Thyroid hormone resistance (THR): a case report

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Abstract

Resistance to thyroid hormones (RTH) is a syndrome characterized by reduced response to thyroid hormones with variable degrees of resistance in target tissues. Clinical features, physical exam findings and the study protocol in a woman with RTH are presented. The substitution of arginine by tryptophan in the b isoform of the thyroid hormone receptor gene was demonstrated. RTH is an uncommon cause of thyroid dysfunction. An appropriate workup is necessary, as well as diagnosis confirmation in order to prevent an inadequate and inefficacious treatment of this condition
(Gac Med Mex. 2014;150:461-5)

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KEY WORDS: *Resistance. Thyroid hormones.*

Introduction

The RTH syndrome is a rare entity, with an estimated incidence of 1 in 50,000 live births. It is characterized by a reduced response to thyroid hormones in peripheral target organs. It occurs at the same frequency in males and females, and it affects all ethnical groups. Thyroid function tests usually show an elevated concentration of thyroid hormones with unsuppressed thyroid-stimulating hormone (TSH). The syndrome is produced by mutations in the thyroid hormone receptor[1,2]. Next, the clinical features, findings in physical examination and the treatment protocol in a woman with RTH are presented.

Clinical case

In 1978, when she was 18 years old, a woman, now aged 43, was assessed. Her condition consisted in tremor, sweating, heat intolerance, nervousness, anxiety, insomnia and increased volume of the anterior region of the neck. She was diagnosed with Graves' disease and received treatment with tiamazol and an unspecified dose of ^{131}I. In 1996, at 33 years of age, she was evaluated for the first time at the Thyroid Clinic of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. She complained of fatigue, weight gain, palpitations, diarrhea, anxiety and insomnia. She was being treated with levothyroxine and the thyroid functioning tests showed triiodothyronine (T3) and thyroxine (T4) elevations, as well as non-suppressed TSH (Table 1). Findings on physical exam included overweight (body mass index [BMI]: 27.5 kg/m^2) and normal thyroid gland. A thyroid gammagram reported increased uptake (71%) at 24 h.

Absence of anti-thyroid peroxidase, anti-T3 and anti-T4 antibodies was documented. The T4-transporting globulin concentration was 20.1 µg/ml (normal range: 12-30). The presence of a TSH-secreting pituitary adenoma was ruled out by performing a test with the administration of TSH-releasing hormone (TRH), measurement of subunit α (0.2 ng/ml; normal: < 1.8) and pituitary gland magnetic resonance imaging (MRI).

Treatment was started with tiamazol and thyroid hormones at varying doses. During the follow-up, the patient persisted with elevations of T3, T4 and TSH (Table 1) and, thus, she was admitted to the Metabolic Unit to perform a dynamic study.

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Modified version reception: 25-11-2013
Date of acceptance: 16-01-2014

Table 1. Thyroid function tests and treatment during the follow-up

	April 1996	June 1996	July 1997	September 1999	March 2004	July 2005	January 2006	February 2007	Normal value
T3U (AU)	1.19	1.17	1.22	1	0.87	0.41	0.32	0.37	1.16-3.85 0.32-0.48
T3 (nmol/l)	3.69	3.26	2.92	3.97	2.31	2.5	0.98	0.83	0.75-2.25
T4 (nmol/l)	241.92	191.76	160.87	216.21	108.1	49.23	1.44	96.07	77.22-154.44
TSH (µU/ml)	2.7	4.4	9.5	6	95	56.61	84.87	75.82	0.3-3.5
Tg (ng/ml)	60	55	133	60	24	16.01	21.34	13.38	0-30
Treatment	T4 100 µg/d	–	MTZ 20 mg/d T4 120 µg/d T3 30 µg/d	–	MTZ 10 mg/d	T3 50 µg/d	T3 25 µg/d	T4 100 µg/d T3 20 µg/d	

T3U: triiodothyronine uptake; Tg: thyroglobulin; MTZ: methimazole; AU: arbitrary units.

