

REVISIÓN

Inappropriate Secretion of TSH Syndrome

Síndrome de secreción Inapropiada de TSH

Mahler GA, Bergoglio LM

Laboratorio de Endocrinología. Hospital Nacional de Clínicas. Facultad de Ciencias Médicas.
Universidad Nacional de Córdoba

ABSTRACT

The syndrome of inappropriate secretion of TSH was the term originally coined to indicate two forms of central hyperthyroidism, i.e. thyrotropin (TSH)-secreting pituitary adenomas (TSHomas) and resistance to thyroid hormone action (RTH). Both forms are characterized by high levels of free thyroxine (FT4) and free triiodothyronine (FT3) in the presence of measurable TSH concentrations, a biochemical picture which is in contrast to primary hyperthyroidism where TSH levels are always undetectable. Patients with TSHoma are clinically hyperthyroid, while RTH patients are generally euthyroid (so-called generalized RTH). However, in a minority of RTH thyrotoxic patients, features have been described with such individuals being deemed to have predominant central or pituitary resistance. Although incidence of inappropriate secretion of TSH is generally low, it is essential to rule out the likely causes of discordance in the TSH/T4 (thyroxine) relationship. The distinction between TSHoma and PRTH can be difficult since both conditions do not present significant differences in age, sex, gender or concentrations of TSH, FT4 and FT3. The failure to recognize them as different entities may have deleterious consequences, such as thyroid ablation in patients with central hyperthyroidism, or unnecessary pituitary surgery in those with PRTH. The objective of this review is to properly characterize them with a history of an affected first-degree relative, biochemical dynamic tests, pituitary imaging and genetic testing, according to what has been reported in international literature, and to analyze biochemical difficulties in choosing the best biochemical tools for that purpose, taking into account that no individual biochemical test can validate the differential diagnosis that must be based on a combination of: serum $SU\alpha$, $SU\alpha$ /TSH ratio, TSH response to TRH, TSH response to suppression with LT3, and genetic analysis. **Rev Argent Endocrinol Metab 50:253-264, 2013**

No financial conflicts of interest exist.

Key words: Thyrotropinoma, Resistance to thyroid hormones, Syndrome of inappropriate secretion of TSH

RESUMEN

Síndrome de secreción inapropiada de TSH fue el término acuñado originalmente para describir dos formas de hipertiroidismo central, los adenomas hipofisarios secretantes de tirotrófina (TSH) (TSHoma) y la resistencia a las hormonas tiroideas (RHT). Ambas condiciones están caracterizadas por niveles elevados de tiroxina libre (T4L) y triiodotironina libre (T3L), en presencia de concentraciones medibles de TSH, escenario bioquímico que contrasta con el hipertiroidismo primario donde los niveles de TSH son siempre indetectables. Los pacientes con TSHoma son clínicamente hipertiroides, mientras que los pacientes con RHT son generalmente eutiroides (RHT generalizada). Sin embargo, en una minoría de pacientes tirotóxicos con RHT se han descrito signos y síntomas que los caracterizan como portadores de RHT predominantemente central o hipofisaria (RH). Aunque la incidencia del síndrome de secreción inapropiada de TSH es generalmente baja, es fundamental descartar la discordancia de la relación TSH/T4 (tiroxina). La distinción entre TSHoma y RH puede ser difícil ya que ambas condiciones no presentan diferencias significativas en cuanto a edad, sexo, género ni concentraciones de TSH, T4L y T3L. La falla en reconocerlas como diferentes puede

Recibido: 08-08-2013 Aceptado: 19-09-2013

Correspondencia: Santa Rosa 1564 5000 Córdoba. Teléfax: 0351 - 4337066
liberg@uolsinectis.com.

tener consecuencias deletéreas, como la ablación tiroidea en pacientes con hipertiroidismo central, o cirugía hipofisaria innecesaria en aquellos con RH. El objetivo de esta revisión es caracterizarlas apropiadamente con la historia de un familiar de primer grado afectado, pruebas bioquímicas dinámicas, imágenes hipofisarias y pruebas genéticas, acorde a lo reportado en la literatura internacional, y al mismo tiempo, analizar las dificultades bioquímicas al elegir la mejor herramienta para tal fin; teniendo en cuenta que ninguna por sí sola puede avalar el diagnóstico diferencial que debe basarse en una combinación de pruebas: concentración sérica de $SU\alpha$ y relación $SU\alpha/TSH$, tipo de respuesta de TSH al TRH, respuesta de TSH a la supresión con LT3 y análisis genético. **Rev Argent Endocrinol Metab 50:253-264, 2013**

Los autores declaran no poseer conflictos de interés.

Palabras clave: tirotrofina, resistencia a las hormonas tiroideas, síndrome de secreción inapropiada de TSH

INDEX

1. Abbreviations	254
2. Introduction	255
3. Objective	255
4. Pathogenesis of different conditions.....	255
4.1 Resistance to Thyroid Hormones.....	255
4.1a Clinical manifestations of Resistance to Thyroid Hormones.....	256
4.2. Thyrotropinoma.....	257
4.2a. Clinical manifestations of Thyrotropinoma	257
4.3. Abnormality in the serum binding proteins.....	258
4.4. Specific and nonspecific antibodies.....	258
5. Biochemical tests for the differential diagnosis between Thyrotropinoma and Resistance to Thyroid Hormones.....	259
5.1- Thyrotropin.....	259
5.2- Thyroid Hormones.....	259
5.3- Thyrotropin α subunit.....	259
5.4- Liothyronine suppression test	260
5.5- Thyrotropin-Releasing Hormone stimulation test	260
5.6- Selenium/Copper ratio.....	260
5.7- Peripheral Thyroid Hormones markers	260
6. Complementary studies	261
7. Treatment	261
7.1. Thyrotropinoma.....	261
7.2. Resistance to Thyroid Hormones.....	262
8. Conclusion	262
9. Bibliography	262

1. ABBREVIATIONS

Cu:	Copper	ICTP:	Carboxy terminal telopeptide of type I collagen
DBD:	DNA-binding domain	LBD:	Ligand binding domain
FDH:	Familial dysalbuminemic hyperthyroxinemia	LH:	Luteinizing hormone
FSH:	Follicle stimulating hormone	LT3:	Liothyronine
FT3:	Free triiodothyronine	LT4:	Levothyroxine
FT4:	Free thyroxine	MRI:	Magnetic resonance imaging
GH:	Growth hormone	NCoR:	Nuclear corepressor
GRTH:	Generalized resistance to thyroid hormones	PRL:	Prolactin
HAMA:	Human anti mouse antibodies		

