HYPERTHYROIDISM CAUSED BY TSH-PRODUCING ADENOMA

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Objectives. To present a new case of central hyperthyroidism caused by thyrotropin (TSH)-producing adenoma.

Design. Case report.

Setting. Departments of Internal Medicine, Diagnostic Radiology and Biochemistry, University of the Orange Free State, Bloemfontein.

Subject and outcome measures. A 36-year-old woman with symptoms and signs of hyperthyroidism was diagnosed as having an elevated free thyroxine (T_4) level and non-suppressed THS level.

Results. Magnetic resonance imaging (MRI) examination of the pituitary gland showed a macro-adenoma of the adenohypophysis, $2 \times 1.5 \times 1$ cm in diameter. The patient did not have any other alteration in secretion of the pituitary hormones. Hyperthyroidism was successfully treated with adenomectomy. The only postoperative complication was permanent diabetes insipidus.

Conclusion. THS-producing adenomas are rare but possible causes of hyperthyroidism. MRI examination helps to distinguish TSH adenoma from another form of central hyperthyroidism, namely the syndrome of pituitary resistance to thyroid hormone (PRTH).

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Tumours originating from the hypophysis and producing thyrotropin (TSH) are very rare. At present approximately 280 TSH-secreting adenomas (TSH-omas) have been reported in the literature.[1] TSH-omas are usually benign adenomas arising from monoclonal expansion of neoplastic thyrotropes. Causative oncogenes have not yet been identified.[2] Inappropriate secretion of TSH manifests with signs and symptoms of hyperthyroidism, which are not different from

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those occurring in the more conventional forms of thyroid hyperfunction such as toxic nodular goitre and auto-immune Graves' disease.[3] Failure to diagnose the TSH-oma may result in inappropriate thyroid gland ablation and further expansion of the pituitary tumour.

CASE REPORT

A 36-year-old woman with symptoms of hyperthyroidism was referred to our endocrine clinic by a gynaecologist, whom she had consulted for secondary amenorrhoea. The clinical history revealed palpitations, weight loss (–5 kg), heat intolerance and emotional instability lasting for at least 4 months. There was no family history of thyroid disease.

The physical examination was concordant with hyperthyroidism. The patient had a diffusely enlarged thyroid gland without bruit, lid lag and lid retraction (but no exophthalmus) and sinus tachycardia (pulse 98/min). Blood pressure was 120/80 mmHg. Examination of the neuromuscular system showed a fine tremor of the fingers and rapid ankle reflexes. The rest of the physical examination was within normal limits. Ophthalmoscopy showed the fundus to be normal.

Laboratory results confirmed hyperthyroidism; the free thyroxine (T_4) level was 32 pmol/l (normal 11 - 21 pmol/l), and the TSH level 7.5 μU/ml (normal 0.4 - 5 μU/ml). Tests for antimicrosomal and antithyroglobulin antibodies were negative. The blood count and the findings on routine biochemical examination were within normal limits.

The uptake of ^{131}I by the gland was increased by 54% after 24 hours (normal 15 - 45%).

Because of the increased level of TSH in this hyperthyroid patient, magnetic resonance imaging (MRI) of the pituitary gland was performed. MRI showed a non-homogeneous mass ($2 \times 1.5 \times 1$ cm in diameter) involving the pituitary fossa and expanding suprasellarly. The stalk was displaced anteriorly and superiorly. The mass was close to but separated from the optic nerves (Figs 1 and 2). On post-contrast study there was slight non-homogeneous enhancement of the mass (Fig. 3).

The full hormonal profile of adenohypophysis was examined and did not show any pathological changes (except the above-mentioned high level of TSH). Examination of the alpha subunits of TSH was not available.

