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EFFECTS OF OCTREOTIDE THERAPY ON PERMANENT ATRIAL FIBRILLATION IN A PATIENT WITH TSH ADENOMA-CASE REPORT

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Secondary hyperthyroidism due to a thyrotropin - secreting (TSH) pituitary adenoma is a rare cause of hyperthyroidism, representing 0.5-2.0% of all pituitary adenomas. We report a case of a 36 year old female who presented with signs of thyrotoxicosis, elevated T3, T4, TSH, atrial fibrillation, as a result of TSH adenoma. She was successfully treated with Somatostatin analogue without surgical intervention. The investigation and treatment of this condition is discussed.

Keywords: TSH adenoma, Octreotide, atrial fibrillation

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EFFECTS OF OCTREOTIDE THERAPY ON PERMANENT ATRIAL FIBRILLATION IN A PATIENT WITH TSH ADENOMA-CASE REPORT

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INTRODUCTION

Thyroid-stimulating hormone (TSH)–secreting pituitary adenomas are rare, representing around 2% of all pituitary adenomas [1]. There had been Fifty-two cases from 24 medical centers in nine countries reported between 1987 and 1991 [2]. Thyroid-stimulating hormone–secreting pituitary lesions are often delayed in diagnosis, are frequently macroadenomas and plurihormonal in terms of their pathological characteristics, have a heterogeneous clinical picture, and are difficult to treat [3]. The criteria that are required to confirm this entity are the following. The patient is clinically thyrotoxic while serum levels of free T4 and/or free T3 are elevated and serum TSH concentration is normal or increased. Visualization of the pituitary by magnetic resonance imaging shows a pituitary tumor. The concentration of TSH alpha -subunits in blood is above normal, as is the ratio of TSH alpha /TSH [4]. Decreased or lack of response of TSH during the TRH test has a good sensitivity and excellent specificity in patients with intact thyroid, with a slight decrease in sensitivity after thyroidectomy [5]. Although in principle this thyrotoxicosis is not accompanied by eye signs, unilateral exophthalmus may ensue from a thyrotropin secreting pituitary tumor due to invasion of one orbit [6]. Pituitary TSH adenoma produce normal forms of TSH but secrete them in variable amount and differing biological activity, explaining the variable degree of hyperthyroidism in these patients [7]. Surgical resection remains the basis for definitive treatment of TSH adenomas [8]. Losa et al. found a relapse in 3 of 5 operated and postoperatively irradiated patients without postoperative TSH inhibition [9]. Octreotide has been shown to reduce TSH secretion in almost all cases, normalize thyroid hormone levels, and shrink tumors in up to one third of patients receiving long term treatment [10]. Long-term medical therapy with somatostatin analogs is indicated adjunctively in patients with TSH-secreting pituitary adenomas who failed to be cured after surgery or who were awaiting the effects of radiation. The use of somatostatin analogs as primary therapy was generally reserved to patients who refused surgery or who were poor surgical candidates [11]

CASE REPORT

Patient M.M. 36-years-old, mother of two, was referred to Endocrinology department with classical signs of hyperthyreosis, elevated T3, T4, TSH, atrial fibrillation, popliteal vein thrombosis and pituitary macroadenoma confirmed by magnetic resonance imaging (MRI) scan. The patient was treated for hyperthyreosis since 1999, with antithyroid drugs (Thyamazol and Propiltiouracil) and was diagnosed as having diffuse goiter. The patient had elevated levels of thyroid hormones (T3=5,8 nmol/L - normal range 1,2-2,8 nmol/L and T4= 396nmol/L - normal range 60-160nmol/L) and TSH (TSH=9,6 mIU/L - normal range 0,17-4,05mIU/L). Thyroid antibodies were negative (TgAt=12, TPOAt=5,2). The patient had regular checkups at the Department for Nuclear Medicine Tuzla, and at the same time received antithyroid drugs with occasional breaks, depending on the subjective symptoms and levels of thyroid hormones and TSH until 2005. Due to a suspicion of secondary hyperthyroidism

a CT scan of neurocranium was performed in 2005 (at this time MRI was unavailable in our clinic). Also additional hormones of pituitary gland FSH, LH, prolactin were all in the normal range. CT scan did not reveal any pathological processes in the pituitary gland so it was decided to proceed with antithyroid therapy (low doses of Methiamazol). For the past eight years the patient suffered from atrial fibrillation and was treated with various combinations of antiarrhythmics including Propafenon, Verapamil, Propranolol and Metoprolol. In May 2009 she had popliteal vein thrombosis and was started on anticoagulant therapy.

