



Clinical and Hormonal Characteristics of Patients with Syndrome of Inappropriate Secretion of Thyrotropin

Uygunsuz Tirotropin Sendromlu Hastaların Klinik ve Hormonal Özellikleri

Şefika Burçak Polat, Cevdet Aydın, Gülfem Kaya, Neslihan Çuhacı, Reyhan Ersoy, Bekir Çakır

Ankara Atatürk Training and Research Hospital, Clinic of Endocrinology, Ankara, Turkey

Abstract

Purpose: Normal or elevated thyrotropin (TSH) levels in the presence of elevated thyroxine is defined as syndrome of inappropriate secretion of TSH. The two main clinical conditions that can lead to this syndrome are TSH-secreting adenoma (TSHoma) and resistance to thyroid hormone. Establishing the correct diagnosis is crucial in order to decide on the most appropriate treatment option. Herein, we present the data of seven patients who were hospitalized for the differential diagnosis of the two clinical entities.

Material and Method: Our database was reviewed for patients diagnosed with syndrome of inappropriate secretion of TSH in our hospital between 2010 and 2014. After exclusion of the other rare causes, seven patients who were hospitalized for the differential diagnosis of TSHoma and resistance to thyroid hormone were included.

Results: The final diagnosis was resistance to thyroid hormone in four patients, TSHoma in two and equivocal in one. Two patients diagnosed with TSHoma were operated and had positive staining with TSH. Both of the TSHoma cases had macroadenoma on pituitary magnetic resonance imaging and visual field defect, while two of four patients with resistance to thyroid hormone had microadenoma. Alpha-subunit/TSH molar ratio was above 1 in all patients diagnosed with TSHoma while it exceeded 1 in two patients with the final diagnosis of resistance to thyroid hormone. Thyrotrophin-releasing hormone stimulation test revealed a blunted response in all patients with TSHoma and a positive response in all with resistance to thyroid hormone.

Discussion: Differential diagnosis of resistance to thyroid hormone and TSHoma can be a clinical challenge and requires complex hormone testing and imaging methods. Since incidental pituitary tumors are not rare, presence of an adenoma should not rule out the diagnosis of resistance to thyroid hormone.

Keywords: Syndrome of inappropriate thyrotropin secretion, thyrotropin-secreting adenoma, thyroid hormone resistance

Öz

Amaç: Bir hastada artmış serum serbest tiroksin varlığında normal veya yüksek tirotropin (TSH) düzeyi uygunsuz TSH sendromu olarak adlandırılır. Bu sendroma yol açabilecek iki önemli hastalık; TSH sekrete eden hipofiz adenomu (TSHoma) ve tiroid hormon direncidir. Ayırıcı tanıyı doğru yapmak, en uygun tedavi seçeneğini belirlemek açısından önemlidir. Burada hospitalize edilerek iki klinik antitenin ayırıcı tanısı yapılan yedi hasta sunulmuştur.

Gereç ve Yöntem: 2010-2014 yılları arasında uygunsuz TSH tanısı ile takip edilen hastaların verileri gözden geçirildi.

Bulgular: Yedi hastanın dördünde kesin klinik tanı tiroid hormon direnci, iki hastada TSHomaydı. Bir hastada klinik tanı netleştirilemedi. TSHoma tanısı ile takip edilen iki hastada opere oldu ve adenom TSH ile pozitif boyandı. TSHoma olgularının her ikisinde de makroadenom ve görme alanı defekti saptanırken, tiroid hormon direnci olgularının ikisinde de mikroadenom tespit edildi. Alpha-subunit/TSH molar oranı TSHomalı hastaların tümünde ve dirençli hastaların ikisinde birin üzerinde saptandı. Tüm tiroid hormon direnci tanısı konulan hastalarda tirotropin serbestleştirici hormon uyarısına pozitif TSH yanıtı mevcuttu.

Tartışma: Tiroid hormon direnci ve TSHoma ayırıcı tanısı klinisyen için zorlayıcıdır ve kompleks hormonal testler ve görüntüleme yöntemleri gerektirir. İncidental hipofiz tümörleri sıklıkla bu nedenle adenom varlığı direnç tanısını dışlamamalıdır.