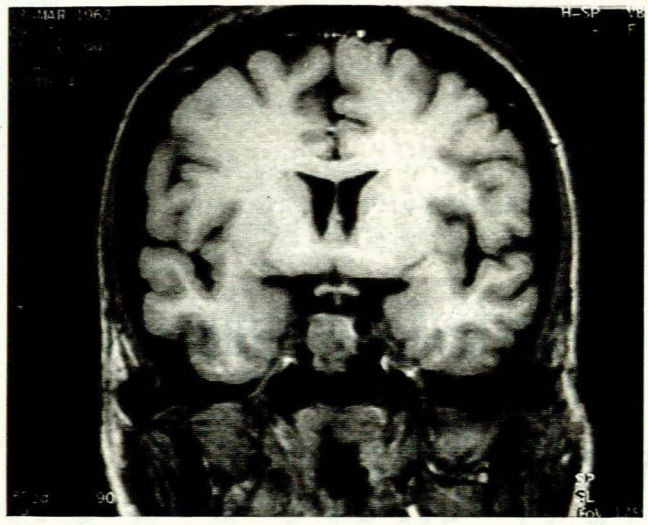

Fig. 2. Coronal T1WI gradient echo shows a non-homogeneous expanding suprasellar mass but no involvement of the cavernous sinuses and optic nerves.

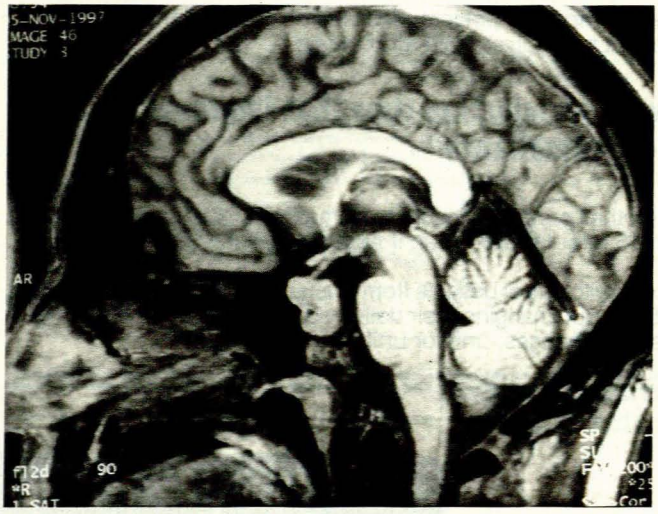

Fig. 1. Sagittal T1WI gradient echo shows a non-homogeneous mass involving the pituitary fossa and expanding suprasellarly. Optic nerves are not involved.

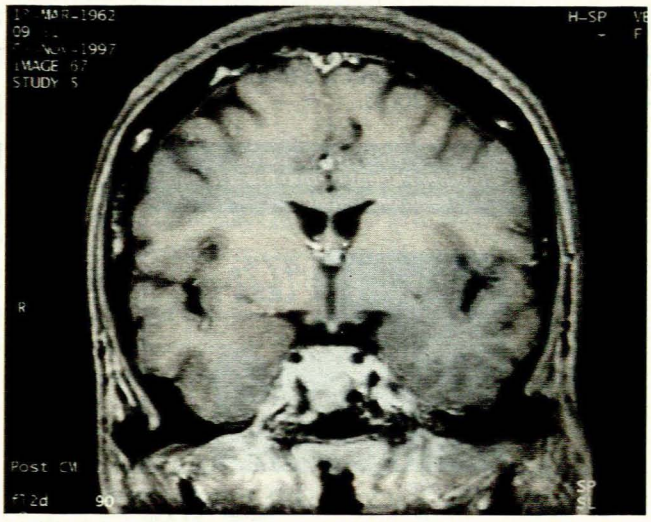

Fig. 3. Coronal T1WI gradient echo after injection of contrast agent (Gd-DTPA) shows a slight non-homogeneous enhancement of the mass.

THERAPY

The patient was treated for 2 months with a β-blocker (propranolol 40 mg 3 times a day) and carbimazole (40 mg/day) because of clinical symptoms of hyperthyroidism. During that period her symptoms of hyperthyroidism ceased. The free T_4 levels did not normalise, but decreased from 32 to 24 pmol/l. The TSH level remained unchanged (7.6 μU/ml).