In November 2009 MRI scan of the neurocranium showed the existence of macroadenoma of pituitary gland. Patient was then referred to the Endocrinology department.

Once she was admitted to the hospital additional test were done including ACTH, prolactin, progesterone, estradiol, FSH, LH, growth hormone, testosteron, HCG, IgF1, parathormone, 17-OH, 17-KS, cortisol, all were within normal range. Level of sex hormone binding globulin (SHBG) was elevated.

In order to differentiate between secondary and tertiary hyperthyroidism TRH stimulation test was performed. TRH test was negative confirming that this was a case of secondary hyperthyroidism. Based on the negative TRH test, MRI of the pituitary gland, serum levels of T3, T4 and TSH, and a complete endocrinological workup we were able to confirm the diagnosis of TSH-secreting adenoma of pituitary gland.

We were unable to determine levels of alpha subunit of TSH in our clinic.

Additional test were performed including electrolytes, microelements, CIC, immunoelectrophoresis, immunophenotyping, allergy tests. These tests revealed an increased value of IgE in plasma. Allergy prick tests were positive for multiple nutritional and inhalant allergens.

At the moment of admission ECG showed atrial fibrillation with fast ventricular rate of 180 per minute (Figure 1). She was treated with maximum doses of Propafenon, Metoprolol and Warfarin. Warfarin was started due to popliteal vein thrombosis, but also due to atrial fibrillation.

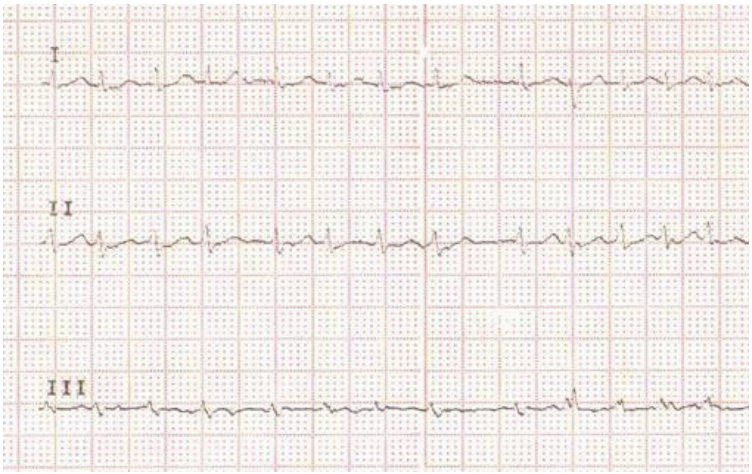

Figure 1. ECG tracing of atrial fibrillation with fast ventricular rate

Echocardiography showed tachycardial myopathy and dilatation of right ventricle, initial dilatation of the left ventricle, mild mitral regurgitation, and second-degree tricuspid regurgitation with pressure gradient of 35mmHg. (Figure 2).