Anahtar kelimeler: Uygunsuz tirotropin sendromu, tirotropin sekrete eden adenoma, tiroid hormon direnci

Introduction

Normal or elevated thyrotropin (TSH) level in the presence of elevated thyroxine (T_4) is defined as syndrome of inappropriate secretion of thyrotropin TSH (SITSH) (1). Two main clinical conditions that can lead to this syndrome are TSH-secreting adenoma (TSHoma) and resistance to thyroid hormone (RTH) (2). The other

rare causes include measurement errors due to interfering antibodies against TSH, T_4 or triiodothyronine (T_3), amiodarone therapy, familial dysalbuminemic hyperthyroxinemia, and acute psychiatric illnesses (3). An adequate review of the patient's history is usually adequate for ruling out medications, systemic and acute psychiatric illnesses as causes of SITSH. RTH is a clinical

entity characterized by decreased sensitivity of thyroid hormone receptor (TR) β to the thyroid hormone. The syndromes of RTH are classified into two major types: generalized RTH (GRTH), and pituitary RTH (PRTH). In GRTH, the responsiveness to thyroid hormone is reduced in all target tissues, including the pituitary. In PRTH, which differs from GRTH, the apparent manifestations of thyroid hormone excess are at the level of peripheral tissues (4). The incidence of RTH is reported as 1 in 50,000 live births and most of the cases are inherited in an autosomal dominant fashion whereas around 15% of the cases are sporadic (5). The clinical picture changes from asymptomatic cases with only isolated biochemical abnormality to hypo-hyperthyroidism symptoms. Most of the patients are clinically euthyroid (6). The most prevalent clinical findings are goiter (65-95%), hyperactivity (33-68%) and tachycardia (33-75%). In rare cases, growth retardation, retarded bone growth, mental retardation, sensory neural deafness or nystagmus can be detected (7).

There is no specific treatment that can improve TR β function. In most cases, hypothyroidism is compensated by elevated free hormone levels, but that compensation is not observed in patients with limited thyroid reserve due to prior destructive therapies. In such cases, hormone replacement can be given to keep TSH in normal or near normal ranges. Large glands can be treated with high doses of L-triiodothyronine (LT3) (8).

TSHoma is a rare cause of hyperthyroidism. It consists of less than 2% of all pituitary adenomas (9). It should be considered in all patients with hyperthyroidism and diffuse goiter without extrathyroidal signs of Graves' disease. TSHoma secretes the hormone autonomously that TSH cannot be stimulated with thyrotropin-releasing hormone (TRH) or inhibited by exogenous thyroid hormone. Biologic activity of the secreted TSH varies and serum TSH level in those patients can change from normal to significantly high values. In 25% of patients, there is cosecretion of another pituitary hormone along with TSH and it is mostly growth hormone (GH) or prolactin (PRL) (10). In addition to classical thyrotoxicosis symptoms, diffuse goiter, visual field defects, headache, menstrual disorder, and galactorrhea may be present. Transsphenoidal surgery is the most appropriate primary therapy (11). However, surgical cure is obtained in only one third of patients since most of them are macroadenoma and, post operatively, the patients need additional therapies such as bromocriptine or somatostatin analogues. Octreotide normalizes hormone levels in more than 90% of patients and decreases the tumor size (11). Differential diagnosis of TSHoma and RTH is often difficult in the clinical basis and requires complex hormone tests and imaging methods. Establishing the correct diagnosis is crucial in order to decide on the most appropriate treatment option. Delay in diagnosis in a TSHoma case may lead to increase in size of the tumor and would decrease the success of the primary surgery since those tumors are already large at the time of diagnosis. Misdiagnosis in a RTH case would lead to unnecessary surgery or radioiodine therapy. Herein, we present clinical and laboratory data of seven patients who were hospitalized for the differential diagnosis of the two clinical entities.

Materials and Methods

Our database was reviewed for patients diagnosed with SITSH at our hospital between 2010 and 2014. After exclusion of the other rare causes, seven patients who were hospitalized for the differential diagnosis of TSHoma and RTH were included. The hormone tests that were performed in order to differentiate the two clinical entities were as follows; TRH stimulation test, T₃ suppression test, alpha-subunit/TSH molar ratio and sex hormone-binding globulin (SHBG) determination. Lack of stimulation with TRH (less than 100%) and unsuppressed TSH with T₃ (after 3 days 50, 3 days 100 and 3 days 200 mcg T₃ administration TSH >1 μ U/L), increased baseline SHBG and alpha-subunit/TSH molar ratio (>1) and radiologic evidence of a pituitary adenoma on magnetic resonance imaging (MRI) were considered as supportive for the diagnosis of TSHoma. Stimulation of TSH by TRH and suppression by T₃, low alpha-subunit/TSH, and negative pituitary imaging were considered supportive for the diagnosis of RTH. Genetic testing for TR β gene mutation was performed in selected cases. All patients were screened for adenoma by pituitary MRI. In addition to that, thyroid ultrasonography (USG) was performed for each patient by the same experienced endocrinologist.

