Case Report

TSH Secreting Pituitary Adenoma

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Abstract

Thyrotropin (TSH) secreting pituitary adenomas are a very rare cause of hyperthyroidism. They typically present with signs and symptoms of hyperthyroidism and rarely can be asymptomatic. TSH secreting tumors account for 1 percent of all pituitary adenoma. They are a rare cause of thyrotoxicosis in which adenomas completely or partially lose feedback regulation of thyroid hormones and lead to sustained stimulation of thyroid gland. The most definitive treatment of thyrotropin (TSH)-secreting pituitary adenomas is transsphenoidal removal of tumor after restoring euthyroidism. We report a case of pituitary adenoma associated with elevated serum free thyroid hormones and non-suppressed TSH levels.

Introduction

Thyrotropin (TSH)-secreting pituitary adenomas account for less than 1 percent cases of all causes of hyperthyroidism and 1 percent of all functioning pituitary tumors.[1]

Classical hyperthyroidism typically presents with raised thyroid hormone with suppressed TSH. Hyperthyroidism caused by increased TSH production is either neoplastic (TSH secreting pituitary adenomas) or non-neoplastic resistance to thyroid hormone (RTH). Most of them present with classical symptoms of hyperthyroidism and few may have some or no symptoms at all. In clinical practice it is not uncommon to find cases of non-suppressed TSH and total thyroid hormones. This can be due to increased amount of thyroid binding proteins. It is often very difficult to distinguish between thyrotropin (TSH)-secreting pituitary adenomas and resistance to thyroid hormone (RTH) due to complex and expensive investigating procedures.

A 68 year old lady being investigated for collapse, with no signs and symptoms of hyperthyroidism, was found to have raised TSH with raised free thyroid hormone with a coexistent finding of pituitary macroadenoma. This case is a very rare presentation of raised free hormones and TSH in presence of an incidental pituitary adenoma.

Case Report

A 68 yr old lady presented to the emergency with a single episode of loss of consciousness lasting for 5 minutes and the working diagnosis was posterior circulation transient ischemic attack. Cardiac investigations did not show any evidence of atrial fibrillation. There was no previous history of thyroid disorder. Examination did not reveal any abnormality. There were no signs and symptoms suggestive of hyperthyroidism. Thyroid was not enlarged. MRI was done which showed a pituitary mass of (1.70 cm x 1.85 cm). She was found to have raised TSH and raised free thyroid hormones. This was repeated by various methods over the last one year which showed similar thyroid profile except the latest one showed higher level of free thyroid hormone. (Table 1)

Visual field studies over the last one year showed no abnormality. Her FSH and LH were suggestive of menopause, prolactin was not raised and IGF-1 was low. Raised SHBG 195 nmol/l (Ref 19.80-155.20) and raised alpha sub unit TSH 11.5 ng/ml (Ref 0.9-3.3 ng/ml) were noted at Quest lab (USA). The alpha subunit result is strongly suggestive of a glycoprotein-secreting tumor, probably TSH-secreting tumor. Unfortunately alpha subunit and TSH were not done together which would have allowed for calculation of the molar ratio thus facilitating the diagnosis. Patient's sisters and her son had normal thyroid function tests. Thyrotropin releasing hormone (TRH) stimulation test could not be performed due to non-availability of TRH. That would have further confirmed the diagnosis of thyrotropin (TSH)-secreting pituitary adenomas. Her genetic analysis which was done at Oxford Lab (UK) ruled out RTH.

The high T3, T4 along with inappropriately high TSH, elevated alpha subunit; MRI with pituitary tumor (1.70 cm x 1.85 cm) imaging study and the macroadenoma are suggestive of thyrotropin secreting pituitary adenomas.

She has remained clinically asymptomatic and in sinus rhythm during the last year of follow up but her recent free T4 and T3 levels has gone up (Table 1).

Patient along with family were not keen for transsphenoidal surgery of pituitary macroadenoma. The possibility of optic chiasmal compression due to enlargement of tumor was explained to her.

Discussion

Thyrotropin (TSH)-secreting pituitary adenomas account for less than 1 percent cases of all causes of hyperthyroidism

Table1 : Thyroid function tests since diagnosis

Dates	19/07/07	24/07/07	02/05/08	27/05/08
TSH*	5.01 µIU/ml (0.34-5.6)	4.11 µIU/ml (0.49-4.67)	4.10 µIU/ml (0.27-4.20)	4.41 µIU/ml (0.27-4.20)
Free T4	2.88 pg/ml (2.5-3.9)	2.42 pg/ml (0.71-1.85)	3.45 pg/ml (0.93-1.70)	3.28 pg/ml (0.93-1.70)
Free T3	6.32 ng/dl (0.58-1.64)	5.64 ng/dl (1.64-3.45)	7.64 ng/dl (1.80-4.60)	6.18 ng/dl (1.80-4.60)
Method	Beckman Coulter Unicel DXI 800 Chemi-luminescent immunoassay Analyser	Abbott's Architect Chemilumi-nescent im-munoassay Analyser	Roche's COBAS 6000 Electro Chemilu-minescent immunoassay Analyser	Roche's COBAS 6000 Electro Chemilumines-cent immunoas-say Analyser

*TSH was diluted linearly which rules out TSH assay interference.

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Received: 29.09.2008; Revised: 05.01.2009; Accepted: 24.02.2009

and 1 percent of all functioning pituitary tumors.[1] In cases of thyrotropin (TSH)-secreting pituitary adenomas, biologically active thyrotropin (TSH) is secreted in autonomous fashion. TSH can be variable from normal range to markedly elevated.