PRTH:	Pituitary resistance to thyroid hormone	THBP:	Thyroid hormone binding protein
RTH:	Resistance to thyroid hormones	THR:	Thyroid hormones receptor
rT3:	Reverse T3	THRβwt:	Wild type thyroid hormone receptor β
Ru:	Ruthenium	THRβmut:	Mutant thyroid hormone receptor β
Se:	Selenium	TRβ:	Thyroid hormone receptor β gene
SHBG:	Sexual hormones binding globuline	TREs:	Thyroid hormone response elements
SMRT:	Silencing mediator for retinoid and thyroid hormone receptors	TRH:	Thyrotropin-releasing hormone
SUα:	α subunit	TSH:	Thyrotropin
TBG:	Thyroxine binding globulin	TSHoma:	Thyrotropin-secreting pituitary adenomas
TC:	High-resolution computed tomography	TTR:	Transthyretin
TH:	Thyroid hormones	TT3:	Total triiodothyronine
		TT4:	Total thyroxine

2. INTRODUCTION

The apparently paradoxical dissociation between high levels of thyroid hormones (TH) and unsuppressed serum thyrotropin (TSH), has led to the widespread use of the term “syndrome of inappropriate secretion of TSH” to describe this condition, which is essential to rule out the likely causes of discordance in the TSH/T4 (thyroxine) relationship¹. Among these causes are: a) abnormality in the serum proteins of TH transport -either by an excess of acquired or inherited thyroxine binding globulin (TBG) or transthyretin (TTR)-, an increase in the affinity of albumin by T4 in the familial dysalbuminemic hyperthyroxinemia (FDH), or defects in the conversion of T4 to triiodothyronine (T3). (b) Presence of anti-T4 antibodies, and c) methodological artifacts⁽²⁾.

The conditions in which there is a persistent secretion of TSH despite high levels of TH (real inappropriate secretion of TSH), can be divided between those associated with hyperthyroidism, such as pituitary resistance to the TH (PRTH) and thyrotropin-secreting pituitary adenomas (TSHoma), and those characterized by euthyroidism as the generalized resistance to the TH (GRTH)⁽²⁾.

Resistance to the TH (RTH) is an autosomal dominant syndrome with reduced sensitivity to the TH at variable degree⁽²⁾. Most of the cases (85 %) are due to heterozygotes mutations in the TH receptor (THR) gene, which affects the binding domain to the ligand and determines a deterioration in the union and/or the transactivation of T3^(3,4). RTH patients achieve a normal metabolic state at the expense of high levels of TH, maintained by TSH secretion in response to hypothalamic thyrotropin-releasing hormone (TRH). However, this compensation varies among tissues and individuals, and can coexist both excess and deficiency of TH⁽²⁾.

PRTH is characterized by manifestations of excess of TH in peripheral tissues and may include several conditions not related between them, such as non-neoplastic pituitary hyperplasia, pituitary defect of type 2,5'-deiodinase, and GRTH with hyposensitivity at pituitary level⁽²⁾.

TSHomas comprise less than 2 % of all pituitary adenomas. They present clinically with hyperthyroidism. Most of them are macroadenomas (larger than 1 cm)⁽⁵⁾ and have the negative regulation by TH impaired. Regarding the cause of the defect, it is unknown, although it could involve somatic mutations in the TH receptor β (THRβ)⁽⁶⁾.

3. OBJECTIVE

The incidence of inappropriate secretion of TSH is generally low, however, to establish the differential diagnosis between different clinical conditions included under the syndrome, is usually complex. The objective of this review is to properly characterize such conditions, and to analyze biochemical difficulties in their differential diagnosis, emphasizing the best biochemical tools for that purpose.

4. PATHOGENESIS OF DIFFERENT CONDITIONS

4.1. Resistance to Thyroid Hormones

Receptors of TH (THR) belong to the super family of nuclear receptors and are encoded by two different genes: TRα and TRβ located on chromosomes 17 and 3, respectively. Each one of them, structurally similar, generates by alternative splicing two isoforms: THRα1 and THRα2, and THRβ1 and THRβ2 by different transcription start points^(7,8).

THRα1, THRβ1 and THRβ2 proteins have identical DNA binding domain (DBD) and the ligand

binding domain (LBD) sites. $\text{THR}\alpha 2$ joins the TH response elements (TREs), but due to a change in the sequence of LBD, it does not bind TH, thus does not function as a proper THR⁽⁹⁾. $\text{THR}\alpha 1$ is predominantly expressed in heart, bone, and brain⁽¹⁰⁾, while $\text{THR}\beta 1$ does it widely in all tissues, and the $\text{THR}\beta 2$ primarily in anterior pituitary, hypothalamus, retina, inner ear and brain⁽¹¹⁾.

The THR homodimerizes or heterodimerizes with retinoic acid receptor and binds to specific sequences of DNA termed TREs. In the absence of T3, the THR (heterodimer and homodimer) are associated with corepressors as the nuclear corepressor (NCoR), and the silencing mediator for retinoid and thyroid hormone receptors (SMRT), that repress or silence the transcription of genes positively regulated by the ligand. The union of T3 to the THR releases the corepressors and recruits nuclear coactivators as NCoA-1, NCoA-2 and NCoA-3⁽¹²⁾.

To date more than 124 mutations were found in $\text{THR}\beta$, which except in one family, all were found in 7 to 10 $\text{TR}\beta$ gene exons, and 15 % were *de novo* mutations⁽¹³⁾. The mutants ($\text{THR}\beta\text{mut}$) interfere with the function of the wild type $\text{THR}\beta$ ($\text{THR}\beta\text{wt}$), a phenomenon known as dominant negative effect. This supposes the occupation of the TREs for the $\text{THR}\beta\text{mut}$ which translates into effects alone or combined such as: non-union of T3, affinity reduced by T3, affinity limited by corepressors, or impaired interaction with coactivators^(14,15).

The nature of the mutations found in the RTH and their effect on the structure of the $\text{THR}\beta$, suggests that disease can be mediated by a defect in the release or the recruitment of coregulatory proteins of the $\text{THR}\beta$, more than the inability of the $\text{THR}\beta$ to bind the ligand. This hypothesis is based on the fact that the deletion of a $\text{THR}\beta$ allele does not cause any disease, while the expression of a single mutant allele of $\text{THR}\beta$ leads to RHT due to their negative dominant properties⁽¹⁶⁾.

This complexity is parallel to the clinical phenotype of the syndrome, whose characteristics and severity vary among patients. The types of mutations of $\text{THR}\beta\text{mut}$ cannot predict invariably the severity of the disease, so that individuals with the same genetic lesion may not have the same symptoms⁽¹⁷⁾. The severity of the resistance depends on the degree of damage in the LBD and interaction with tissue specific nuclear cofactors⁽¹⁴⁾. Due to the variable distribution of isoforms of the THR in different tissues in the same subject, is possible to find different clinical phenotypes. Another fac-

tor that can regulate the degree of resistance in a tissue is the relative expression of $\text{THR}\beta\text{mut}$ with regard to $\text{THR}\beta\text{wt}$ ⁽¹⁸⁾.

