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Three Cases With Inappropriate TSH Syndrome

Uygunsuz TSH Sendromlu Üç Olgu

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Abstract

Inappropriate thyroid-stimulating hormone (TSH) syndrome or central hyperthyroidism is a rare disorder characterized by inappropriately normal or elevated levels of TSH and elevated levels of T3 and T4. The syndrome is associated with TSH-secreting pituitary adenoma (TSHoma) or thyroid hormone resistance (THR). Thyroid-releasing hormone stimulation test and T3 suppression test can be useful for the differential diagnosis of central hyperthyroidism. In the present study, we report three cases of inappropriate TSH syndrome diagnosed after TRH stimulation and T3 suppression tests. *Turk Jem 2012; 16: 105-8*

Key words: Inappropriate TSH syndrome, thyroid hormone resistance, TSHoma

Özet

Uygunsuz tiroid stimülan hormon (TSH) sendromu veya santral hipertiroidizm T3 ve T4 yüksekliği ile birlikte uygunsuz olarak normal veya yüksek TSH ile karakterize nadir bir hastalıktır. Bu sendrom TSH sekrete eden hipofiz adenomu (TSHoma) veya tiroid hormon rezistansı (THR) ile ilişkilidir. Tiroid Releasing Hormon stimülasyon testi ve T3 supresyon testi santral hipertiroidinin ayırıcı tanısında faydalı olabilir. Bu olgu sunumunda TRH stimülasyon ve T3 supresyon testi sonrası uygunsuz TSH sendromu tanısı konan üç olguyu sunduk. *Türk Jem 2012; 16: 105-8*

Anahtar kelimeler: Uygunsuz TSH sendromu, tiroid hormon rezistansı, TSHoma

Introduction

In most patients with hyperthyroidism, T_3 and T_4 levels are high while thyroid-stimulating hormone (TSH) is too low to detect. Some patients may have inappropriately normal or elevated levels of TSH, which is called inappropriate secretion of TSH or central hyperthyroidism (1). Ones likely laboratory errors are excluded, the differential diagnosis should be between TSH-secreting pituitary adenoma (TSHoma) and thyroid hormone resistance (THR) in inappropriate TSH secretion (2). Although THR is usually an autosomal dominant disorder caused by mutations in the thyroid hormone receptor β gene, 15% of the cases are sporadic (1,3). Its incidence has been reported to be 1/50.000 (1). Patients with THR exhibit THR in the pituitary and/or peripheral tissues (4). Clinically, THR has two forms. In the first form known as generalized resistance to thyroid hormone (GRTH), pituitary and peripheral tissues show resistance to T_3 while in the second form known as pituitary resistance to thyroid hormone (PRTH), there is pituitary resistance to T_3 (5). In patients with PRTH, increased peripheral response to thyroid hormones has also been described (4).

Among conditions causing hyperthyroidism, TSHoma is considered to be extremely rare. This adenoma is present in less than 1% of pituitary adenoma patients. A possible explanation for being so rare is that thyrotropic cells comprise less than 5% of all pituitary cells (6). Its prevalence has been reported to be one in a million (1).

In this study, we discuss the differential diagnosis of 3 cases with inappropriate TSH syndrome.

Case 1

A 29-year-old female patient presented with thyroid function disorder. In her history, laboratory tests revealed a serum free T_3 of 5.1 pg/ml (normal: 1.4-4.4 pg/ml), serum free T4 of 2.7 ng/dl (normal: 0.7-1.8 ng/dl) and serum TSH of 2.2 μIU/ml (normal: 0.4-4.6 μIU/ml). She was prescribed propylthiouracil (PTU) 150 mg tid per day. A month