TRH-stimulation tests were conducted and thyroid hormones peripheral action indices were measured. The TRH-stimulation test was carried out by administering 200 µg of TRH (T.R.H. PREM™ Barcelona, Spain) by the intravenous route, with measurements of TSH and prolactin before and 15, 30, 60, 90 and 120 min after adminstration.

Predefined variables included thyroid function, ferritin, sex hormone-binding globulin (SHBG), creatine phosphokinase (CPK) and total cholesterol tests.

During three days, 100 µg of liothyronine per day were administered and, subsequently, 200 µg per day for three more days. Weight and vital signs were measured daily. The TRH-stimulation test and the measurement of parameters were repeated in the morning before the dose increase and at the end of the study.

In the baseline measurement, an inappropriately elevated TSH concentration (97.55 µU/ml) was found, in spite of normal concentrations of T3 (107.92 nmol/l) and T4 (1.72 nmol/l) (Table 2). After the administration of TRH, the TSH response is proportional to baseline concentration. In normal individuals, after the administration of supraphysiological doses of thyroid hormone, TSH-stimulation suppression is observed. Conversely, individuals with RTH show a TSH response to stimulation with TRH, although the majority shows partial suppression with the increase of the thyroid hormone dose[3]. In the baseline state, a TSH normal response to the administration of TRH was documented, which was proportional to the increased level of TSH; however, in spite of the progressing increase of the thyroid hormone dose, a TSH increase was continued to be seen only with partial suppression. TSH remained detectable throughout the entire study (Table 2). This pattern indicates resistance to the effects of thyroid hormone in the pituitary gland.

In spite of the consumption of an isocaloric diet, a 5.1% weight loss was observed, as well as an increase in heart rate (HR), which suggests sensitivity to thyroid hormone administration (Table 2).

In normal individuals, cholesterol, SHGB and ferritin show a response to thyroid hormone administration. In this case, after the liothyronine 200 µg take, ferritin was increasd by 151.3% and cholesterol was decreased by 22%, showing the effect of thyroid hormone intake. Conversely, SHGB concentration did not show any change. At the muscular level, sensitivity to hormone administration was also demonstrated, as evidenced by a 72.8% reduction in CPK (Table 2 and Fig. 1). In individuals with RTH, ferritin and SHGB increase and cholesterol and CPK reduction are lower compared with controls. However, varying responses can be observed.

Whole blood DNA was extracted, and amplification and sequentiation of the carboxyl-terminal end exons of the thyroid hormone receptor β (THR β) gene was carried out by means of real time-polymerase chain reaction (PCR). An arginine substitution by tryptophan was found in codon 338 (Fig. 2). This mutation has been reported in more than 30 families with RTH[4-14].

Thyroid functioning tests were performed and the mutation was searched in the parents and one of the three siblings of the patient without abnormalities or presence of the mutation being found.

Table 2. Study protocol to investigate RTH

Day	0	1	2	3	4	5	6	7
Weight (kg)	70.4	69.9	69.6	68.7	67.7	67.1	66.8	66.8
BP (mmHg)	110/60	120/80	120/60	110/70	100/60	110/70	110/70	100/60
HR (beats/min)	60	64	74	76	80	66	78	
T3U (AU)	0.38				0.38			0.37
TT3 (nmol/l	1.72				4.34			9.65
TT4 (nmol/l	107.92				89.86			83.21
TSH (µU/ml)	97.66				17.39			2.07
Tg (ng/ml)	14.06				9.66			6.03
Ferritin	26.7				37.7			67.1
CPK	254				83			69
Cholesterol (mg/dl)	268				226			209
SHBG (nmol/l)	12				14			13
0-min TSH	90.16				16.4			1.93
15-min TSH	240.82				90.62			17.92
30-min TSH	283.29				85.28			16.24
60-min TSH	227.17				65.53			11.15
90-min TSH	141.76				43.78			6.64
120-min TSH	127.89				35.05			5.33
T3 dose (µg/d)	–	100	100	100	200	200	200	

AU: arbitrary units; BP: blood pressure; Tg: thyroglobulin; TT3: total triiodothyronine; TT4: total thyroxin.