The levels of TSH, free triiodothyronine (fT₃), free thyroxine (fT₄), thyroid autoantibodies [thyroid peroxidase antibody (anti-TPO) and thyroglobulin antibody (anti-Tg)], and thyroglobulin were measured in all patients using chemiluminescence methods (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA and Unicel DXI 800, Beckman Coulter, Brea, CA). The normal ranges for TSH, fT₃ and fT₄ were 0.4-4 μ U/mL, 1.57-4.71 pg/mL and 0.61-1.12 ng/dL, respectively.

Results

Table 1 summarizes the demographic, clinical, laboratory and the radiologic data of the seven patients. Three patients were female and 4 were male. Clinically, two patients were asymptomatic, 3 had tachycardia and weight loss and 1 had goiter. No patient had evidence of ophthalmopathy or dermopathy. The youngest patient was 20 and the oldest was 52 years of age. None of the patients received anti-thyroid therapy with thionamides, had thyroid operation or radioactive iodine treatment. The final diagnosis was RTH in 4 patients, TSHoma in two and equivocal in one patient. In all 4 patients with RTH, there was inappropriate TSH hormone profile in at least 1 first-degree relative.

Both of the TSHoma cases had macroadenoma on MRI (Figure 1) and visual field defect while 2 of 4 patients with RTH had microadenoma on MRI (Figure 2). The patients clinically diagnosed with TSHoma were operated and histopathological evaluation revealed adenoma with positive TSH staining. TSHoma cases had positive imaging with In-111 octreotide scintigraphy (Figure 3).

In all cases, serum fT₄ was elevated with unsuppressed TSH values. Two patients had elevated TSH while 5 had normal range values that were inappropriate for their elevated fT₄ levels. All the patients had enlarged thyroid volumes measured by USG. Alpha-subunit/TSH molar ratio exceeded 1 in 2 patients with the final diagnosis of RTH and was above 1 in all patients diagnosed with

TSHoma. TRH stimulation test revealed a blunted response in all patients with TSHoma and a positive response in all patients with THR. SHBG was at least 1.5 times higher than normal in patients with TSHoma, whereas it was within the normal range in RTH patients. In all patients with RTH, TSH was suppressed $<1 \mu\text{IU/mL}$ after nine days of T_3 administration. We could not perform the test in 2 patients with the final diagnosis of TSHoma since they had severe tachycardia and could not tolerate T_3 replacement. Case 5 was a diagnostic challenge since he had clinical and hormonal features of both diseases. He was a 20-year-old male admitted with the complaint of failure to gain weight. His body mass index was 18 and his weight was stable for the last three years. His thyroid function tests (TFT) was compatible with SITSH. He was not using any drug that could interfere with the TFT. The results suggestive of TSHoma were: 1) macroadenoma 1.3 cm in

diameter detected with pituitary MRI, 2) alpha subunit/TSH molar ratio of 4.1, 3) negative genetic analysis, 4) one normal thyroid function test result when he was 14 years old (all tests performed by then were abnormal). The results suggestive of RTH were: 1) TSH stimulation with TRH and significant suppression with T_3 , 2) negative octreotide scan, 3) regression in adenoma size on MRI performed 6 months after the initial imaging (1.3→1 cm) without any treatment, 4) TSH value not being affected significantly after 3 days of short acting octreotide. We screened heterophile antibody against TSH which could interfere test results and it was negative. In that case, we decided to follow up the patient with pituitary imaging in every 6 months together with anterior pituitary hormone profile.

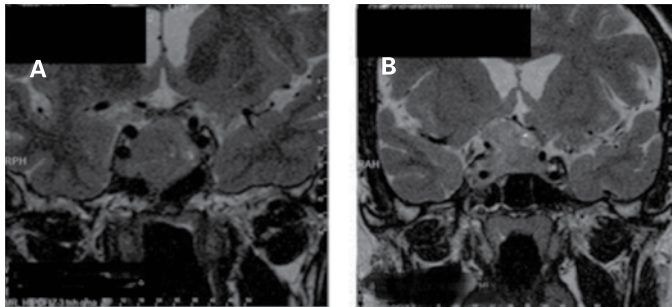


Figure 1. Macroadenomas in two patients with thyrotropin-secreting adenoma detected with pituitary magnetic resonance imaging



Figure 2. Macroadenoma of the 4th patient diagnosed with resistance to thyroid hormone