TH levels elevated in patients with RTH require that both thyrotroph and TRH hypothalamic releasing neurons present resistance⁽¹⁹⁾. Thus, the PRTH may result from alterations in the three major sites involved in the physiological mechanism that regulates the hypothalamus-pituitary-thyroid axis: the hypothalamic dorsomedial nucleus (which acts as a metabolic sensor), and TRH-producing neurons, and the pituitary thyrotrophs⁽²⁰⁾.

It should also consider that 15 % of individuals with RTH has no mutation in the THR and that the RTH with mutations in the THR is clinically and biochemically indistinguishable from the RTH without gene mutations. Therefore, the absence of a mutation does not necessarily exclude the diagnosis of RTH⁽²¹⁾.

4. 1a. Clinical manifestations of resistance to thyroid hormones

Although the two broad categories described, GRTH and PRTH, have been clinically defined with conceptual purposes, the RTH is a complex disorder that can present as a whole spectrum of possible symptoms⁽²²⁾.

The GRTH manifests itself as a general inability to appropriately respond to the elevation of HT, causing a loss of negative feedback on the hypothalamus-pituitary-thyroid axis, leading to the no suppression of TRH, TSH, T3 and T4, and a parallel decrease in response of peripheral tissues to T3 and T4. This decrease in peripheral sensitivity allows the GRTH to imitate the clinical aspects of hypothyroidism, despite high levels of T3 and T4⁽²³⁾.

In the PRTH there is also a loss of negative feedback on the hypothalamus-pituitary-thyroid axis, causing no suppression of TSH, TRH and TH, but with enough sensitivity of peripheral tissues to T3 and T4 to induce symptoms of thyrotoxicosis⁽²⁴⁾.

When mutations in the THR associated with GRTH are expressed in either of the two isoforms, $\beta 1$ or $\beta 2$, show an inhibition of the response to T3 proportional to the effects caused, existing a general decrease in the response but preserving the increased ratio $\beta 2$ greater than $\beta 1$. In contrast, mutations present in the PRTH shows a selective damage on the expression of the $\text{THR}\beta 2$, resulting in a relationship $\beta 1$ equal to $\beta 2$ in the T3 response⁽²³⁾.

TABLE 1. Frequency of signs and symptoms in RTH. (IQ: intellectual quotients)
Translated from Weiss RE, Dumitrescu AM, Refetoff S 2010 Approach to the patient with resistance to thyroid hormone and pregnancy. *J Clin Endocrinol Metab* 95:3094-3102.

Clinical manifestation	Frequency (%)
Goiter	66-95
Emotional disturbances	60
Recurrent ear and throat infections	55
Delayed bone age > 2 SD	29-47
Attention deficit hyperactivity disorder	40-60
Sinus tachycardia	33-75
Hyperkinetic behavior	33-68
Low Body mass index (in children)	33
Learning disability	30
Short stature (< 5th percentile)	18-25
Hearingloss (sensorineural)	10-22
Mental retardation (IQ<70)	4-16

The mutations of THR β 2 that cause a disproportionate inhibition in the response to T₃, can disrupt the ability of the pituitary gland and the hypothalamus of sensing properly T₃ levels rather than the periphery, therefore in the PRTH on the hypothalamus-pituitary-thyroid axis loses all or part of their T₃ levels sensing ability, which causes a TSH and a TRH not suppressed, and an increase in the circulating TH. In these individuals, mutant receptor THR β 1, less affected than THR β 2, would retain the ability to respond to this increase in TH and would produce peripheral thyroid toxicity⁽²³⁾.

In table 1 the clinical manifestations and their frequencies are presented in the RTH. The combination of goiter, palpitations and tachycardia occurs in 75 % of patients with GRTH and almost all who have PRTH⁽¹⁸⁾.

4.2. Thyrotropinoma

The term TSH-secreting pituitary tumor includes two opposite conditions regarding its functional expression: true thyrotropic neoplasia (TSHoma) which causes secondary hyperthyroidism, also called central hyperthyroidism, and pituitary hyperplasia resulting from a long term primary hypothyroidism⁽⁵⁾.

Most of TSHoma (72 %) secrete only TSH, with an overproduction of the α subunit (SU α). In 28 % of adenomas, there are concomitant secretion of TSH and other anterior pituitary hormones, main-

ly growth hormone (GH) and/or prolactin (PRL). This may be due to the fact that somatotroph and lactotroph cells share with thyrotrophs common transcription factors, such as Prop-1 and Pit-1^(5,25).

The first case of TSHoma was documented in 1960 by measuring TSH concentration by bioassay⁽²⁶⁾, and since then approximately 400 cases have been described. The introduction of ultrasensitive immunoassays enabled the earlier differential diagnosis between primary hyperthyroidism and TSHoma before the stage of macroadenoma⁽²⁷⁾.

TSHomas consist of a defect in the negative regulation of TSH by the TH. The mechanism by which this regulation is lost is unknown, but may involve a defect in signaling via the THR⁽⁶⁾. Somatic mutations in the THR, the increased expression of the growth factor of fibroblasts, the loss of heterozygosity and the polymorphisms, in particular of the somatostatin receptor 5, are involved in the pathogenesis of the tumor⁽²⁷⁾. Patients have physical signs and symptoms of excess of TH, and the TSHomas are almost always presented as macroadenomas that can cause visual and vascular complications⁽²⁸⁾. As thyrotrophic cells consist of less than 5 % of all the pituitary gland cells, the TSHomas represent about 2 % of pituitary tumors⁽²⁹⁾, with a prevalence in the population of around one in a million, so they are a rare cause of hyperthyroidism compared with primary hyperthyroidism. However, this secondary hyperthyroidism should be excluded in the differential diagnosis, since not recognizing it can lead to inappropriate treatments with serious consequences for the patient, including hypopituitarism, and complications in the visual field of vision due to compression of the optic chiasm⁽³⁰⁾.

4.2a. Clinical manifestations of Thyrotropinoma

The clinical aspects of patients with pure thyrotropinomas are of hyperthyroidism of variable severity, with diffuse goiter uninodular or multinodular, and approximately in the 72 % of the cases, there is association with any sign or symptom of tumor compression, such as headache, visual disturbance, or hypopituitarism⁽³¹⁾.

It is relatively common that these patients are initially diagnosed as primary hyperthyroid, and treated with antithyroid drugs, radioiodine and/or thyroid surgery, which can alter permanently the thyroid status. In rare cases, thyrotropinomas may be clinically silent and diagnosed as non-secretory adenomas⁽³¹⁾.

A partial or total hypopituitarism was observed in 25 % of cases, with headache in 20-25 %, and visual defects in approximately 50 % of patients, as a result of the suprasellar extension or invasion⁽²⁵⁾.

The most frequent association with concomitant hypersecretion of GH and/or PRL, may cause acromegaly and/or amenorrhea/galactorrea⁽²⁵⁾.

