

Тиреотропинома: поздний диагноз и эффективность терапии

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Современные лечебно-диагностические алгоритмы позволяют своевременно выявить нарушения функции щитовидной железы, назначить адекватное лечение. Между тем в процессе интерпретации тиреоидного статуса необходимо учитывать крайне редкую, но реально существующую возможность развития тиреотоксикоза центрального генеза, диагностика которого, как показывает общемировая практика, затруднена.

Представлен клинический случай ТТГ-продуцирующей аденомы гипофиза у женщины 47 лет, длительное время получающей тиреостатики по поводу тиреотоксикоза. Пациентке был установлен диагноз болезнь Грейвса, однако истинной причиной тиреотоксикоза являлась тиреотропинома. Основные лабораторные проявления тиреотоксикоза центрального генеза заключались в сочетании эпизодов нормального или повышенного уровня ТТГ с высокой или нормальной концентрацией свободного Т4. При МРТ выявлена макроаденома гипофиза. Наличие клинических проявлений тиреотоксикоза позволило исключить синдром резистентности к тиреоидным гормонам. Пробное лечение октреотидом купировало клинические и лабораторные проявления тиреотоксикоза, что обусловило выбор консервативного метода в качестве первой линии терапии. Обсуждаются особенности клинико-лабораторных проявлений, а также принципы дифференциальной диагностики и современных методов лечения ТТГ-продуцирующих аденом гипофиза.

Ключевые слова: клинический случай, тиреотоксикоз, ттг продуцирующая аденома гипофиза, тиреотропинома.

TSH-secreting pituitary adenoma: late diagnosis and effectiveness of therapy

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The modern therapeutic and diagnostic algorithms allow timely detection of pituitary disorder to prescribe adequate treatment. Meanwhile, when interpreting the thyroid status, physicians need to take into account the extremely rare but the actually existing possibility of central thyrotoxicosis. The worldwide practice shows that diagnosis of this condition is rather challenging. We report a clinical case of a TSH-secreting pituitary adenoma in a 47-year-old female who received a long-term thyrostatic therapy for thyrotoxicosis. The patient was diagnosed with Graves' disease; however, thyrotoxicosis was actually caused by TSH-oma. The key laboratory signs of central thyrotoxicosis included the combination of episodes of normal or elevated TSH level with the high or normal free T4 level. MRI showed a pituitary macroadenoma. The clinical manifestations of thyrotoxicosis made it possible to rule out the thyroid hormone resistance syndrome. The attempted therapy with octreotide eliminated the clinical and laboratory signs of thyrotoxicosis, so the conservative method was selected as first-line therapy. The features of clinical and laboratory signs, as well as the principles of differential diagnosis and modern methods for treating TSH-secreting pituitary adenomas are discussed.

Keywords: case report, thyrotoxicosis, TSH-secreting pituitary adenoma, TSH-oma.

Topicality

Thyrotoxicosis syndrome is a common disease [1]. Modern diagnostic and treatment algorithms enable timely diagnosis and adequate treatment of thyroid gland (TG) dysfunctions. When interpreting thyroid status parameters, one should keep in the mind an extremely low but potential risk of central thyrotoxicosis, the diagnosis of which is difficult. Many patients are misdiagnosed with Graves' disease, followed by inappropriate treatment with thyrostatics, thyroidectomy, and/or radioablation. The purpose of this publication is to attract attention of practicing endocrinologists to the peculiarities of clinical and laboratory manifestations of central thyrotoxicosis caused by TSH-secreting pituitary adenomas (thyrotropinoma) and discuss current treatments for these patients.

CASE REPORT

A 46-year-old female patient A. was admitted to the Endocrinology Department of the Regional Clinical Hospital №1 of the Ochapovskiy Research Institute with complaints of palpitations, body tremor episodes, and discomfort in the neck.

Past medical history

The patient had a 10-year history of palpitation episodes. In 2013, an examination of the thyroid status revealed no pathological changes (**Table 1**); an ultrasound examination of the thyroid gland found no structural changes (volume, 9.7 cm³).