TSH-producing pituitary adenomas are usually macroadenomas at the time of presentation due to delay in diagnosis. A diffuse goiter can be present in up to 80 percent cases but absent in this case.[2] Visual field defect in about 40% and menstrual disturbances and galactorrhea in 30 percent. Thyrotoxic symptoms and signs were absent in this case but present in majority of cases (56% severe and 36% moderate) and only 12% may be asymptomatic.[2] Thyrotropin (TSH)-secreting pituitary adenomas can be associated with secretion of GH in 15%, prolactin in 10% and rarely with gonadotrophins.[3]

In clinical practice it is not uncommon to find cases of non-suppressed TSH and total thyroid hormones but this could be due to increased amount of thyroid binding proteins. Thyroid hormones circulate bound to carrier proteins (thyroxine binding globulins (TBG, albumin, pre-albumin). Elevated thyroid binding globulins can be drug-induced (oral contraceptive pill tamoxifen), or due to pregnancy and infectious disease like active hepatitis.[4] This can result in high levels of total thyroid hormones but determining free thyroid hormones can rule out cases of elevated total T4.

In presence of anti-animal immunoglobulin (Ig) in serum, TSH may show false high which can be ruled out by serial dilution by performing different assay using different antibodies and by removal of immunoglobulin fraction by using polyethylene glycol (PEG) or protein G. In some cases of genetic variants of albumin, free T4 can be overestimated in one step assays and by performing equilibrium dialysis these interference can be avoided.[5] The main differential diagnosis of non-suppressed TSH and raised free thyroid hormones would include neoplastic (TSH-secreting pituitary tumor) or non-neoplastic RTH.

Both entities are rare and distinguishing between TSH secreting adenoma and RTH is very difficult due to non-availability of some diagnostic tools and expensive private healthcare in India.

The syndrome of RTH is characterized by reduced responsiveness of target tissues to circulating hormones which results in raised TSH in presence of raised T4 and T3,

Clinicians should keep an eye out for these rare entities but the first step should be to check free thyroid hormones (free T4 and T3) and repeating it again after few weeks if patient is asymptomatic rather than investigating at outset. This case was incidentally found on routine practice of endocrinology in tertiary centre in New Delhi. There are several ways (Table 2) to differentiate TSH secreting adenoma and RTH but none of them are confirmatory.

The presence of pituitary adenoma on MRI or CT very strongly supports the diagnosis of TSH-secreting pituitary adenoma but 10% of the normal population can have incidentaloma on MRI.[6] There is a possibility of RTH coexisting with pituitary incidentaloma, so in all cases of unsuppressed TSH, biochemical testing should be performed before surgical intervention.

In our case, presence of raised SHBG, alfa TSH unit, and presence of pituitary adenoma is strongly suggestive of Thyrotropin (TSH)-secreting pituitary adenomas. TRH test could not be performed due to non-availability of thyroid releasing hormone (TRH) in India. T3 (triiodothyronine) suppression test was avoided as there was risk of atrial fibrillation.

Table 2 : Tests which help to differentiate between thyrotropin (TSH)-secreting pituitary adenomas and RTH

Tests	RTH	Thyrotropin (TSH)-secreting pituitary adenomas
Thyroid function tests in relatives.	Similar pattern in first degree relatives of an index case suggests RTH	Familial cases have not been described
Serum alfa subunit	Normal	High usually >1 up to 5.7 has been found[3]
Molar ratio of alfa subunit and TSH	Usually 1	More than 1
SHBG	Normal	Raised
Thyroid function test (TFTS) in relatives	May be abnormal	No reported cases
TRH stimulation test	TSH response is either preserved or exaggerated	Failed response (TSH increment<150%) following TRH stimulation[3]
Specific genetic test	Specific genetic test available	No specific genetic testing
Short T3 (triiodothyronine) suppression test.[3]	Patients with RTH are more likely to have a fall in serum TSH concentrations in response to T3 (90 percent versus 12 to 25 percent)[3]	Less likely to have fall of TSH
Doppler Ultrasound of thyroid after T3 suppression therapy. Both have increased color flow Doppler sonography (CFDS) pattern and peak systolic velocity (PSV).[7]	After T_3 both parameters normalized in most patients with RTH	Color flow remained the same in all 8 patients of TSH secreting adenomas
Octreotide test[8]	No or little decrease in TSH	Marked decrease in TSH is usually seen
CT or MRI of pituitary	Normal	Usually macroadenoma and minority microadenomas

The most definitive treatment for patients with TSH-secreting pituitary adenomas is transsphenoidal resection of the tumor. The outcome is not very poor as only one-third patients are cured and one-third show improvement and one-third show no change. Pituitary radiation alone or in conjunction with pituitary surgery has not been found useful. Octerotide, a somatostatin analogue was effective in most patients, but most of these patients had already undergone surgery.[3] Our patient has not been keen for surgery. A slow-release formulation of a somatostatin analog, lanreotide improves hyperthyroid symptoms but has not shown to reduce the size of tumor. Antithyroid drugs should be avoided as they may increase the size of tumor due to suppression of thyroid hormone. The challenges to clinicians are to distinguish between thyrotropin (TSH)-secreting pituitary adenomas and resistance to thyroid hormone (RTH) once raised free thyroid hormones with non-suppressed TSH has been confirmed.

Acknowledgments

We are grateful to Dr Vinita Jha for writing up article and Dr Krishna Chatterjee for his expert advice on this case and arranging genetic screen for RTH.

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