Discussion

A of case RHT due to a R338W mutation in THRβ is reported. The patient attended after having been treated with ^{131}I ablation, with thyroid tests showing T3 and T4 elevation, with TSH inappropriately unsuppressed while on treatment with levothyroxine. After discontinuing the treatment with thyroid hormones, in spite of having received ^{131}I, thyroid hormones and TSH levels remained elevated. This is due to the regeneration capability of the thyroid gland in response to the TSH stimulus. The persistence of this thyroid tests pattern led to suspect and explore the presence of other less common causes of TSH inadequate secretion. The study protocol revealed that the patient was partially sensitive to the effects of thyroid hormones in peripheral tissues. Conversely, in spite of the administration of thyroid hormones, TSH demonstrated a response to TRH, thus indicating RTH.

The RTH syndrome is characterized by a reduced response to thyroid hormones. Thyroid function tests often show T3 and T4 elevation, with normal or elevated TSH concentration. Sensitivity to thyroid hormone is variable in different organs, and clinical presentation, heterogeneous[2,15]; isolated central presence of the RTH syndrome has even been described[4,16,17].

Individuals with RTH can be asymptomatic or have symptoms consistent with deficiency and/or excess of thyroid hormones. In isolated central resistance to thyroid hormones there is a lack of TSH-secretion suppression at the anterior pituitary gland, which causes increases in T3 and T4 concentrations. Peripheral tissues normally respond to thyroid hormones increased levels by causing thyrotoxicosis symptoms[17]. In generalized resistance, most tissues do not respond to thyroid hormones and euthyroidism or hypothyroidism occurs, depending on the degree of compensation achieved with the increase of thyroid hormones. Clinical