In March 2015, a repeated examination for tachycardia incidentally revealed high normal TSH levels and an elevated concentration of free thyroxine (fT4). Thyroid

Table 1. Thyroid status parameters

Date	TSH, mIU/mL (reference values, 0.35–4.9)	fT4, pmol/L (reference values, 12.0–22.0)	fT3, pmol/L (reference values, 3.07–6.9)	Tyrosol dose, mg
2013	3.2	20.7	3.2	-
03.15	4.9	36.02		
04.15	5.14	20.7	9.0	
05.15	21.7	17.0	5.74	20
06.15	35.3	17.6	8.07	30
08.15	5.4	21.4	11.0	
10.15	11.4	21.7	9.0	5
11.15	12.0	29.7	10.7	10

Table 2. Hormonal test results (11.26.15)

Indicator	Value	Reference values
TSH, μ IU/mL	12.2	0.35–4.5
Total T3, nmol/L	3.31	0.92–2.79
Free T3, pmol/L	10.7	3.50–6.50
Total T4, nmol/L	192	58–161
Free T4, pmol/L	29.7	11.5–22.7
TPO Ab, U/mL	Abs	up to 60
TSHR Ab, IU/mL	0.1	0.0–1.75
Luteinizing hormone, mIU/mL	7.14	1.9–12.5
Follicle-stimulating hormone, mIU/L	4.66	2.5–10.2
Prolactin, mIU/L	275.56	59–619
IGF-1, ng/mL	193.0	94–252
ACTH, pg/mL	15.8	0.0–46.0

Abbreviations: TSH — thyroid-stimulating hormone; total T3 — total triiodothyronine, free T3 — free triiodothyronine, total T4 — total thyroxine, free T4 — free thyroxine, TPO Ab — thyroid peroxidase antibodies, TSHR Ab — TSH receptor antibodies, IGF-1 — insulin-like growth factor 1, ACTH — adrenocorticotrophic hormone.

peroxidase antibody (TPO Ab) levels were within reference values. A retest of the indicators in April 2015 revealed increased levels of TSH and free triiodothyronine (fT3). A diffuse toxic goiter was diagnosed; treatment was started with tyrosol at an initial dose of 20 mg per day, and then, because of the lack of efficacy, the dose was increased to 30 mg per day. Administration of tyrosol was accompanied by an increase in the TSH level with simultaneous exceedance of reference fT3 values, with fT4 concentrations being normal. The patient was recommended continuing the tyrosol treatment (30 mg per day). The patient terminated the treatment three weeks later due to the development of urticaria. Termination of the thyrostatic (08. 2015) was accompanied by a decrease in TSH and an increase in fT3, with the fT4 level remaining within reference values. Re-administration of 5 and 10 mg of tyrosol was accompanied by a change in all thyroid status indicators (October and November 2015). Because of failure of the treatment and the need to determine further treatment, the patient (diagnosis of a medically uncompensated diffuse toxic goiter, grade 2, moderate severity) was referred to the Endocrinology Department of the Regional Clinical Hospital №1 of the Ochapovskiy Research Institute.

Medical life history

In 2011, the patient was diagnosed with a retinal detachment (unknown etiology); laser therapy was conducted. In December 2014, she underwent surgery for uterine fibroids. The patient denied pathology of the pituitary and thyroid glands in relatives.

Examination findings

The general patient's condition was satisfactory. The patient was normally developed and well-nourished, with a height of 160 cm and body weight of 62 kg. The skin was moderately hydrated; there was a slight tremor in the fingers. The TG (WHO grade 0) was densely-elastic and heterogeneous, without palpable nodular lesions. There were no eye symptoms of thyrotoxicosis. Under therapy with 2.5 mg of bisoprolol, the heart rate was 80 beats per min, and blood pressure was 120/80 mm Hg. The results of a repeated hormonal test are shown in **Table 2**.