Signs and symptoms of hypopituitarism should be carefully evaluated. The gonadal axis is frequently affected. Menstrual disorders are present in all females with mixed TSH/PRL tumors and in one third of those with pure TSHoma. Central hypogonadism, delayed puberty and decreased libido have been described in male patients with either 'pure' or mixed TSH/PRL adenomas⁽³²⁾.

4.3. Abnormality in the serum binding proteins

In blood, TT4 and TT3 circulate bound to the thyroid hormone binding protein (THBP): TBG, albumin and TTR. This binding serves as extrathyroidal deposit of TH, and ensures an uninterrupted contribution to various tissues⁽³³⁾. Any abnormality in the THBP, either in their concentration or in their affinity to the TH, cause significant alterations in its binding capacity, which lead to changes in the proportion of free and binded hormones in circulation. However, the thyroid status of an individual remains unchanged while the concentration of serum free thyroxine (FT4) remains within normal levels^(33,34).

Changes in the TH caused by abnormalities in the THBP can create confusion in the diagnosis of thyroid dysfunction, since a discordance between the levels of TSH and TT4 is established, and as these abnormalities in the THBP coexist in non thyroidal disease, can also make difficult its diagnosis and treatment⁽³⁴⁾.

Therefore, the identification and quantification of abnormalities in the THBP in patients with discordance between TSH and TT4, added to ambiguous clinical findings, is very important, especially if it lacks a reliable method to measure FT4. This will facilitate the unequivocal diagnosis of thyroid dysfunction in the euthyroid hyperthyroxinemia, euthyroid hypothyroxinemia or euthyroxinemic hyperthyroidism⁽³⁵⁾.

4.4. Specific and nonspecific antibodies

Physicians should be aware of the potential interferents in immunoassays, and always suspect

about inconsistent results with the clinical state of patient, since the wrong interpretation, as a result of such interference, can cause misdiagnosis, unnecessary investigations, delay in the beginning of treatment or, still worse, the instauration of an inadequate treatment⁽³⁶⁾.

Although the RTH and autoimmune thyroid disease can co-exist, the presence of autoantibodies increases the suspicion that circulating substances may interfere with the determination of TH, and more rarely with TSH⁽³⁷⁾. The presence of endogenous both specific and non-specific antibodies, may cause in single or double antibody immunoassays TH, falsely diminished or high values, depending on the nature of the interference and the design of the assay⁽³⁸⁾.

With respect to the nature of the interference, specific endogenous antibodies or autoantibodies have analite-specific interference (anti T4 and T3 antibodies), while non-specific endogenous antibodies or heterophile antibodies have method-specific interference [HAMA (human anti-mouse antibodies) and rheumatoid factor among others⁽³⁸⁻⁴⁰⁾.

With regard to the design of the assay, those that use labeled analogs or one step assays, in which the assays antibodies, the patient serum and the tracer are in contact all along the procedure, are the most susceptible to interference. Meanwhile the two steps methods, where the extraction of the TH is followed by a wash step, which eliminates all other components of the serum before adding the labeled hormone, seem less or no affected by the autoantibodies⁽³⁸⁾.

The prevalence of the interference depends on the method capability for autoantibodies detection. It is low in healthy patients, but it can increase up to 10 % in patients with autoimmune disease, although in most of them there is no an obvious substantial interference⁽³⁸⁾.

Heterophile antibodies produced interference by the common mechanism of promoting the binding between the capture antibody and the signal antibody in the absence of the analyte. This type of non-specific binding result in falsely elevated values. On the other hand if heterophile antibodies bind only to the capture antibody, and affect the variable region or block sterically the binding, even when not directly bind the site recognized by the analyte, the values will be falsely decreased. This type of interference has been described mainly for TSH by immunometric methods, although it

has been also demonstrated for a competitive assay of FT4⁽³⁾. Most current methods use sufficient quantities of HAMA blockers (such as nonspecific murine IgG) to suppress the interference, however, in some specimens with high titers of antibodies, may persist a clinically important interference⁽³⁸⁾.

For electrochemiluminiscent methods using ruthenium (Ru) as luminescent material, there are antibodies that can reduce the amount of emissions produced by excited Ru, producing –both in immunometric as in competitive assays– falsely elevated or diminished values respectively⁽⁴¹⁾.

Ru is a transition metal used in electrical contacts in alloys with Palladium and Platinum with high resistance to wear, in the production of electronic systems with thick film technologies, and in the manufacture of electric contact-resistant. Induction of antibodies anti-Ru could result from the entry of the Ru into the food chain or by exposure to residues on the clothing⁽⁴²⁾.

5. BIOCHEMICAL TESTS FOR THE DIFFERENTIAL DIAGNOSIS BETWEEN THYROTROPINOMA AND RESISTANCE TO THYROID HORMONES

The distinction between TSHoma and RTH using biochemical tests represents a major challenge since no single test is conclusive, so the diagnosis should be based on a combination of tests like determination of TSH, TH, SU α , peripheral markers of the TH action that will be mentioned later, and dynamic tests of stimulation of TSH with TRH and TSH suppression with T3⁽¹⁰⁾.

5.1. Thyrotropin

There is significant overlap in the TSH values among patients with TSHoma and RTH⁽⁴³⁾. Although all patients with TSHoma secrete large amounts of TH, the TSH concentration varies from normal (possibly due to intact feedback) to very high (for a possible increase of their biological activity due to changes in the glycosylation of the molecule), unlike other pituitary secreting adenomas as somatotropinomas and corticotropinomas which always secrete large amounts of hormones⁽⁴⁴⁾.

In addition in the TSHomas there are an increase of the frequency of pulses with normal amplitude, an increase in the basal (non-pulsating release), and a significant change (two hours delay)

in the circadian rhythm, that translates into higher TSH values in the morning⁽⁴⁴⁾.

The RTH in turn is associated with the secretion of different isoforms of TSH in which chains of carbohydrates have a higher percentage of exposed Galactose/N-acetylglucosamine, which leads to an increase in biological activity with the presence of goiter and thyroid hypersecretion, despite normal levels of immunoreactive TSH⁽⁴⁵⁾.

5.2. Thyroid Hormones

In Table 2 are shown different clinical or physiological conditions that presenting with euthyroid hyperthyroxinemia and should be differentiated from TSHoma or RTH.

Most of these conditions can be differentiated with the clinical history of the patient and by measuring FT3 and FT4⁽²⁵⁾. TT4 normal levels were found in several patients with TSHoma, even when they had and severe signs and symptoms of hyperthyroidism. This indicates that the measurement of the free TH is mandatory⁽²⁵⁾.

In the RTH, the concentration serum of rT3 (reverse T3) is high⁽³⁷⁾, while TT4 and TT3 can be slightly to very increased, but maintaining a normal TT3/TT4 relationship⁽²⁾, in contrast to the disproportionate increase of T3 characteristic of autoimmune thyrotoxicosis⁽⁸⁾.