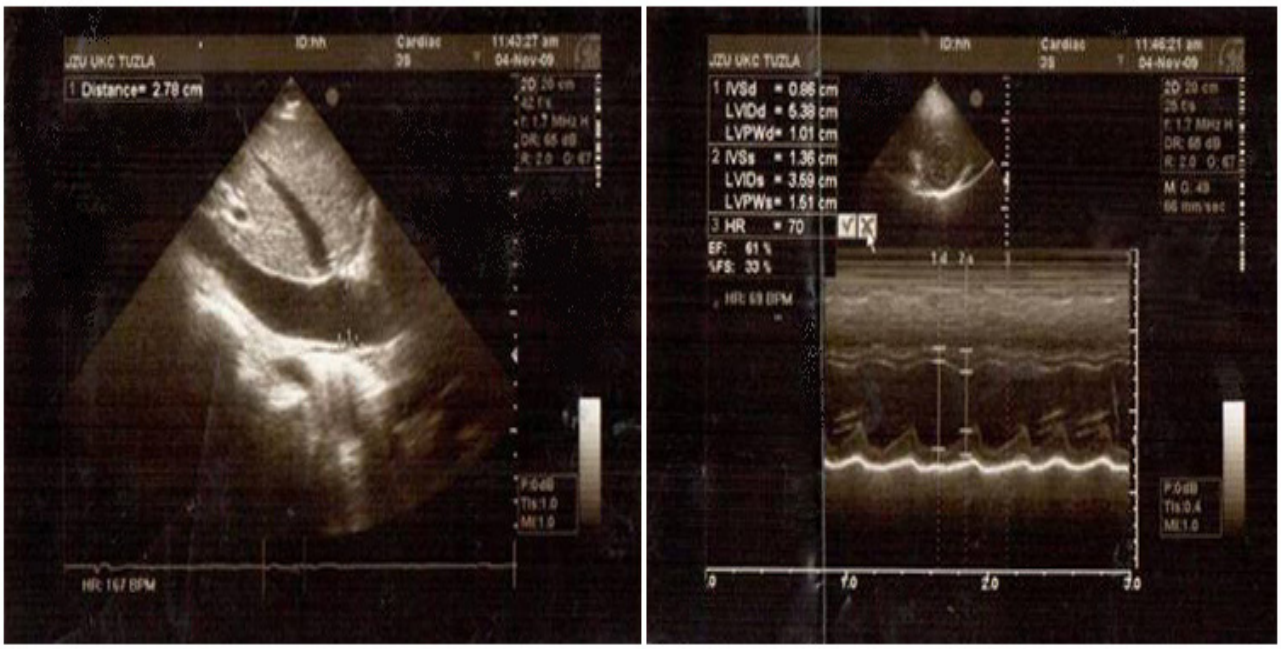

Figure 2. Echocardiography longitudinal section of VCI and parasternal cross-section at the level of mitral valves

The patient refused the surgical treatment, so conservative treatment with octreotide was started with 0,1mg three times daily. After 8 days of therapy a significant drop in TSH and thyroid hormone levels was registered (T3=1.89; T4=153.19; TSH=0.80).
At the same time there was a significant reduction in ventricular rate of atrial fibrillation. Ventricular rate control was achieved with minimal doses of Metoprolol (Figure 3.)

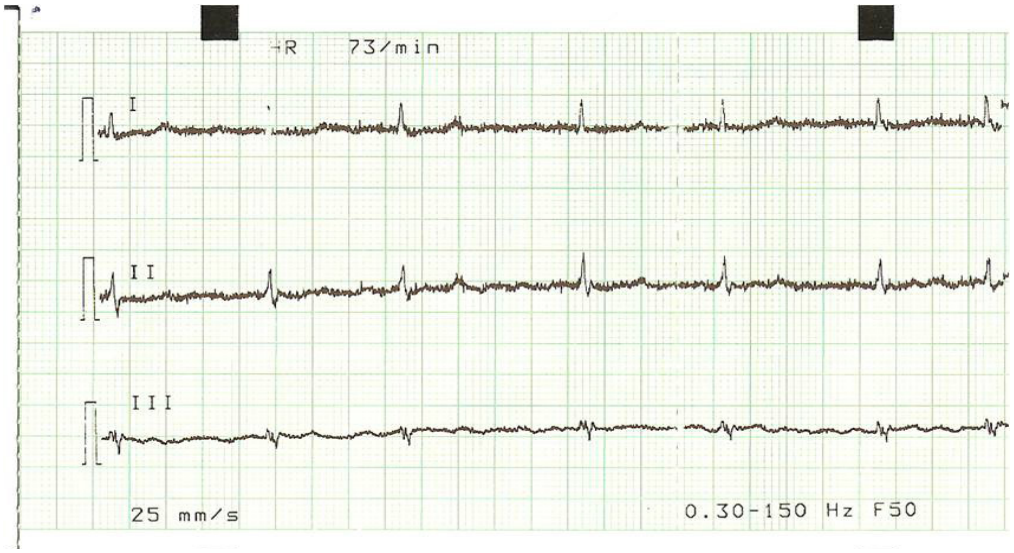

Figure 3. Atrial fibrillation, with ventricular rate of 70/min.

The patient was discharged with normal levels of T3, T4, TSH, atrial fibrillation with normal ventricular rate, with recommended therapy of Octreotide 0,1mg s.c. bid, and minimal doses of Metoprolol 12,5mg bid.
After two months of Octreotide therapy follow-up ECG revealed normal sinus rhythm. Atrial fibrillation was converted to sinus rhythm without any specific antyarrhytmic therapy. (Figure 4.)

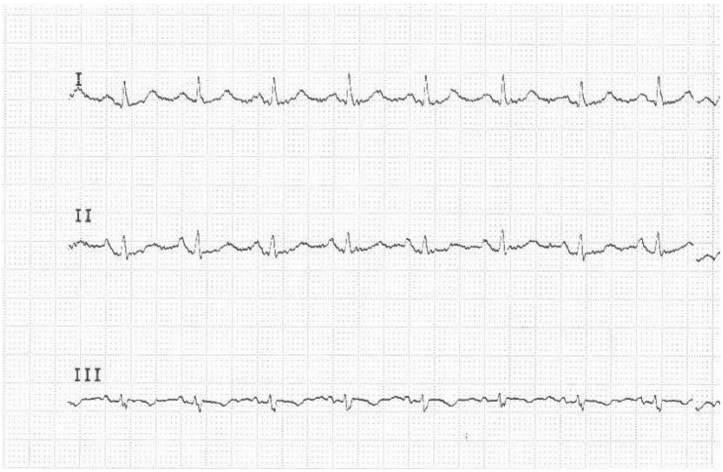

Figure 4. Sinus rythm, with rate of 80 bmFollow-up echocardiography registered normal morphology of the heart muscle with minor mitral end tricuspid regurgitation.
Control MRI scan of the pituitary gland showed cystic degenerative changes of macroadenoma (Figure 5).