Results of laboratory and instrumental tests

The concentration of alkaline phosphatase was within normal limits, and the level of total cholesterol was slightly elevated (5.8 mmol/L; normal range, 2.3–5.17 mmol/L). A slightly increased level of the sex hormone

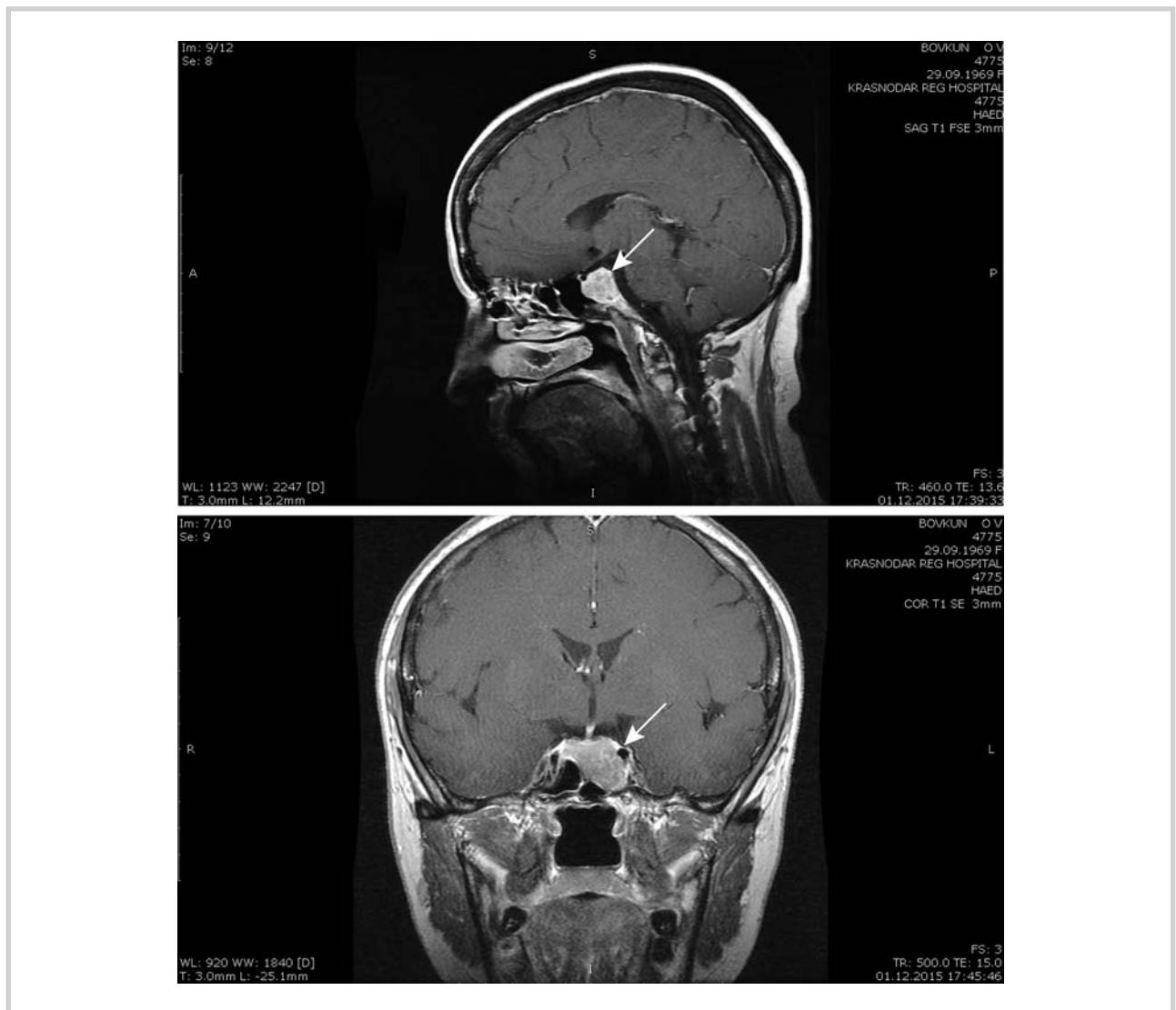


Figure 1. MRI of the brain: a pituitary macroadenoma.

binding globulin, 154.3 nmol/L (normal range, 34.3–147.7 nmol/L), was detected.