5.3. Thyrotropin α subunit

Absolute values of SU α have excellent sensitivity and specificity, although as it has been said,

TABLE 2. Conditions associated with euthyroid hyperthyroxinemia. Translated and modified from Beck-Peccoz P, Brucker-Davis F, Persani L, Smallridge RC, Weintraub BD 1996 Thyrotropin-secreting pituitary tumors. *Endocr Rev* 17:610-38.

Increased circulating transport proteins (albumin, TTR TBG)
FDH
Abnormal TTR forms
Anti-TSH or TH antibodies
Neonatal period
Systemic illness
Acute psychiatric illness
Drugs (amphetamine, amiodarone, oral contrast agents)
Replacement therapy with LT4 (levothyroxine)
Defects in the conversion of T4 to T3
TSHoma
RTH

individually used could mislead the diagnosis in postmenopausal women, in which the determinations of LH and FSH (who share $SU\alpha$ with TSH) are common⁽⁴³⁾. $SU\alpha$ concentration is a measure of the excessive secretion of TSH in the TSHoma at the expense of an increase in the pulsatility, as intrinsic feature of the adenoma, and not by the action of stimulatory peptides or neurotransmitters⁽⁴⁴⁾.

High levels of $SU\alpha$, or a relationship $SU\alpha$ ($\mu\text{g/L}$) /TSH (mU/L) $\times 10$ greater than 1⁽⁴⁶⁾, are indicative of TSHoma in more than 90 % of the cases, although a normal result does not exclude this diagnosis⁽²⁷⁾.

5.4. Liothyronine suppression test

Werner test that measures the response to high dose of liothyronine (LT_3) is used to assess the presence and extent of hormone resistance, and allows getting a diagnosis of RHT when mutation in $THR\beta$ has not been identified. The aim of using LT_3 instead of LT_4 is its faster action -which reduces the period of administration of the hormone-, and the reduction of symptoms in sensitive individuals due to its shorter half life, although the test is contraindicated in patients with heart problems⁽³⁷⁾.

Oral administration of 100 $\mu\text{g/day}$ of T3 for 10 days, is effective to demonstrate autonomy (TSHoma) or refractoriness (RTH) of the pituitary thyrotrophs to the TH⁽⁵⁾.

In Figure 1 it can be seen the response of the peripheral tissues in normal and RTH individuals to administration of LT_3 . Attenuated SHBG (sex hormone binding globulin) stimulation, and suppression of ferritin, cholesterol, and creatine kinase (CK) is compatible with RTH⁽⁸⁾.

5.5. Thyrotropin-Releasing Hormone stimulation test

The test is performed with 200 to 500 μg TRH intravenously injection, and TSH is measured at 0, 15, 30, 45 and 60 minutes post injection⁽⁴⁷⁾.

RTH patients have a normal or exaggerated response while patients with TSHoma usually show a flat response⁽⁴⁸⁾. Decreased or absent response has good sensitivity and excellent specificity in patients with intact thyroid although a slightly decreased sensitivity after the thyroidectomy⁽⁴³⁾. The lack of response, suggests that TRH receptor may be absent or may not be functional, however is present in the majority of tumors⁽⁵⁾. A normal or

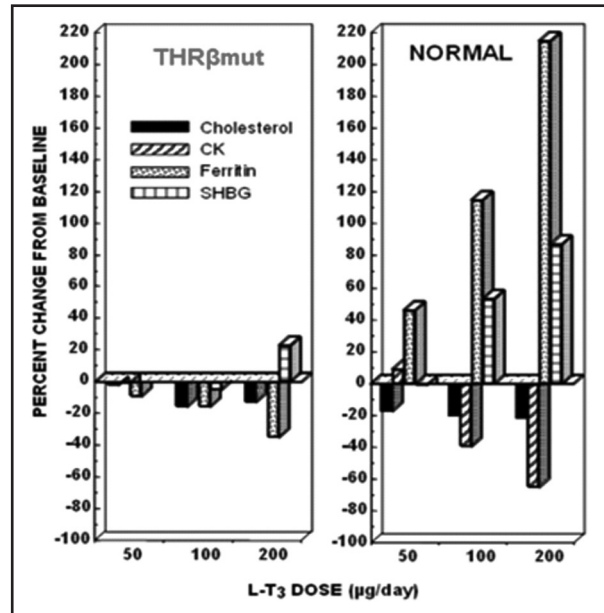


Figure 1. Response of peripheral tissue in normal and RTH-subjects to LT_3 administration. Translated and adapted from Refetoff S, Dumitrescu AM www.thyroidmanager.org. Thyroid hormone resistance syndromes 2012.

partial response would indicate possible etiological or molecular differences between TSHomas^(49,2).

5.6. Se (Selenium)/ Cu (Copper) ratio

Serum Cu levels increase by action of the TH mainly by increase of the synthesis and release of ceruloplasmin by the liver, and decreases due to intracellular competition of the proteins that bind Cu (Metallothionein)⁽⁵⁰⁾.

In the TSHomas, high levels of TH would similarly increase Se and Cu in the serum with only a small net effect on the Se/Cu ratio, while in the RTH, the induction of Cu is abolished due to the dysfunctional $THR\beta$, leading to a higher Se/Cu ratio in these patients⁽⁵⁰⁾.

5.7. Peripheral Thyroid Hormones markers

Some of them are measured *in vivo*, as basal metabolic rate, cardiac systolic time intervals, “Achilles” reflex time, while other as SHBG, cholesterol, angiotensin converting enzyme, soluble interleukin-2receptor, osteocalcin, carboxy terminal telopeptide of type I collagen (ICTP), etc. are measured *in vitro*. In particular, SHBG and bone parameters (ICTP) were satisfactory to differentiate hyperthyroid patients with TSHoma of those with PRTH⁽²⁵⁾. Similar to common forms of

hyperthyroidism, 80 % of patients with TSHoma have high levels of SHBG and ICTP, unlike patients with PRTH having normal values^(51,52).

6. COMPLEMENTARY STUDIES

As well as other tumors of the sellar region, nuclear magnetic resonance (MRI) is the study of images of preference for displaying a TSHoma. The high-resolution computed tomography (CT) is the alternative method in case of contraindications to MRI, as in patients with pace maker. Most of the TSHomas are diagnosed in the stage of macroadenomas, and in two-thirds of the cases there are different degrees of suprasellar extension or invasion of sphenoidal sinus⁽²⁵⁾.

In the RTH, thyroid radioiodine uptake is increased and perchlorate discharge no occurs.

The chronic administration of long-acting somatostatin analogues in patients with central hyperthyroidism, caused a marked decrease in FT3 and FT4 in almost all patients with TSHoma, while patients with PRTH did not respond. Therefore, treatment with them for at

least two months may be useful in the differential diagnosis⁽⁵³⁾.