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later, upon observing that FT4 had increased to 3.9 ng/dl, PTU dose was doubled. This was repeated every month and PTU dose was increased up to 600 mg tid per day. As euthyroidism was not achieved despite a high-dose PTU treatment, she was referred to our endocrinology department. In her physical examination, her thyroid gland was diffuse large. The patient was clinically euthyroid and there was no family history of thyroid disease. PTU treatment was then stopped. After 3 weeks, in the laboratory tests, FT_3 was 4.6 pg/ml, FT_4 was 2.7 ng/dl and TSH was 1.8 µIU/ml. Thyroid autoantibodies including antimicrosomal autoantibodies and antithyroglobulin autoantibodies were negative. Ultrasonography revealed that both lobes were large while scintigraphy showed that the activity distribution increased homogeneously. In the TRH test, TSH responses were found as 1.4, 14.8 and 10.5 µIU /ml during the 0^{th},30^{th} and 60^{th} minutes, respectively. In T_3 suppression test, 50 µg, 100 µg and 200 µg of T_3, divided into two equal doses for each day, were administered to the patient respectively for three days. Peripheral markers of thyroid hormone response were analyzed during basal period and on the 3rd, 6th and 9th days; and they were found to be within the normal levels (Table 1). At the end of the test, TRH test was repeated; and TSH responses were found to be 0.08, 0.9 and 0.5 µIU/ml during the 0th, 30^{th} and 60th minutes, respectively, which was a two-fold increase. Magnetic resonance image (MRI) of the pituitary was normal. The thyroid function tests of the patient's first degree relatives –father and three siblings- were found to be normal. GRTH was considered in the patient, however, no treatment was recommended since the patient was clinically euthyroid.

Case 2

A 33-year-old female patient presented to another clinic with complaints of weight loss and menstrual irregularity. Her laboratory tests revealed a serum prolactin of 40.3 ng/mL (4.0-15.2 ng/mL); T_3 of 6.2 pg/ml, T_3 of 2.5 ng/ml and TSH of 6.2 µIU/ml. PTU was started. After detecting a pituitary macroadenoma measuring 4 x 5 x 7 cm on pituitary MRI, transsphenoidal subtotal excision of pituitary adenoma was performed. She received postoperative radiotherapy and subsequently developed amenorrhea. Up to two months before contacting us, the patient had continued to take PTU. She presented to our endocrinology department with a complaint of amenorrhea. In her ultrasonography, the right thyroid lobe was measured 22 x 29 x 56 mm, and the left lobe was measured 21 x 24 x 53 mm in size. Laboratory results were as follows: FT_3: 7.8 pg/ml, FT_4: 3.1 ng/dl, TSH: 2.0 µIU/ml, FSH: 2.6µIU/ml, LH: 0.6 µIU/ml, PRL: 15.8 ng/ml, Cortisol: 3.9µg/dl, GH: 4.4 ng/ml (0.1-7.02), IGF-1:150 ng/ml (140-405), SHBG: 202 mmol/l (30-100), TSH alpha subunit level: 1.32 mUI/ml(0.05-0.9), alpha subunit/ molar TSH:>1. TSH values measured in TRH stimulation test were: 0 minute: 2.2, 30 minutes: 2.2, 60 minutes: 2.3, 90 minutes: 2.5 and 120 minutes: 2.6. No sufficient response was observed to insulin tolerance test and GnRH test. The patient was diagnosed with TSHoma and panhypopituitarism as her SHGB, alpha subunit level, and alpha subunit/molar TSH ratio were high, there was no response to TRH test, and the patient had undergone surgery for pituitary macroadenoma previously. The patient was given a treatment with 20 mg octreotide LAR/once a month, 5 mg prednisolone/daily and cyclic estrogen-progesterone. The patient is currently euthyroid and on replacement therapy.

Case 3

A 20-year-old female patient presented to the endocrinology outpatient clinic with the complaints of alopecia, weight loss (<1kg) and palpitation for the last one month. Her laboratory tests were as follows: FT_3: 3.9 pg/ml, FT_4: 1.5 ng/dl, TSH: 4.6 µIU/ml. Her thyroid ultrasonography was normal in the presence of negative thyroid autoantibodies including antimicrosomal autoantibodies and antithyroglobulin autoantibodies. Pituitary MRI revealed a normal pituitary. TSH response to TRH was measured as: 0 minute: 2.8, 30 minutes: 9.8, 60 minutes: 10.6 µIU/ml. The results of T3 suppression test are shown in Table 1. TSH responses to TRH after T3 suppression test were as follows: 0 minute: 0.9, 30 minutes: 2.9, 60 minutes: 2.6, 90 minutes: 1.8, 120 minutes: 1.2 µIU/ml and SHBG: 185 mmol/l. After the examinations carried out, the patient was diagnosed with PRTH. The patient was then prescribed β-blocker and started to be followed up.