Table 1. Demographic, clinical, laboratory and the radiologic data of all cases

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age	30	34	52	32	20	47	35
Sex	F	F	M	M	M	F	M
Symptom	Goiter	Tachycardia	Tachycardia and weight loss	Tachycardia	Failure to gain weight	None	None
Inappropriate TSH syndrome in family	+ (Sibling)	+ (Sibling)	-	+ (Parent)	-	-	+ (Sibling)
Goiter on thyroid ultrasonography	+	+	+	+	+	+	+
TSH (0.4-4 mIU/L)	1.32	4.5	1.8	1.3	3.8	4.67	1.25
fT ₃ (2.0-4.4 pg/mL)	4.9	5.2	10.8	3.9	6.2	15.49	5.32
fT ₄ (0.9-1.7 ng/dL)	2.44	3.2	3.5	3.0	2.25	5.4	1.99
Genetic test	∅	∅	∅	Positive	Negative	∅	∅
αsubunit/TSH	0.43	0.8	14	2.5	4.1	6	1.5
TSH stimulation with TRH (uIU/L)	x11	x10	x1.6	x10.2	x5	x1.9	x12
TSH after T ₃ suppression test (mIU/L)	0.1	0.1	-	0.02	0.01	-	0.11
Heterophile antibody	-	-	-	-	Negative	-	-
Hipofiz MRI	None	None	Macroadenoma	Microadenoma	Macroadenoma	Macroadenoma	Microadenoma
Clinical diagnosis	RTH	RTH	TSHoma	RTH	?	TSHoma	RTH

F: Female, M: Male, TSH: Thyrotropin, TRH: Thyrotropin-releasing hormone, T₃: Triiodothyronine, fT₃: Free triiodothyronine, fT₄: Free thyroxine, MRI: Magnetic resonance imaging, RTH: Resistance to thyroid hormone, TSHoma: Thyrotropin-secreting adenoma

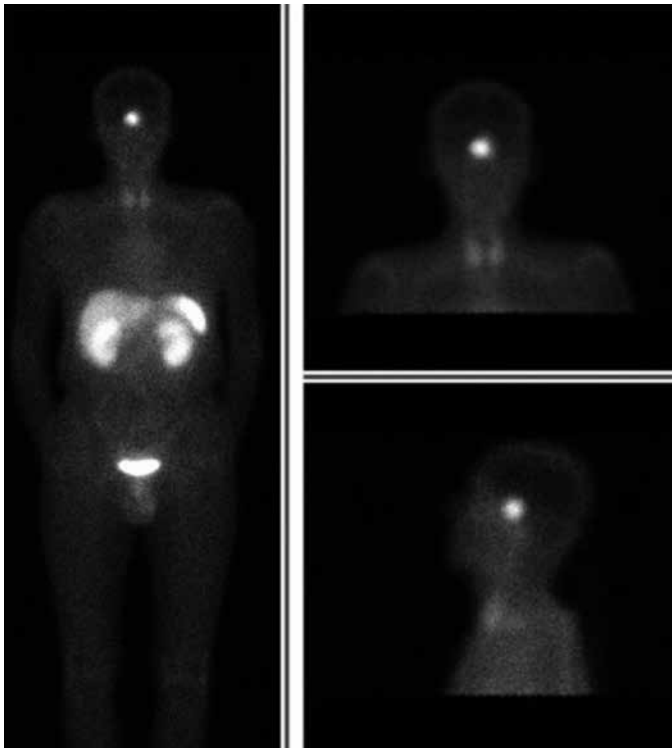


Figure 3. Appearance of the macroadenoma on octreotide scan in case 6

Discussion

SITSH is an unusual condition of normal or elevated secretion of TSH in the presence of high levels of thyroid hormones. Early diagnosis is important to increase the success rate in TSHoma cases, but the clinician should be confident that the pituitary mass is not an incidentaloma to avoid the unnecessary surgery and related morbidity. For the RTH patients, incidence of nonfunctioning pituitary adenomas should at least equal to that of the normal population. However, if RTH is associated with thyrotroph hyperplasia and this predisposes to adenoma formation, the incidence of RTH-associated pituitary tumors may be even greater (12,13). In addition, there are pseudo adenoma cases in the literature in patients with pituitary hyperplasia due to primary hypothyroidism or hypergonadotropic hypogonadism (14,15,16). In a report by Gurnell et al. (13) pituitary hyperplasia in a patient with RTH was reversible and regressed after thyroid hormone replacement. This suggestion might be true for our two patients with RTH who had microadenoma on MRI and one patient with macroadenoma whose diagnosis was equivocal. On the other hand, in rare cases with no visible adenoma, there might be a small microadenoma which could be missed on MRI or which is ectopically located. In a recent study, 60% of TSHomas were microadenomas (17,18) and in one case, there was an ectopic TSHoma that was localized in the pharyngeal region (19). Hormonal evaluation in patients with SITSH includes basal hormone and dynamic tests. First, the clinician should rule out other rare causes, such as interfering antibodies against TSH. Then comes the three steps; serum alphasubunit/TSH molar ratio, TRH stimulated TSH measurement and T₃ suppression test.

