tetraiodothyroacetic acid
						Autoimmunity negative			

F: Female; M: Male; ADHD: Attention Deficit Hyperactivity Disorder; THR: Thyroid Hormone Resistance; TSH: Thyroid Stimulation Hormone; T4: Thyroxine; T3: Triiodotironine; Tg: Tyroglobuline; SHBG: Sex hormone binding globulin; mU: Milli-international units; MRI: Magnetic Resonance Imaging; EKG: Electrocardiogram.

▸ **Table 2** Adult patients with thyroid hormone resistance in our sample.

Family	Age	Relation	Sex	Background	Symptoms	Labs	Imaging	Genetics	Treatment
1	67 years	Grandfather	M	Diagnosed with hyperthyroidism. Thyroidectomized	No		Ultrasound, MRI and EKG normal	c.1348>T; p. (Leu450Phe) in heterozygosity in exon 10 of THRB gene	No
	41 years	Father	M	No interest	Goiter	TSH: 2.45 mUI/l	Ultrasound: Enlarged thyroid with a 7.6 mm cystic nodule	c1633:C>T (p.Leu450Phe)	No
						T4: 2.2 ng/ml	MRI and EKG normal	in exon 10 of THRB gene	
						T3: 5.5 pg/ml			
						Autoimmunity negative			
						α Subunit < 0.3 mUI/ml			
						SHBG: 22 nmol/L Prealbumin 25 mg/l			
						Albumin 4.8 g/dl			
	42 years	**Paternal uncle**	**M**	**Diabetes**	**Tachycardia**	**TSH: 0.64 mUI/l**	**Ultrasound, MRI and EKG normal**	**c.1348>T; p. (Leu450Phe) in heterozygosity in exon 10 of THRB gene**	**No**
						T4: 2.35 ng/ml			
						T3: 4.97 pg/ml			
						α Subunit 0.28 mUI/ml			
						SHBG: 20 nmol/l			
						prealbumin: 27 mg/l			
						albumin 4.8 g/dl			
	30 years	**Paternal cousin**	**M**	**Diabetes**	**No**	**TSH: 4.8 mUI/L**	**Ultrasound, MRI and EKG normal**		**No**
						T4: 2.42 ng/ml			
						t3 libre: 5.17 pg/ml			
						α Subunit: 0.3 mUI/ml			
						SHBG: 34 nmol/l			
	43 years	**Paternal uncle**	**M**	**Diabetes**	**Multinodular goiter**	**TSH: 3.4 mUI/l**	**Ultrasound: Multinodular goiter**		**No**
				Diagnosed with RTH		**T4 libre: 2.5 ng/dl**	**MRI and EKG normal**		
						T3l: 5.8 pg/ml			
						Tg: 34 ng/ml			
						Autoimmunity negative			
						α Subunit: < 0.3 mUI/ml			
						SHBG: 29 nmol/l			
						Albumin: 5 mg/dl, Prealbumin: 25 mg/dl			

▸ **Table 2** continued.

Family	Age	Relation	Sex	Background	Symptoms	Labs	Imaging	Genetics	Treatment
2	48 years	Maternal aunt	F	Diagnosed with RTH	No	TSH: 3.2 mUI/l	Ultrasound: Diffuse goiter	p.L450F(c.C1663T) in exon 10 of THRB gene	No
						T4: 2.5 ng/dl	MRI and EKG normal		
						T3: 5.3 pg/ml			
						Tg: 27 ng/ml			
						Autoimmunity negative.			
						α Subunit: < 0.3 mUI/ml			
						SHBG: 31 nmol/l			
						albumin: 5 mg/dl, prealbumin: 28 mg/dl			
	19 years	Cousin	M	Diagnosed with RTH	No	TSH: 3.1 mUI/l	Ultrasound, MRI and EKG normal		No
						T4: 2.46 ng/dl			
						T3: 5.1 pg/ml			
						Tg: 23 ng/ml			
						Autoimmunity negative.			
						α Subunit: < 0.3 mUI/ml			
						SHBG: 29 nmol/l			
						albumin: 5.5 mg/dl, prealbumin : 26 mg/dl			
	27 years	Mother	F	No interest	No	TSH 3.2 mUI/ml	Ultrasound multinodular goiter		No
						T4 2.29 ng/ml	MRI and EKG normal		
						T3 4.59 pg/ml			
						Autoimmunity negative.			
						α Subunit: 0,3 mUI/ml			
						SHBG: 26 nmol/l			
	60 years	Grandmother	F	No interest	No	TSH: 3.8 mUI/ml	Ultrasound, MRI and EKG normal		No
						T4: 2.32 ng/ml			
						T3 libre: 5.27 pg/ml			
						Tg: 24 ng/ml			
						α Subunit: 0.3 mUI/ml, SHBG: 27 nmol/l			
						prealbumin: 28 mg/dl			
						albumin: 6 mg/dl			
3	33 years	Father	M	No interest	No	TSH: 3.5 mUI/l	Ultrasound, MRI and EKG normal	C1313 > A (pArg438His) in exon 7 of THRB gene	No
						T4 libre: 2.56 ng/dl			