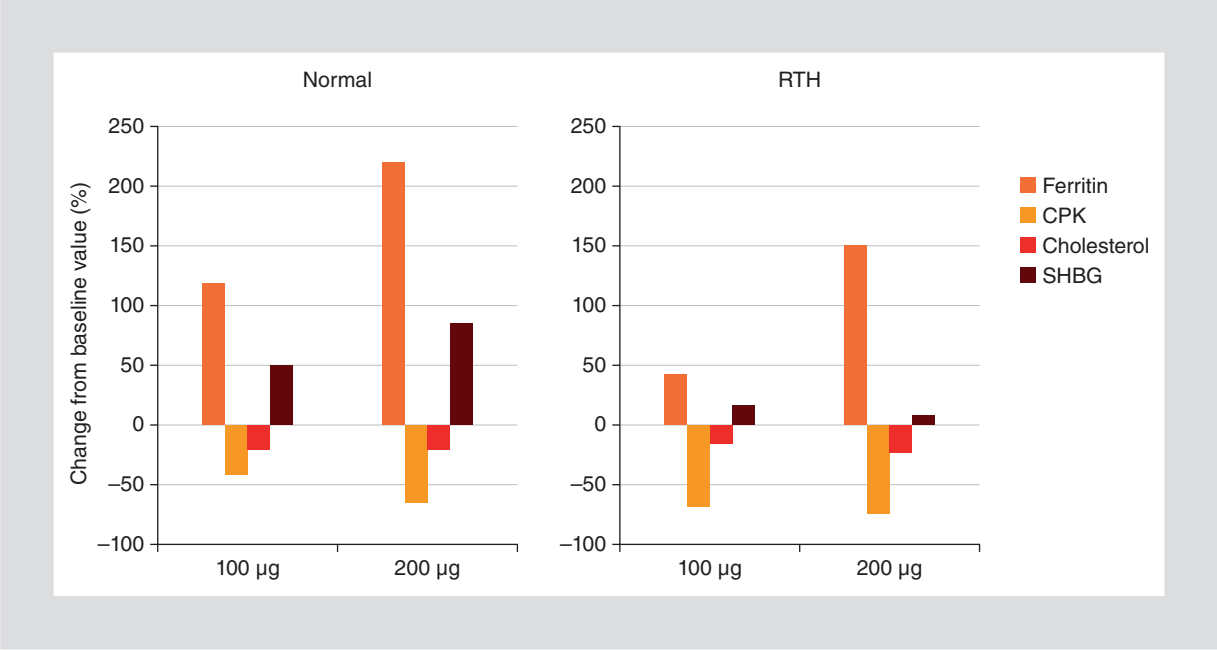

Figure 1. *Response to the administration of thyroid hormones. Response to the administration of liothyronine (T3) incremental doses in a RTH case (right) and in a normal individual (left). A dose-dependent ferritin and SHBP increase is observed, together with a decrease of total cholesterol and CPK, which is lower in the RTH case.*

manifestations are also influenced by the distribution of thyroid hormones receptors. In mammals, there are four isoforms of the receptor: β1, β2, α1 and α2, encoded by genes at the 17q11.2 (α) and 3p24 (β) chromosomes. Their expression is overlapped, but the α1 form is mainly expressed in skeletal and cardiac muscle; β1, in the brain, the liver and the kidney, and β2, in the pituitary gland and the hypothalamus; thyroid hormone does not bind to the α2 form of the receptor[2,18].

In the presence of RTH, tissues expressing the α and β isoforms show a reduced response to the effect of thyroid hormones, with a certain degree of compensation; those subjects who selectively express the α isoform, respond to thyroid hormones elevation, and those who express exclusively the β isoform are refractory to their effects. The cause of the syndrome was a mutation in the β isoform of the receptor and, thus, the lack of response at the pituitary gland, the increase in HR and the response at the level of skeletal muscle can be explained by the distribution of the thyroid hormones receptor isoforms. Individuals with RHT show heterogeneous clinical manifestations due to the distribution of receptors, to compensatory mechanisms and to the effect of previous and/or current treatment[19].

Several mutations have been described as causing the syndrome; most are grouped in the carboxyl-terminal region of the gen, to which the thyroid hormone binds. In most cases, the hereditary pattern is autosomal dominant, and affected individuals are heterozygous to the mutant allele[5].

The diagnosis of RTH is not simple. Other causes of inadequete secretion have to be ruled out and a detailed assessment is required, including thyroid hormone administration. It is suspected in the presence of goiter or history of goiter with inappropriately high concentrations of TSH for the T4 concentration.

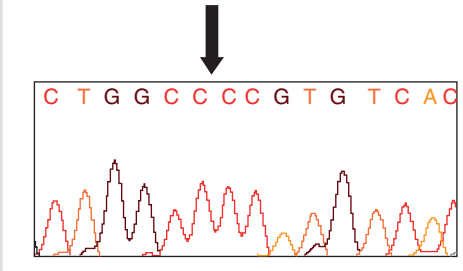

Figure 2. *Analysis of the THRB gene sequence. Analysis of the THRB exon 9 sequence showing a substitution of cytosine by thymine in nucleotid 1297, which causes a substitution of arginine by tryptophan at codon 338 (R338W). C: cytosine, T: thymine, G: guanine; A: adenosine.*

There is no treatment to correct the syndrome. The lack of an adequate diagnosis often leads to establish a treatment with ^{131}I due to an erroneous Grave's disease diagnosis. Patients with no treatment usually show compensation with the increase of thyroid hormones. Hormone replacement therapy is indicated in individuals that have received previous ablation or in those with incomplete compensation. Optimal dose should be individualized and elevated doses may be required. β-blockers and anxiolytics can be used in the presence of thyrotoxicosis[20]. In the presented case, the patient receives thyroid hormones and β-blockers.

To our knowledge, this case is the first RTH report in a Mexican woman due to a *THRβ* gene *de novo* mutation.

Conclusion

In spite of being rather uncommon, RTH syndrome must be considered in cases where thyroid function tests and clinical manifestations suggest its presence. To establish the diagnosis, an appropriate workup is required in order to allow for inadequate and ineffective treatment to be avoided.

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