Alpha subunit is increased in 70% while alpha subunit/TSH molar ratio is increased in 80% of patients with TSHoma. There is no universally accepted cut off value for the molar ratio and it changes according to sex and menopausal status. For instance in post menopausal women, it is accepted as normal at values up to 29 whereas 0.9 is the suggested cut off in men (20,21). In our cases the molar ratio was above 1 in all patients with TSHoma, but it was also above 1 in 2 patients with RTH. This test alone is not diagnostic for TSHoma, but it is reliable especially when alpha subunit level is significantly high. TRH stimulation test is another dynamic test used during clinical evaluation of patients with SITSH. In RTH, we expect more than two-fold increase in TSH after TRH injection. In some resistance cases, there may be an exaggerated increase as it is observed in primary hypothyroidism. In TSHoma, TRH stimulation fails to cause more than a two-fold rise in TSH secretion in 80% of cases. However, 20% of patients with TSH-secreting tumors have normal TSH secretion in response to TRH stimulation (21). T₃ suppression test is another dynamic test which can be used in differential diagnosis. Combination of T₃ suppression and TRH stimulation tests increases the specificity and the sensitivity of the diagnostic work up (22). However, it is not possible to perform this test in patients with severe tachycardia, coronary heart disease or heart failure. Screening family members and measurement of markers of peripheral thyroid hormone action are other helpful methods in separating the two inappropriate TSH secretion entities. Since RTH is dominantly inherited, the hormonal abnormalities in siblings or parents supported our diagnosis in four cases with RTH. However, around 15-20% of all RTH cases are sporadic, thus, negative family history does not rule out the clinical condition. Measurement of SHBG, cholesterol and ferritin levels might be helpful. Exceptions are the findings of normal SHBG levels in patients with mixed GH/TSH adenoma due to the inhibitory action of GH on SHBG synthesis and secretion, and of high SHBG in RTH patients treated with estrogens or showing profound hypogonadism (21). Another parameter that can be useful for the differential diagnosis is the evaluation of the sensitivity to somatostatin analog. More than 90% of TSHomas are sensitive and two or more administrations of long-acting analog are usually sufficient to induce significant decreases or normalization of circulating free thyroid hormone (22). Octreotide scan is not standardized and routinely used in clinics but may be beneficial in cases whose other test results are equivocal. Genetic testing can be performed for detecting TR β mutations in patients with suspicion of RTH; it is practical and may save time and costs for the other diagnostic procedures but, unfortunately, it is not available in every medical center. In one study including 99 patients with SITSH, RTH was diagnosed in 68 patients. In 16 (23.5%) of 68 patients with resistance, genetic testing was negative (23). Therefore, it should be kept in mind that negative TR β mutation does not rule out the diagnosis of RTH. In such cases, there may be a novel mutation which has not been defined yet or a mutation in the alpha receptor.

Conclusion

In summary, standard diagnostic testing may not distinguish a TSHoma from thyroid hormone resistance especially in cases

with incidental pituitary adenomas. Diagnostic work up can be exhausting requiring dynamic hormone tests and imaging methods. If the diagnosis is still equivocal, observation of the patient with frequent clinical evaluation and pituitary imaging can be preferred or the clinician may try long-acting octreotide therapy and follow the hormonal response and change in the mass size.

Disclosure

We want to thank Mr. S. Refetoff and his colleagues for making the genetic analysis and contributing to the clinical evaluation of case 5.

Ethics

Informed Consent: Consent form was filled out by all participants. Peer-review: Externally and Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Şefika Burçak Polat, Cevdet Aydın, Concept: Şefika Burçak Polat, Cevdet Aydın, Design: Gülfem Kaya, Data Collection or Processing: Reyhan Ersoy, Analysis or Interpretation: Bekir Çakır, Literature Search: Neslihan Çuhacı, Writing: Şefika Burçak Polat, Neslihan Çuhacı.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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