Sixty-five days after the diagnosis of a pituitary adenoma the patient underwent a trans-sphenoid adenomectomy.

Histological examination showed polygonal cells with round nuclei and basophilic cytoplasma. The tissue had a trabecular structure, and hypophysis adenoma was diagnosed.

Outcome of operation

The operation, trans-sphenoid adenomectomy, was successful. The level of free T_4 decreased to a hyperthyroid level (6.3 pmol/l), and the TSH level to 1.52 μU/ml 10 days after the removal of the TSH adenoma. Administration of carbimazole was stopped after the operation. Replacement therapy with thyroxine 0.05 mg/day was started immediately and free T_4 levels were kept at upper normal limits (19.4 - 20.1 pmol/l) during the 8 months after the operation. TSH is still being produced and remains between 1.7 and 2.3 μU/ml with no tendency to increase. The levels of other hormones of adenohypophysis are within normal limits 8 months after the operation. The only complication is persistent diabetes insipidus, which developed after the operation and is being adequately treated with desmopressin (DDAVP) 0.1 ml twice daily.

The postoperative MRI (8 months after neurosurgery) showed fibrotic changes and a fatty pad between the dorsum sellae and residual adenohypophysis. The stalk was not dislocated (Figs 4 and 5).

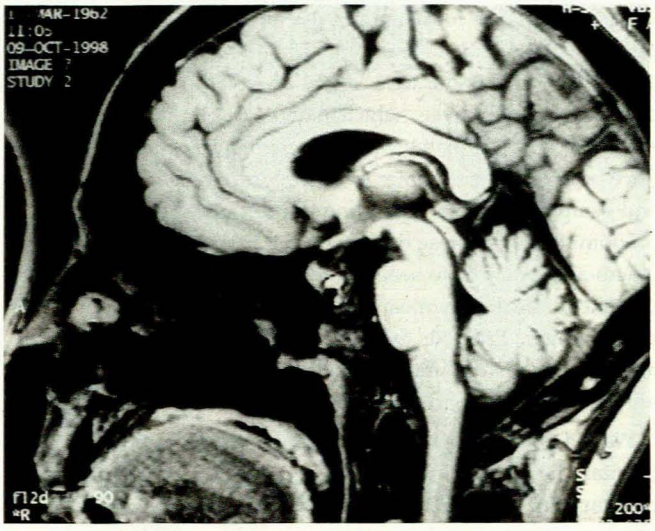

Fig. 4. Sagittal T1WI gradient echo shows a sharply circumscribed hyperintense mass between the residual adenohypophysis and dorsum sellae, which corresponds to fatty tissue. There is no evident neurohypophysis.

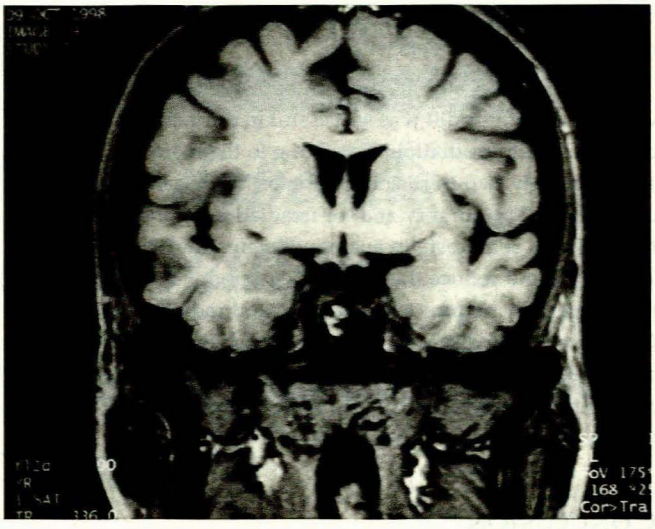

Fig. 5. Coronal T1WI gradient echo shows a small lobulated hyperintense mass corresponding to fatty tissue.