7-TREATMENT

7.1. Thyrotropinoma

Failure to diagnose a TSHoma can have serious consequences for the patient, as surgery or thyroid ablation, which in turn can lead to increased volume of the tumor becoming an invasive macroadenoma⁽⁵⁾.

The first choice of treatment is pituitary surgery, although usually the complete removal is not possible since these lesions are usually diagnosed in the stage of macroadenoma and are invasive. Only a third of patients achieved cure with this procedure⁽⁵⁴⁾.

Pituitary radiotherapy or treatment with somatostatin analogues are alternative valid if surgery is contraindicated or has previously failed⁽⁵⁴⁾.

Although the efficacy of the conventional radiotherapy in the treatment of these tumors appear as minor than in other pituitary tumors, contin-

TABLE 3. Differential diagnosis between TSHomas and RTH. Adapted from Beck-Peccoz P, Persani L www.thyroidmanager.org. Thyrotropin-secreting pituitary adenomas 2012

Parameter	TSHomas mean ± SE	RTH mean ± SE	P
Female/Male Ratio	1.3	1.4	NS
Familial cases	0 %	82 %	< 0.0001
TSH mU/L	3.0 ± 0.4	2.3 ± 0.3	NS
FT4 pmol/L	38.8 ± 3.9	29.9 ± 2.3	NS
FT3 pmol/L	14.0 ± 1.2	11.3 ± 0.8	NS
Lesions at CT or MRI	99 %	23 %	< 0.0001
Germinal TRβ Mutation	0 %	84 %	< 0.0001
High TSH Biological/immunological	38 %	90 %	NS
High SUα levels	69 %	3 %	< 0.0001
High SUα/TSH ratio	81 %	2 %	< 0.0001
Elevated SHBG and/or ICTP	90 %	8 %	< 0.0001
Blunted TSH response to TRH test	87 %	2 %	< 0.0001
Abnormal TSH response to T3 suppression ^a	100 %	100 % ^b	NS
FT4/FT3 reduction/normalization during long-acting somatostatin analogues ^c	92 %	0 %	< 0.0001

^aWerner's test (80-100 µgT3 for 8-10 days). Quantitatively normal responses to T3, i.e. complete inhibition of both basal and TRH-stimulated TSH levels, have never been recorded in either group of patients.

^bAlthough abnormal in quantitative terms, TSH response to T3 suppression test was qualitatively normal in 45/47 RTH patients.

^cTwo or more injections of somatostatin analogues (e.g., Octreotide-LAR 20-30 mg every month or Lanreotide Autogel 120 mg every 6-8 weeks).

ues to be widely used due to the relatively low cure rate that have the surgical option, and the non existence of other therapeutic methods with proven possibility of definitive cure. Radiosurgery ("Gamma Knife") could have greater efficacy in the treatment of residual lesions, especially in the cavernous sinus, if experience with this method would be less limited⁽³¹⁾.

Treatment with somatostatin analogues revealed that TSH levels are normalized in 70 % of patients, and in 38 % of them, tumor size decreases in 20 %⁽⁵⁵⁾. Only in cases of partial or complete resistance to them, dopamine agonists could be used, either associated or isolated, considering that they have less therapeutical efficiency⁽³¹⁾.

7.2. Resistance to Thyroid Hormones

In the RTH no treatment can correct the defect completely, and would be important not to intervene only with the purpose of normalizing TSH or TH levels, but to make the correct diagnosis, and to avoid surgical and/or antithyroid treatment in asymptomatic patients⁽³⁷⁾.

The 3,5,3'-triiodothyroacetic acid (TRIAc), analog TH, was useful in the treatment of RTH, as well as other drugs like the dextrothyroxine (D-T₄) that can suppress TH concentrations by the suppression of TSH⁽⁵⁶⁾.

Other drugs that decrease TSH concentrations include glucocorticoids, somatostatin and dopamine agonists such as bromocriptine and pergolide which can reduce the concentration of TSH, but lose effectiveness when used over an extended period of time⁽³⁷⁾. Somatostatin analogues have a limited use due to their side effects and the inability to keep the TSH suppressed. They may also cause a paradoxical increase of TSH in some patients⁽⁵⁶⁾.

Patients who have not been properly diagnosed and have surgery or radioiodine thyroid ablation performed to correct the biochemical abnormalities, present a recurrence of goitre, dysfunction of the pituitary-thyroid axis and subsequent hypothyroidism. They should be treated with supraphysiological doses of LT₄ (500 to 1000 µg/day) to reduce the potential risk of thyrotrophic hyperplasia and adenoma⁽¹⁸⁾.

Surgical treatment of goiter is not effective at long term, because on the contrary to autoimmune thyroid disease, in the goiter there is no underlying destructive process and recurrence is significant, so it is more effective to inhibit the growth of the thyroid gland by the suppression of TSH⁽³⁷⁾.

A single supraphysiological daily dose of LT₃, is effective in reducing the size of goiter with notable cosmetic advantages, without side effects. At the moment, and considering the high incidence of failure in the outcomes of the surgery, that seems to be the treatment of choice, with an adjusted LT₃ dose depending on the concentration of TSH, thyroglobulin and size of the goiter⁽⁵⁷⁾.

8. CONCLUSION

The TSHoma and the RTH constitute the main etiologies of syndrome of inappropriate secretion of TSH characterized by non-suppressed TSH and high levels of TH.

The distinction between TSHoma and PRTH can be difficult since both conditions do not present significant differences in age, sex, gender or concentrations of TSH, FT4 and FT3. No individual biochemical test can validate the differential diagnosis that must be based on a combination of evidence and observations: serum concentration of SU α and relationship SU α /TSH, TSH response to TRH, TSH response to suppression with LT₃, genetic analysis for the presence of mutations in the gene of THR β , and history of an affected first-degree relative. The latter is virtually diagnostic of RTH, since the disorder is familial in 80-90 % of cases.

The co-secretion of others (GH, PRL), pituitary hormones, as well as imaging studies such as MRI and CT of pituitary gland can contribute to differential diagnosis.

The importance of the differential diagnosis of these rare clinical conditions, are related to diagnostic and therapeutic challenges that they presented. Therefore, the failure to recognize them as different entities may have deleterious consequences, such as thyroid ablation in patients with central hyperthyroidism, or unnecessary pituitary surgery in those with PRTH. Conversely, early diagnosis and proper treatment of the TSHomas can improve the cure rate and prevent serious neurologic and endocrine complications, visual defects by the compression of the optic chiasm, headaches and hypopituitarism.