Table 1. Results of the T_3 suppression tests

	Case 1					Case 3			
	Normal	**Baseline**	**Day 3**	**Day 6**	**Day 9**	**Baseline**	**Day 3**	**Day 6**	**Day 9**
FT_3 (pg/ml)	1.4-4.4	5.3	6.7	8.1	13.8	4.7	5.1	6.9	11.7
FT_4 (ng/dl)	0.7-1.8	2.9	2.3	1.8	1.7	1.5	1.4	1.1	1.1
TSH (µIU/ml)	0.4-4.6	1.2	0.7	0.1	0.06	2.9	2.3	0.9	0.2
SHBG (mmol/l)	30-100	14	-	14	-	159	194	198	-
Cholesterol (mg/dl)	125-350	172	147	157	-	106	110	109	111
TG (mg/dl)	40-160	198	251	285	-	39	44	48	40
CPK (U/l)	24-195	33	34	46	51	89	97	90	82
Body weight (kg)	-	69	68	69	68	52.5	52	53.5	53.3
Ferritin (ng/ml)	13-400	58	70	88	88	35	36	36	49
E2 (pg/m)						56	66	96	290

Discussion

TSH is suppressed by thyroid hormones through negative feedback in the hypothalamic-pituitary-thyroid axis. In case of elevated serum levels of free thyroid hormones with non-suppressed TSH, one should suspect inappropriate TSH secretion. (1,7). Once increased thyroxine-binding protein (TBG), presence of antibodies connected to T3 and T_4, amiodarone treatment, familial dysalbuminaemic hyperthyroxinaemia (FDH), high-dose or intermittent L-thyroxine treatment which are among other causes of inappropriate TSH release are ruled out,THR and TSHoma should be investigated (1,2). In our three cases, FT_3 and FT_4 levels were high and TSH levels were not suppressed. After likely laboratory errors were excluded, differential diagnosis was made between TSHoma and THR.

THR is a rare genetic disorder. While both pituitary and peripheral tissues show resistance to T_3 in GRTH, pituitary shows resistance to T3 in PRTH. In PRTH, hyperthyroidism features including heart (tachycardia) and brain (nervousness, insomnia, attention deficit, hyperactivity) symptoms may be present, nevertheless, the other organ systems may not be involved (8). In our cases, the patient with GRTH was clinically euthyroid while the patient with PRTH had hyperthyroidism symptoms such as palpitation, weight loss and alopecia. Although both of the forms are clinically different, they are genetically the same (5,7,9). Despite the fact that THR is usually an autosomal dominant disorder, 10-15% of cases can be sporadic (1,10). Even though mutation analyses of TRβ gene provide early diagnosis of THR and, thus, prevent family members from being scanned unnecessarily, gene mutation analysis could not be performed in our patients and their families, however, thyroid function tests of the first degree relatives of the cases were normal and/or there was no history of thyroid gland disease.

TSHomas are rare pituitary tumors that cause hyperthyroidism by secreting TSH (5). Most of them are macroadenoma in the pituitary (6,7,11), as found in our case. Differential diagnosis should be made between TSHoma and THR, which are two significant causes of TSH syndrome. Differential diagnosis is important as the treatment of the central hyperthyroidism differ from each other. Patients with GRTH are frequently asymptomatic and are incidentally detected. Symptoms in some patients with GRTH can display clinical characteristics varying between hypothyroidism and hyperthyroidism (1,9). However, our patient with GRTH (case 1) was clinically asymptomatic; she presented with a complaint of goiter and her diagnosis was made by examination.

In PRTH, hyperthyroidism symptoms are at the forefront as peripheral tissues respond to elevated thyroid hormone (1,5). In TSHomas, hyperthyroidism and goiter are present; symptoms of cephalalgia, visual field defect and hypopituitarism can also be observed (1,7). Our patient with TSHoma (case 2) had symptoms of hyperthyroidism in addition to the complaints of panhypopituitarism.

Peripheral markers of thyroid hormone like SHGB and angiotensin converting enzyme (ACE) are often elevated in TSHomas, however, they are usually normal in cases with THR (1). TSH α-subunit and α-subunit/ TSH molar ratio should be checked in such patients. While α-subunit level is high in 66% of those with TSHoma, α-subunit/TSH molar ratio is high in 80% of them. As α-subunit is also secreted along with LH and FSH, α-subunit/TSH molar ratio is a more specific test (1,5,7). In our case with TSHoma (case 2), α-subunit level ratio and α-subunit/TSH molar ratio were also high.