DISCUSSION

TSH-producing adenoma of the pituitary gland is characterised by non-suppressed secretion of thyrotropin despite elevated serum thyroid hormone in patients with clinical symptoms and signs of hyperthyroidism. There are 2 known causes of central hyperthyroidism: (*i*) TSH-omas; and (*ii*) the syndrome of pituitary resistance to thyroid hormone (PRTH). In TSH-omas the serum TSH levels, as well as free T_4 and free tri-iodothyronine (T_3) concentrations, usually show a broad range of values and no correlation between TSH and thyroid hormones. Variations in the biological activity of secreted TSH molecules probably account for such findings.[1] In the majority of patients with TSH-omas, circulating alpha-subunits are elevated and their testing can contribute to early diagnosis. Unfortunately we have not had access to this laboratory test. Another diagnostic aid is absent or impaired TSH response to thyrotropin-releasing hormone (TRH) because of lack of TRH receptors by TSH-omas, but contrary findings have also been reported.[4,5]

Patients with PRTH show increased secretion of TSH in response to administration of TRH.[6] TSH-omas can be demonstrated by imaging techniques such as computed tomography (CT), MRI or octreotide scanning.[7] Unlike patients with TSH-omas, patients with PRTH do not have symptoms of pituitary enlargement.[6] Increased or normal levels of TSH in a hyperthyroid patient are an indication for a CT scan, or preferably MRI, of the pituitary gland. The MRI gives better

images and allows for better pre-operative evaluation of the pituitary gland and surrounding structures, especially the optic nerves. The MRI in our case clearly proved the macro-adenoma of the adenohypophysis, which showed the suprasellar extension. Approximately 90% of reported cases of TSH-omas have been macro-adenomas (> 1 cm).[1] In some patients, signs and symptoms due to expanding tumour mass may predominate over those due to thyroid hyperfunction. Invasive macro-adenomas have been found more frequently in patients mistakenly treated by means of thyroid ablation (surgery or radio-iodine).[8] Previous thyroid ablation may induce an aggressive transformation of the tumour, as seen after adrenalectomy for Cushing's disease in Nelson's syndrome.[9]

We did not find any other alteration of the secretion of pituitary hormones, but in approximately 30% of patients the pituitary tumour secretes other hormones, usually growth hormone (16%) or prolactin (11%) or rarely gonadotropins (1%).[1] Concomitant growth hormone (GH) hypersecretion can be accompanied by typical acromegalic features, while hyperprolactinaemia usually presents with amenorrhoea and galactorrhoea, whereas thyrotoxic manifestations are often less prominent.[6] Patients with PRTH do not have other pituitary hormone excesses or deficiencies.

Neurosurgery is still the main therapeutic option for patients with TSH-oma,[10] and it was successful in our patient. It may be combined with irradiation. According to the literature, approximately two-thirds of TSH-omas have been brought under control by surgery and/or irradiation.[1] Conservative therapy with somatostatin analogue (octreotide) can suppress TSH levels and reduce the size of the tumour.[11] It is considered to be especially helpful when surgery and radiotherapy have failed to cure the disease. It is not yet established whether octreotide may be an alternative to surgery and irradiation in treatment of patients with TSH-omas.[12] Diabetes insipidus is a known complication of pituitary gland surgery.

Conclusion

A 36-year-old woman was found to have hyperthyroidism due to TSH-secreting pituitary adenoma. Surgical removal of the TSH-secreting adenoma (TSH-oma) induced clinical and biochemical remission of the hyperthyroidism. TSH-omas are rare but possible causes of thyroid hyperfunction and should be considered in a hyperthyroid patient with non-suppressed TSH levels. Specific investigations are needed to differentiate TSH-secreting adenoma from the syndrome of pituitary resistance to thyroid hormone (PRTH).

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