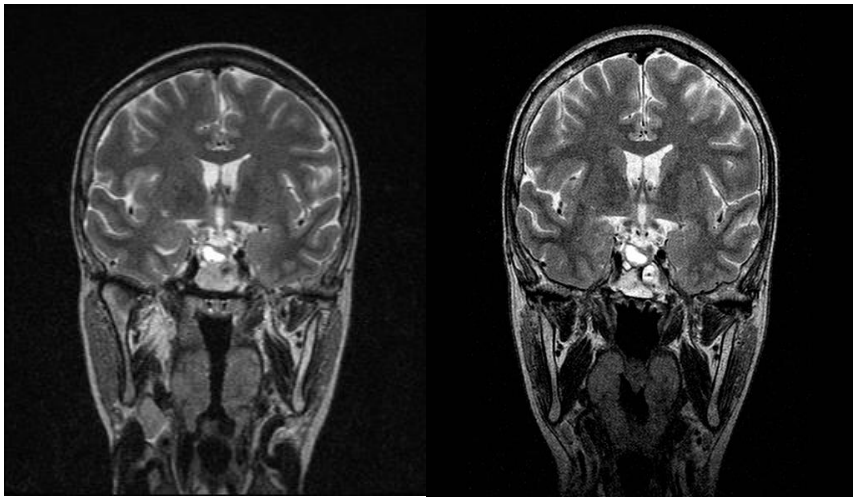

Figure 5. MRI of pituitary macroadenoma before (left) and after (right) two months of octreotid therapy.

The most significant effects after two months of therapy with octreotide are shown in table 1.

Table 1. Effects of octreotide (after two months of therapy)

Before treatment	After treatment
Atrial fibrillation	Sinus rhythm
Echocardiography: tachycardial myopathy with sings of right ventricle dilatation and initial left ventricle dilatation.	Echocardiography: Normal morphological findings
T3, T4, TSH increased	Normal level of T3, T4, TSH
IgE: 1490 increased	IgE: 960 significantly lower
Thyrotoxicosis	Normal clinical findings
Irregular menstrual cycles	Regular menstrual cycles
Acuity weakened (reported by patient)	Acuity better (reported by patient-VOU was not determined)
MRI - pituitary macroadenoma	MRI pituitary macroadenoma with cystic degeneration (morphological changes)

Therapy with Octreotide was continued with depot formulation once monthly. During this period the patient did not have any adverse effects related to octreotide. After two months of therapy serum levels of thyroid hormones and TSH were in normal range, patient was free of any signs and symptoms of hyperthyroidism.