According to thyroid ultrasound (01.12.15), there were signs of isoechoic nodules in both lobes, up to 8 mm in diameter, with perinodal blood flow, diffuse changes in the TG, normal blood flow of 15 cm/s, and $V = 8.5 \text{ cm}^3$.

According to TG scintigraphy (02.12.15), images of both lobes were not enlarged; the thyroid shape was normal; contours were smooth and obscure. The distribution of a radiotracer was diffusely heterogeneous: moderately diffuse areas of enhanced radiotracer uptake («hot» zones) were present in all fields of both lobes. Impression: moderate diffuse changes in both thyroid lobes.

MRI of the pituitary gland (01.12.15) revealed a space-occupying lesion (17.7×27.1×19.5 mm) of the intrasellar and infrasellar location; the lower left contours of the lesion were located under the left internal carotid artery. The pituitary stalk was displaced to the right (**Fig. 1**).

The patient was examined by an ophthalmologist (03.12.15) who diagnosed peripheral degeneration of the retina, mild myopia, and a condition after retinal laser coagulation in both eyes. An examination by a neurosurgeon (03.12.15) revealed a space-occupying lesion of the intrasellar and infrasellar location.

Central thyrotoxicosis, a TSH-secreting pituitary adenoma, was suggested based on the clinical picture of the disease and hormonal test results, including elevated levels of TSH, fT3, and fT4 in the absence of TSH receptor antibodies, specific changes in the thyroid status associated with administration of thyrostatics (a decrease in fT3 to 5.74 pmol/L, an increase in TSH to 35.3 $\mu\text{IU/mL}$, and subsequent normalization of the TSH level (5.4 mIU/mL after tyrosol discontinuation), laboratory signs of hyperthyroidism (fT4, 21.47 pmol/L; fT3, 11.0 pmol/L), as well as a MRI-detected pituitary macroadenoma. The patient was referred to the Endocrinology

Table 3. Hormonal test results after 6-month treatment with long-acting somatostatin analogues

Indicator		Reference values
TSH, μ IU/mL	1.75	0.35–4.94
Free T3, pmol/L	4.68	2.6–5.7
Free T4, pmol/L	14.86	9.01–19.1
Luteinizing hormone, mIU/mL	3.04	1.68–15.0
Follicle-stimulating hormone, mIU/L	4.52	1.37–8.08
Prolactin, mIU/L	330	126–628

Research Center (ENC) to clarify the diagnosis and determine a treatment tactics.

At the ENC (19.01.16), the patient was diagnosed with a pituitary macroadenoma with TSH hypersecretion and central thyrotoxicosis. Neurosurgery was planned. Administration of a long-acting somatostatin analogue at a dose of 20 mg intramuscularly once in 28 days was recommended for pretreatment of thyrotoxicosis.

Therapy with long-acting somatostatin analogues resulted in euthyroidism (March 2016): TSH, 2.162 mIU/L; fT4, 15.35 pmol/L; fT3, 4.4 pmol/L. There were no signs of a mixed secreting adenoma (prolactin, 42 mIU/L; IGF-1, 122 ng/mL). MRI (01.12.15) verified a pituitary macroadenoma of 20×27×18 mm in size, with an parasellar and infrasellar spread. Given the patient's refusal of neurosurgical treatment as well as high sensitivity to therapy with somatostatin analogues, continuation of conservative treatment with long-acting somatostatin analogues and reconsideration of indications for surgery in 6 months were recommended. Thyrotoxicosis complications included initial osteopenia of the radial bone (up to –1.1 SD, Z-criterion) and hypovitaminosis D; vitamin D drugs were prescribed. The patient was discharged in a satisfactory condition.

21.06.16, the patient was interviewed by telephone: a satisfactory condition was achieved due to therapy with long-acting somatostatin analogues; there were no complaints and palpitation episodes. The results of hormonal status evaluation (21.06.16) are presented in **Table 3**.