▶ **Table 2** continued.

Family	Age	Relation	Sex	Background	Symptoms	Labs	Imaging	Genetics	Treatment
						T3: 6 pg/ml			
						Tg: 27 ng/ml			
						Autoimmunity negative.			
						α Subunit: < 0.3 mUI/ml			
						SHBG: 31			
						albumin: 5 mg/dl, prealbumin : 27 mg/dl			
4	39 years	Mother	F	Thyroidectomized	Palpitations, diarrhea	TSH 8.03 mU/l	Ultrasound and EKG normal	c.1357 C > T (p.Pro452Ser) in THRB gene	Levotiroxine. Tetraiodothy-roacetic acid
						T4L 2.07 ng/dl	MRI: Enlarged pituitary gland		
	36 years	Maternal uncle	M	Diagnosed with RTH	Diarrhea	TSH 1.69 mUI/ml	Ultrasound: Gland minimally enlarged		No
						T4 2.24 ng/dl	MRI and EKG normal		
						Albumin 4.6 g/dl			
	64 years	Maternal grandmother	F	Diagnosed with hypothyroidism	Goiter	TSH 5.69 mUI/l	Ultrasound: Diffuse goiter		Levotyroxine
						T4 3.15 ng/ml			
						Tg 165.7 ng/ml			
						Autoimmunity negative			
5	70 years	Paternal Grandmother	F	Diagnosed with hyperthyroidism treated with antithy-roids and radioiodine	Nervous-ness, tachycardia	TSH 2.12 mU/l	Scintigraphy: Right lobe hyperactivity	c.1357 C > T (p.Pro452Ser) in THRB gene	No
						T4 1.88 ng/dl	Ultrasound, MRI and EKG normal		
						Albumin 4.4 g/dl			
						Autoimmunity negative			
	42 years	Father	M	Hypercholesterolemia	Nervousness, sweating	TSH 0.98 mU/l	Ultrasound and EKG normal		Propranolol
						T4 1.81 ng/dl	MRI: The pituitary stalk and anterior pituitary are displaced to the left. Neurohypophysis in posterior location		
						T3 4.9 pg/ml			
						Autoimmunity negative			

F: Female; M: Male; ADHD: Attention Deficit Hyperactivity Disorder; THR: Thyroid Hormone Resistance; TSH: Thyroid Stimulation Hormone; T4: Thyroxine; T3: Triiodotironine; Tg: Tyroglobuline; SHBG: Sex hormone binding globulin; mU: Milli-international units; MRI: Magnetic Resonance Imaging; EKG: Electrocardiogram.

In conclusion, it is necessary to think about resistance to thyroid syndrome in cases of patients with elevated free T4 and T3 concentrations, with normal or inadequately elevated TSH, in the absence of acute illness or drugs, to diagnose it. Prompt molecular diagnosis and genetic counseling could prevent unnecessary tests and inappropriate treatments.

Author Contributions

M. Angeles Santos Mata has concepted the idea, reviewed literature, and written part of the article. Ana B. Ariza Jimenez has analyzed the data, reviewed literature, written part of the article, and checked final article. Francisco Macias Lopez and Carmen de la Camara Moraño have collected patients.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Notice
This article was changed according to the following Erratum on February 23rd 2022.

Erratum
In this article the authors names were not displayed correctly. Correct are: Maria Angeles Santos Mata, Ana Belen Ariza Jimenez, Francisco Macias Lopez and Carmen de la Camara Moraño.