9. BIBLIOGRAPHY

1. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, Livolsi VA, Nicoli-Sire P, John R, Ruf J, Smyth PP, Spencer CA, Stockigt JR. 2003. Guidelines Com-

- mittee, National Academy of Clinical Biochemistry. Laboratory medicine practice guidelines: Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid* 13:3-126 (Versión en español: Bergoglio LM, Mestman JH 2005. Guía para el diagnóstico y seguimiento de la enfermedad tiroidea. *Rev Argent Endocrinol Metab* 42:1-134, 2005
2. **Refetoff S, Weiss RE, Usala SJ.** The syndromes of resistance to thyroid hormone. *Endocr Rev* 14:348-99, 1993
 3. **Wu SY, Cohen RN, Simsek E, Senses DA, Yar NE, Grasberger H, Noel J, Refetoff S, Weiss RE.** A novel thyroid hormone receptor-beta mutation that fails to bind nuclear receptor corepressor in a patient as an apparent cause of severe, predominantly pituitary resistance to thyroid hormone. *J Clin Endocrinol Metab* 91:1887-95, 2006
 4. **Lado-Abeal J, Dumitrescu AM, Liao XH, Cohen RN, Pohlenz J, Weiss RE, Lebrethon MC, Verloes A, Refetoff S.** A de novo mutation in an already mutant nucleotide of the thyroid hormone receptor beta gene perpetuates resistance to thyroid hormone. *J Clin Endocrinol Metab* 90:1760-7, 2005.
 5. **Beck-Peccoz P, Brucker-Davis F, Persani L, Smallridge RC, Weintraub BD.** Thyrotropin-secreting pituitary tumors. *Endocr Rev* 17:610-38, 1996
 6. **Ando S, Sarlis NJ, Oldfield EH, Yen PM.** Somatic mutation of TR-beta can cause a defect in negative regulation of TSH in a TSH-secreting pituitary tumor. *J Clin Endocrinol Metab* 86:5572-6, 2001
 7. **Lazar MA.** Thyroid hormone receptors: multiple forms, multiple possibilities. *Endocr Rev* 14:348-99, 1993
 8. **Refetoff S, Dumitrescu AM.** www.thyroidmanager.org Thyroid hormone resistance syndromes, 2012.
 9. **Macchia PE, Takeuchi Y, Kawai T, Cua K, Gauthier K, Chassande O, Seo H, Hayashi Y, Samarut J, Murata Y, Weiss RE, Refetoff S.** Increased sensitivity to thyroid hormone in mice with complete deficiency of thyroid hormone receptor alpha. *Proc Natl Acad Sci USA* 98:349-54, 2001
 10. **Cheng SY.** Thyroid hormone receptor mutations and disease: beyond thyroid hormone resistance. *Trends Endocrinol Metab* 16:176-82, 2005
 11. **Abel ED, Boers ME, Pazos-Moura C, Moura E, Kaulbach H, Zakaria M, Lowell B, Radovick S, Liberman MC, Wondisford F.** Divergent roles for thyroid hormone receptor beta isoforms in the endocrine axis and auditory system. *J Clin Invest* 104:291-300, 1999
 12. **Koenig RJ.** Thyroid hormone receptor coactivators and corepressors. *Thyroid* 8:703-13, 1998
 13. **Refetoff S, Dumitrescu AM.** Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transporters and deiodination. *Best Pract Res Clin Endocrinol Metab* 21:277-305, 2007
 14. **Hayashi Y, Weiss RE, Sarne DH, Yen PM, Sunthornthepvarakul T, Marcocci C, Chin WW, Refetoff S.** Do clinical manifestations of resistance to thyroid hormone correlate with the functional alteration of the corresponding mutant thyroid hormone-beta receptors? *J Clin Endocrinol Metab* 80:3246-56, 1995
 15. **Liu Y, Takeshita A, Misiti S, Chin WW, Yen PM.** Lack of coactivator interaction can be a mechanism for dominant negative activity by mutant thyroid hormone receptors. *Endocrinology* 139:4197-204, 1998
 16. **Fozzatti L, Lu C, Kim DW, Park JW, Astapova I, Gavrilova O, Willingham MC, Hollenberg AN, Cheng SY.** Resistance to thyroid hormone is modulated in vivo by the nuclear receptor corepressor (NCOR1). *Proc Natl Acad Sci USA* 108:17462-7, 2011
 17. **Yoh SM, Chatterjee VK, Privalsky ML.** Thyroid hormone resistance syndrome manifests as an aberrant interaction between mutant T3 receptors and transcriptional corepressors. *Mol Endocrinol* 11:470-80, 1997
 18. **Agrawal NK, Goyal R, Rastogi A, Naik D, Singh SK.** Thyroid hormone resistance. *Postgrad Med J* 84:473-7, 2008
 19. **Abel ED, Kaulbach HC, Campos-Barros A, Ahima RS, Boers ME, Hashimoto K, Forrest D, Wondisford FE.** Novel insight from transgenic mice into thyroid hormone resistance and the regulation of thyrotropin. *J Clin Invest* 103:271-9, 1999
 20. **Mihály E, Fekete C, Légrádi G, Lechan RM.** Hypothalamic dorsomedial nucleus neurons innervate thyrotropin-releasing hormone-synthesizing neurons in the paraventricular nucleus. *Brain Res* 891:20-31, 2001
 21. **Sadow PM, Reutrakul S, Weiss RE, Refetoff S.** Resistance to thyroid hormone in the absence of mutations in the thyroid hormone receptor genes. *Curr Opin Endocrinol Diabetes* 7:253-9, 2000
 22. **Yen PM.** Molecular basis of resistance to thyroid hormone. *Trends Endocrinol Metab* 14:327-33, 2003.
 23. **Wan W, Farboud B, Privalsky ML.** Pituitary resistance to thyroid hormone syndrome is associated with T3 receptor mutants that selectively impair beta2 isoform function. *Mol Endocrinol* 19:1529-42, 2005
 24. **Beck-Peccoz P, Forloni F, Cortelazzi D, Persani L, Papandreou MJ, Asteria C, Faglia G.** Pituitary resistance to thyroid hormones. *Horm Res* 38:66-72, 1992
 25. **Beck-Peccoz P, Persani L.** www.thyroidmanager.org Thyrotropin-secreting pituitary adenomas, 2012.
 26. **Jailer JW, Holub DA.** Remission of Graves' disease following radiotherapy of a pituitary neoplasm. *Am J Med* 28:497-500, 1960
 27. **Prieto-Tenreiro A, Díaz-Guardiola P.** Long term treatment of a thyrotropin-secreting microadenoma with somatostatin analogues. *Arq Bras Endocrinol Metabol* 54:502-6, 2010
 28. **Ando S, Sarlis NJ, Krishan J, Feng X, Refetoff S, Zhang MQ, Olfield EH, Yen PM.** Aberrant alternative splicing of thyroid hormone receptor in a TSH-secreting pituitary tumor is a mechanism for hormone resistance. *Mol Endocrinol* 15:1529-38, 2001
 29. **Socin HV, Chanson P, Delemer B, Tabarin A, Rohmer V, Mockel J, Stevenaert A, Beckers A.**