T_3 suppression test is important in the differential diagnosis between TSHoma and THR. T_3 is administered with increasing the dose every three days (50 μg, 100 μg, 200 μg divided into two doses to be administered at 12 hour intervals). At the onset of the test and with each dose increment, peripheral markers such as serum cholesterol, triglyceride, creatine phosphokinase (CPK), ferritin, SHBG, prolactin, TSH, heart rate, urinary magnesium, and body weight are checked and TRH stimulation test is performed. While there is no significant change in parameters except heart rate and urine magnesium in cases with GRTH, these markers change in TSHoma as there is no peripheral resistance (9). An increase in the levels of SHGB, ferritin and E2 and, a slight decrease in CPK was detected in our patient with PRTH (case 3), whereas no change was observed in peripheral markers except for the slight increase in ferritin in our patient with GRTH (case 1). Because peripheral markers may be variable, other diagnostic procedures such as TRH test and pituitary MRI should be used in establishing an accurate diagnosis. After administration of a high-dose T_3, TSH levels are not suppressed in TSHoma whereas they are suppressed in THR (9). In our patients with THR (cases 1 and 3), suppression was observed in TSH and T_4 levels subsequent to T3 This test was not performed in our TSHoma patient (case 2), since the diagnosis had been made without a need for T_3 suppression test. None of these tests is of clear-cut diagnostic value, therefore, the use of both T_3 suppression and TRH tests are recommended, because the combination of their results increases the specifity and sensitivity of the diagnosis (8).

After TRH administration, the increase in TSH level is more than double in cases with THR, whereas it increases less than double in cases with TSHoma (1). In our patients with THR (case 1 and 3), TRH tests revealed that TSH level increased more than double. However, in our patient with TSHoma (case 2), the increase in TSH level was less than double (Table 2).

In TSHoma, presence of an adenoma in the pituitary gland can be detected by MRI or octreotide scintigraphy. However, since small non-functioning pituitary adenomas can be incidentally observed in 15% of normal persons, pituitary adenomas can also be incidentally observed through imaging methods in patients with THR (1).

Table 2. Results of TRH stimulation tests

	Baseline	30 min	60 min	90 min	120 min
Case 1-TSH (μIU/ml)	1.4	14.8	14.5	12.5	10.6
Case 2- TSH (μIU/ml)	2.2	2.2	2.3	2.5	2.6
Case 3- TSH (μIU/ml)	2.8	9.8	10.6	10.4	10.1

Anti-thyroid drugs (PTU or methimazole, 200–300 mg and 20–30 mg per day, respectively) or somatostatin analogues, such as octreotide (100 mg s.c., b.i.d. or t.i.d.), along with propranolol (80–120 mg per day orally) medication may be given to the patient to restore euthyroidism before surgery (8). Tumor resection by transsphenoidal surgery alone or together with radiotherapy is the most important treatment of choice for TSHoma. Tumors are usually huge when discovered. Therefore, complete surgical resection of macroadenoma is difficult (1,6). In the medical treatment of TSHoma, long-acting somatostatin analogues are used to control hyperthyroidism and to downsize the tumor (6,11). Octreotid LAR 20 mg treatment led to clinical recovery in our patient with TSHoma.

In many cases with GRTH, endogenous thyroid hormones provide sufficient compensation for resistant tissues by multiplying. In these cases, there is partial resistance to thyroid hormone and as the patients are clinically euthyroid, there is no need for treatment (7,9). Hyperthyroidism treatments such as thionamides, iodine-131 ablation treatments and thyroid surgery should be avoided in asymptomatic patients (1). Although our patient with GRTH (case 1) was asymptomatic, antithyroid drug treatment had unnecessarily been recommended just based on laboratory results. After the patient was diagnosed, follow-up was started without any treatment.

Since patients with PRTH exhibit hyperthyroid features at tissue levels, they generally require treatment to reduce the elevated thyroid hormone levels (7). In adults, treatment is basically symptomatic. Patients who are clinically hyperthyroid could benefit from β-blocker and thionamides. Antithyroid drug use leads to goiter growth. The logical approach in PRTH is using agents that suppress TSH secretion. Glucocorticoides, dopaminergic drugs, somatostatin analogues, and thyroid hormone analogues can be used for this purpose. However, none of these drugs have been an ideal treatment choice due to their side effects (1,9). 3,5,3'-Triiodothyroacetic acid (TRIAC), which is a physiological metabolite of T_3, has been found to improve endogenous thyroid hormone level, TSH, TRH or TSH response and hyperthyroidism symptoms. However, the effects of TRIAC vary and its effect on heart rate is often minimal. Additionally, some studies have failed to show that they have beneficial effects (7,12).

We present these different three cases of inappropriate TSH syndrome to emphasize its rareness and the importance of using tests for the differential diagnosis of inappropriate TSH syndrome.

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