DISCUSSION

Thyrotropin - secreting (TSH) pituitary adenoma is a rare cause of hyperthyroidism, representing 0.5-2.0% of all pituitary adenomas [1,2]. Although rarely encountered in the past, TSH-secreting adenomas have been diagnosed in a gradually increasing rate owing to the application of more sensitive measurement of TSH hormone [12]. In these tumors there is an increased level of thyroid hormones and inappropriate level of TSH which is also high or not suppressed [12] Due to low incidence of this disease, it is rarely included in the differential diagnosis of hyperthyroidism. Therefore, this disease remains unrecognized for a long time as a possible cause of hyperthyroidism, which unfortunately leads to wrong therapeutic approach. This was also the case with our patient where she was initially misdiagnosed as having diffuse toxic goiter and then treated with antithyroid therapy. Latency between the onset of hyperthyroidism and diagnosis of TSH-oma in our patient was 11 years. Similar results were reported by Kienitz et al., [13] where the mean period to proper diagnosis was 12.5 years (range 1-19 years). Therefore, we need to emphasize the importance of early detection of this disease, which can prevent serious complications (neurological compression syndrome caused by aggressive nature of these tumors - tumors to become large and invasive). However, it is necessary to keep in mind that other clinical conditions may have similar clinical presentation such as pituitary TSH hyperplasia and thyroid hormone resistance. Therefore, it is necessary to perform additional hormonal measurements in differential diagnosis including serum level TSH, ά-subunit, molar ratio of ά-subunit /TSH, thyrotropin releasing hormone (TRH) stimulation test, T3 suppression test and sex hormone binding globulin (SHBG) as an indicator of peripheral effects of thyroid hormones. Brucker-Davis et al. suggested that a combination of negative TRH stimulation test, elevated ά-subunit, and ά-SU/TSH ratio is indicative of TSH oma. [14]. In this case we were not able to determine ά-subunit, and ά-SU/TSH ratio. In our case we were able to diagnose TSH adenoma using elevated T3, T4, TSH levels, negative TRH test, and the presence of pituitary macroadenoma on the MRI scan. Therapy of TSH-secreting adenomas can be accomplished by surgery, irradiation therapy and medical treatment with somatostatin analogues or dopamine agonists. Although surgical treatment (transsphenoidal adenomectomy) is essential, it doesn't guarantee complete cure of this disease. Therapeutic options available for other types of pituitary tumors may also be valid for the treatment of TSH secreting tumor. As in the case of other pituitary tumors, there is no single treatment approach which can be effective in the treatment of TSHoma. Conventionally, preoperative management of this tumor involves restoring euthyroidism by suppression of TSH with somatostatin analogues. Somatostatin analogue octreotide acetate has also been used for treatment of many endocrine diseases. In addition it is very helpful tool in the diagnosis of some endocrinological diseases. Many studies reported that octreotide is an effective drug in reducing both TSH and thyroid hormones level as well as reducing tumor size in TSH-secreting pituitary adenoma [13,15]. A study by Lee et al. showed that octreotide therapy was effective in reducing both tumor size and serum level of TSH and thyroid hormones in 55 patients with TSH-oma [16] Another study by Gancel et al. [17]and Mayinger et al. [18], showed significant decrease in the levels of both thyroid hormones and TSH using a long-acting somatostatin analogues, lanreotide in 4 patients with TSH-oma. In our case the use of short-term octreotide therapy produced satisfactory results including the reduction of thyroid hormone levels and TSH, as well as morphological changes in adenoma (cystic degenerative changes). We also had a satisfactory response, using octreotide therapy, in reduction of clinical symptoms and signs of disease that include conversion to sinus rhythm from atrial fibrillation without using specific antiarrhythmic therapy and reduction of SHBG to

normal limits. Based on the results of our study we want to emphasize the importance of short term octreotide therapy in preoperative preparation of patients for effective restoration of euthyroidism in order to minimize the risks of surgery and postoperative complications. Elevated levels of IgE and positive allergen prick test revealed atopy predisposition of our patient. It this case it remains questionable if atopy could represent a possible etiological factor in the development of TSH adenoma, or if it is a part of pathological and clinical presentation of TSH adenoma. After octreotide therapy there was a significant drop in IgE from 1500 to 960. Also our patient had significant menstrual cycle disorders, which were resolved after Octreotide therapy. Menstrual disorders can normally be seen in primary hyperthyreosis, but in this case it is possible that menstrual cycle disorder was produced by elevated levels of SHBG or alpha subunit (due to the fact that alpha subunit is biologically identical in TSH, LH and FSH hormones). Octreotide is a cyclic octapeptide somatostatin analogue, which inhibits the production of growth hormone, TSH, gastrin, secretin, gastrointestinal polypeptides, motilin, enteroglucagone, insulin, glucagons, renin.Cardiovascular effects of octreotide produce hypotension, systemic vasoconstriction, elevation of pulmonary arterial pressure. In patients with acromegaly which have left ventricular hypertrophy, octreotide therapy produces significant reduction of left ventricular mass. With Octreotide therapy we have achieved sinus rhythm, without specific antiarrhythmic therapy, even after eight years of permanent atrial fibrillation. In this case there has been a significant restitution of heart atria, and conversion to sinus rhythm. Exact mechanisms remain uncertain, but it is probably achieved with direct somatostatin effects to cardiovascular system, and possibly with indirect hormonal effects described above.

CONCLUSIONS

Having in mind all these effects of Octreotide therapy we registered in this patient, we believe that there is a need for a review of similar cases of TSH adenoma with atrial fibrillation, together with additional monitoring of serum IgE and atopic predisposition in those patients. Because various authors have also described long periods from the first symptoms to diagnosis, we believe that the diagnosis of TSH adenoma should be made without the need for radiological confirmation. In our opinion elevated levels of T3, T4 and TSH, and a negative TRH test are indicative of TSH adenoma. Octreotide could be used as a first-line therapy if the TSH adenoma is indentified without radiological presence of macroadenoma, while being second line after surgery in case of radiological confirmation of macroadenoma.

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