- The changing spectrum of TSH-secreting pituitary adenomas: diagnosis and management in 43 patients. *Eur J Endocrinol* 148:433-42, 2003
30. **Kienitz T, Quinkler M, Strasburger C J and Ventz M.** Long-term management in five cases of TSH-secreting pituitary adenomas: a single center study and review of the literature. *Eur J Endocrinol* 157:39-46, 2007
 31. **Abucham J, Vieira TC.** Adenomas Hipofisários Produtores de Glicoproteínas: Patogênese, Diagnóstico e Tratamento. *Arq Bras Endocrinol Metabol* 49:657- 73, 2005
 32. **Beck-Peccoz P, Lania A, Beckers A, Chatterjee K, Wemeau JL.** European Thyroid Association Guidelines for the Diagnosis and Treatment of Thyrotropin-Secreting Pituitary Tumors. *Eur Thyroid J* 2:76-82, 2013
 33. **Schussler GC.** The thyroxine-binding proteins. *Thyroid* 10:141-9, 2000
 34. **Bartalena L.** Recent achievements in studies on thyroid hormone binding proteins. *Endocr Rev* 11:47-60, 1990
 35. **Bhatkar SV, Rajan MG, Velumani A, Samuel AM.** Thyroid hormone binding protein abnormalities in patients referred for thyroid disorders. *Indian J Med Res* 120:160-5, 2004
 36. **Tan MJ, Tan F, Hawkins R, Cheah WK, Mukherjee JJ.** A hyperthyroid patient with measurable thyroid-stimulating hormone concentration - a trap for the unwary. *Ann Acad Med Singapore* 35:500-3, 2006
 37. **Weiss RE, Dumitrescu A, Refetoff S.** Approach to the patient with resistance to thyroid hormone and pregnancy. *J Clin Endocrinol Metab* 95:3094-102, 2010
 38. **Després N, Grant AM.** Antibody interference in thyroid assays: a potential for clinical misinformation. *Clin Chem* 44:440-54, 1998
 39. **Kohse KP, Wisser H.** Antibodies as a source of analytical errors. *J Clin Chem Clin Biochem* 28:881-92, 1990
 40. **Levinson SS.** Antibody multispecificity in immunoassay interference. *Clin Biochem* 25:77-87, 1992
 41. **Ohba K, Noh JY, Unno T, Satoh T, Iwahara K, Matsushita A, Sasaki S, Oki Y, Nakamura H.** Falsely elevated thyroid hormone levels caused by anti-ruthenium interference in the Elecsys assay resembling the syndrome of inappropriate secretion of thyrotropin. *Endocr J* 59:663-7, 2012
 42. **Brucker-Davis F, Oldfield EH, Skarulis MC, Doppman JL, Weintraub BD.** Thyrotropin-secreting pituitary tumors: diagnostic criteria, thyroid hormone sensitivity, and treatment outcome in 25 patients followed at the National Institutes of Health. *J Clin Endocrinol Metab* 84:476-86, 1999
 43. **Buijs MM, Gorgels JP, Endert E.** Interference by anti-ruthenium antibodies in the Roche thyroid-stimulating hormone assay. *Ann Clin Biochem* 48: 276-81, 2011
 44. **Roelfsema F, Pereira AM, Keenan DM, Veldhuis JD, Romijn JA.** Thyrotropin secretion by thyrotropinomas is characterized by increased pulse frequency, delayed diurnal rhythm, enhanced basal secretion, spikiness, and disorderliness. *J Clin Endocrinol Metab* 93:4052-7, 2008
 45. **Persani L, Borgato S, Romoli R, Asteria C, Pizzocardo A, Beck-Peccoz P.** Changes in the degree of sialylation of carbohydrate chain modify the biological properties of circulating thyrotropin isoforms in various physiological and pathological states. *J Clin Endocrinol Metab* 83:2486-92, 1998
 46. **Kourides IA, Ridgway EC, Weintraub BD, Bigos ST, Gershengorn MC, Maloof F.** Thyrotropin-induced hyperthyroidism: use of alpha and beta subunit levels to identify patients with pituitary tumors. *J Clin Endocrinol Metab* 45:534-43, 1977
 47. **Elston MS, Conaglen JV.** Clinical and biochemical characteristics of patients with thyroid-stimulating hormone-secreting pituitary adenomas from one New Zealand centre. *Intern Med J* 40:214-9, 2010
 48. **Khandwala H, Lee C.** Inappropriate secretion of thyroid-stimulating hormone. *CMAJ* 175:351, 2006.
 49. **Brucker-Davis F, Skarulis MC, Grace MB, Benichou J, Hauser P, Wiggs E, Weintraub BD.** Genetic and clinical features of 42 kindreds with resistance to thyroid hormone. The National Institutes of Health Prospective Study. *Ann Intern Med* 123:572-83, 1995
 50. **Mittag J, Behrends T, Nordström K, Anselmo J, Vennström B, Schomburg L.** Serum copper as a novel biomarker for resistance to thyroid hormone. *Biochem J* 443:103-9, 2012
 51. **Beck-Peccoz P, Roncoroni R, Mariotti S, Medri G, Marcocci C, Brabant G, Forloni F, Pinchera A, Faglia G.** Sex hormone-binding globulin measurement in patients with inappropriate secretion of thyrotropin (IST): evidence against selective pituitary thyroid hormone resistance in nonneoplastic IST. *J Clin Endocrinol Metab* 71:19-25, 1990
 52. **Persani L, Preziati D, Matthews CH, Sartorio A, Chatterjee VK, Beck-Peccoz P.** Serum levels of carboxyterminal cross-linked telopeptide of type I collagen (ICTP) in the differential diagnosis of the syndromes of inappropriate secretion of TSH. *Clin Endocrinol (Oxf.)* 47:207-14, 1997.
 53. **Mannavola D, Persani L, Vannucchi G, Zanardelli M, Fugazzola L, Verga U, Facchetti M, Beck-Peccoz P.** Different responses to chronic somatostatin analogues in patients with central hyperthyroidism. *Clin Endocrinol (Oxf)* 62:176-81, 2005
 54. **Berker D, Isik S, Aydin Y, Tutuncu Y, Akdemir G, Ozcan HN, Guler S.** Thyrotropin secreting pituitary adenoma accompanying a silent somatotropinoma. *Turk Neurosurg* 21:403-7, 2011
 55. **Chanson P, Weintraub BD, Harris AG.** Octreotide therapy for thyroid-stimulating hormone-secreting pituitary adenomas. A follow-up of 52 patients. *Ann Intern Med* 119:236-40, 1993
 56. **Dong Q, Gong CX, Gu Y, Su C.** A new mutation in the thyroid hormone receptor gene of a Chinese family with resistance to thyroid hormone. *Chin Med J (Engl)* 124:1835-9, 2011
 57. **Anselmo J, Refetoff S.** Regression of large goiter in a patient with resistance to thyroid hormone by every other day treatment with triiodothyronine. *Thyroid* 14:71-4., 2004