DISCUSSION

The presented clinical situation reflects the complexity of the diagnosis of TSH-secreting pituitary adenomas. Despite the fact that endocrinologists are well aware of the risk of central thyrotoxicosis, a low prevalence of thyrotropinoma sometimes complicates the correct diagnosis of the disease. Unusual baseline indicators of the thyroid status (increased levels of thyroid hormones on the background of normal or slightly elevated TSH values as well as a marked increase in the TSH level and decreased concentrations of thyroid hormones upon administration of thyrostatics) suggest examination to identify a TSH-secreting pituitary adenoma.

The prevalence of thyrotropinomas is low and accounts for 0.5–3% of pituitary adenomas. Recently, one case of thyrotropinoma in a child and one case in a young female were reported in the domestic literature [2, 3]; a total of about 350 cases of the disease have been described worldwide since 1960 [4]. The clinical manifestation of TSH-secreting pituitary adenomas occurs in different age periods, with the peak in the fifth decade of life. The pathology equally affects females and males [5].

In the vast majority of cases, TSH-secreting adenomas are macroadenomas and are characterized by secretion of TSH only. Previous surgical or radiological ablations of the TG adversely affect the size and invasiveness of the tumor (macroadenomas are detected in 49% of patients after TG surgery and in 27% of patients without this procedure) [4]. Morphologically, adenomas are fibrous structures, sometimes so dense that they are called «pituitary stones» [6]. Usually, thyrotropinomas are benign, but there are also reports of TSH-secreting carcinomas [7]. The clinical features of thyrotropinoma include a mild course or «silence» of the disease, which is associated with a low biological activity of TSH molecules secreted by adenoma. There are reports of the euthyroid state in patients with incidentally detected thyrotropinomas [8]. However, severe thyrotoxicosis with atrial fibrillation, heart failure, and transient paralysis occurs in every fourth case [4, 9, 10]. The mass effect may cause visual field disturbances (40%), headaches (20%), and partial or complete loss of tropic pituitary functions. Partial hypogonadism occurs in about 1/3 of patients; it manifests as menstrual irregularities in females and as central hypogonadism, delayed sexual development, and decreased libido in males [4].

The thyroid status is of particular importance in patients with thyrotropinomas. Under hyperstimulation condition, a diffuse goiter develops even after partial thyroidectomy. In addition, the TG in thyrotropinoma patients may undergo nodular transformation, but functional autonomy develops rarely [11]. Monitoring of existing nodules is a conventional approach because carcinoma is sometimes detected in these TG nodules [12]. Titers of TPO and TSH receptor antibodies do not differ from those in the general population, however there are reports of Graves' disease developed after adenomectomy.

my and bilateral ophthalmopathy associated with the development of autoimmune thyroiditis as well as unilateral exophthalmus due to pituitary tumor invasion [13, 14].

In a third of patients, thyrotropinomas have a mixed nature because transcription factors Prop-1 and Pit-1 are common to somato-, lacto-, and thyrotrophs [15]. TSH secretion is most often combined with production of the growth hormone (16%) and prolactin (10%) and extremely rarely combined with production of gonadotropic hormones (1.4%). In these cases, manifestations of acromegaly, hyperprolactinemia, and hypogonadism predominate. Also, there are reports of thyrotropinomas associated with syndrome of multiple endocrine neoplasia type 1, McCune-Albright syndrome, and mutations of the AIP gene (in one patient) [4].

The diagnosis of TSH-secreting adenoma should be first differentiated from Graves' disease and multinodular toxic goiter. The diagnostic criteria of thyrotropinoma include an elevated level of thyroid hormones on the background of an increased or normal TSH concentration as well as detection of a pituitary adenoma by a CT/MRI study. Thyrotropinomas are usually resistant to increased levels of thyroid hormones but are very sensitive to narrowing of their spectrum, which explains high TSH secretion and more aggressive tumor growth after thyrostatic therapy, thyroidectomy, and radioiodine therapy. Diagnosis of TSH-stimulating adenoma in patients receiving substitution therapy after previous thyroidectomy or radioiodine therapy is complicated. According to P. Beck-Peccoz and co-authors [5], TSH levels in patients after thyroid ablation are manifold higher than those in untreated patients, with concentrations of thyroid hormones being in the hyperthyroid range. In these cases, the diagnosis may be suggested if the TSH level remains elevated upon treatment with a full replacement dose of levothyroxine. In complex diagnostic situations, functional tests are used: either stimulation tests with the thyroid-releasing hormone and dopamine antagonists or suppression tests with triiodothyronine (Werner's test). Thyrotropinoma patients lack an adequate TSH response in all cases.

Following verification of central thyrotoxicosis, it is necessary to differentiate the diagnosis between thyrotropinoma and thyroid hormone resistance syndrome (THRS); the latter is characterized by increased concentrations of free T3 and T4 along with an elevated or normal TSH concentration.

THRS belongs to a group of very rare diseases caused by a decreased sensitivity of peripheral tissues to thyroid hormones due to mutations in genes encoding thyroid receptors. In 80% of patients, the disease has a hereditary autosomal dominant nature, which may be associated with the development of family forms. The clinical manifestations of THRS depend on the localization and functional activity of mutations. The typical signs include goitre, delayed physical and sexual development, hyperactivity, and tachycardia at rest. In contrast, neurological

symptoms (visual impairments, headache) or clinical signs of pituitary hormone hypersecretion (acromegaly, galactorrhea/amenorrhea) as well as visualization of a pituitary adenoma by MRI/CT are indicative of thyrotropinoma. Small adenoma size, empty sella syndrome, and incidentalomas may complicate differential diagnosis.

To differentiate the diagnosis between THRS and thyrotropinoma, laboratory methods may be helpful. The clinical manifestations of thyrotoxicosis associated with TSH-secreting adenomas include increased levels of the sex hormone-binding globulin (SHBG) and C-terminal telopeptide of type 1 collagen and a decreased cholesterol concentration [16, 17]. However, the method to verify THRS is a molecular genetic study confirming mutations in genes encoding thyroid hormone receptors [18].

When the diagnosis of TSH-secreting pituitary tumor is confirmed, a preferred treatment option is removal of thyrotropinoma, which provides hormonal remission in 75–84% of cases [4, 19, 20]. However, radical removal of macrothyrotropinomas is often associated with technical difficulties caused by fibrosis and invasion of the tumor into the cavernous sinuses, internal carotid artery, or chiasm. In the case of contraindications for surgery or patient's refusal, radiotherapy and/or administration of somatostatin analogues (given the expression of somatostatin receptors in most TSH-secreting adenomas) may be used.

CONCLUSION

The differential diagnosis of thyrotoxicosis syndrome of the central, thyroid (primary), and peripheral (THRS) genesis is particularly important. The presented case is a typical example of a misdiagnosis of primary thyrotoxicosis and unsuccessful treatment with thyrostatics followed by TSH elevation without elimination of thyrotoxicosis symptoms. The disease was differentiated from THRS based on the presence of thyrotoxicosis symptoms, a pituitary macroadenoma, and an elevated SHBG level and the absence of relatives with similar laboratory changes. The treatment with a long-acting somatostatin analogue provided clinical and laboratory remission of thyrotoxicosis, which confirmed the diagnosis of thyrotropinoma. Thus, the correct diagnosis and pathogenetic treatment made it possible to compensate the patient's condition and achieve a significant clinical improvement. The question of tumor size changes over time during conservative therapy and the need for subsequent neurosurgical treatment still remains open. Control MRI one year after the beginning of therapy with a long-acting somatostatin analogue may answer this question.

ADDITIONAL INFORMATION

Consent of the patient. The patient voluntarily signed an informed consent for publication of personal medical information in an impersonal form (in this journal).

Conflict of interests. The authors declare no obvious and potential conflicts of interest related to the publication of this article.

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