CASE REPORT

Pituitary Thyroid Resistance Syndrome

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Summary

Thyroid hormone resistance (RTH) is a rare autosomal dominant disorder, characterized clinically by goiter and biochemically by elevated circulating free thyroid hormone levels in the presence of measurable serum thyroid-stimulating hormone (TSH) concentrations. About 85% of patients with RTH harbor mutations in thyroid hormone receptor [beta] (TR[beta]). Even rarer is pituitary thyroid resistance syndrome. We report a case of a 35-year-old man who presented with hypermetabolic symptoms with elevated levels of thyroid hormones, associated with non-suppressed thyrotropin (TSH). When treated with anti-thyroid drugs, his thyroid hormone levels normalized and TSH increased, suggesting thyroid resistance at the pituitary level.

Key Words: Thyroid hormone resistance, Pituitary thyroid resistance syndrome, Hyperthyroidism

Introduction

Generalised resistance to thyroid hormone (GRTH) was first described by Refetoff et al [1] in 1967 and is characterised by raised circulating levels of thyroid hormones with normal or inappropriately raised levels of thyroid stimulating hormone (TSH) in serum. The clinical phenotype varies. Affected subjects may be asymptomatic and diagnosed incidentally or display symptoms like hyperactivity, short stature, mental retardation, or language abnormalities. In some patients an enlargement of the thyroid gland can be detected [2]. Genetic linkage of GRTH to the human thyroid receptor beta 1 gene (c-erbA beta 1 gene) has been identified and to date 38 different point mutations in several kindreds have been documented [3]. In about 90% of cases, GRTH inherited in an autosomal dominant manner.

Patients with RTH are euthyroid clinically despite the raised levels of free thyroxine because of the inability of the hormone to have the metabolic effects due to the receptor abnormality. In this case, however, the patient had symptoms and signs of thyrotoxicosis despite the raised TSH levels, suggesting pituitary resistance to the hormones.

Case History

A 35-year-old man presented with a three month history of palpitations associated with excessive sweating and irritability. There was no loss of weight or appetite. The palpitation usually occurred once or twice per week and was not related to exertion. There was no history of flushing, chest discomfort or syncope. He had no other medical illnesses or family history of thyrotoxicosis or goiter. There was no history of frequent ear, nose and throat infection.

Examination revealed a young gentleman who had mild tremors with no goiter. His blood pressure was 130/70 mmHg and pulse rate of 90/min with a regular rhythm. There was no exophthalmos or other eye signs. His reflexes were normal. The rest of the systemic examination was unremarkable.

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Investigations showed thyroid stimulating hormone of 2.04 uIU/ml (normal 0.32 –5.00), free thyroxine 38.37 pmol/L (normal 9.14 –23.81) and free triiodothyronine, 8.06 pmol/L (normal 2.58 –5.44). A thyroid scan revealed normal results. His renal profile and fasting blood sugar were normal.

He was initialy started on propranolol 20mg bd. Despite several months on propranolol, he was still symptomatic. Neomercazole 20mg daily was then added and tapered down accordingly until 10mg daily. With this treatment, his symptoms improved. His free T4 came down to 12.25 pmol/l and serum TSH increased to 5.87 uIU/ml. He was diagnosed to have thyrotoxicosis in a pituitary thyroid resistance syndrome.

Discussion

The prevalence of resistance to thyroid hormone is unknown but is thought to be low, probably 1 in 50,000 live births. The phenotype is heterogeneous and ranges from highly symptomatic to subclinical. Of interest, as in this case, is pituitary resistance to thyroid hormone (PRTH). It is characterized by thyroid hormone resistance in the pituitary gland while peripheral tissues retain apparent normal responsiveness. Since the pituitary is resistant, normal amounts of thyroid hormones do not inhibit pituitary TSH secretion. As a result, TSH secretion is excessive, causing overproduction of thyroid hormones in amounts sufficient to satisfy pituitary requirements. The increased T4 and T3 concentrations, however, are excessive for peripheral tissues. At equilibrium, elevated serum T4/T3 levels are thus required to maintain relatively normal TSH secretion but cause peripheral manifestations of thyrotoxicosis [2].

The reason for the nonsuppressed serum TSH levels is due to the pituitary gland expressing the defective TRbeta, which blunts the suppressive effect of thyroid hormone. Studies of TRbeta deficient mice further showed that the TRbeta molecule is not necessary for the upregulation of TSH, but is required for thyroid hormone to exert its full suppressive effect. In the present case, he was diagnosed to have pituitary resistance to thyroid hormone as clinically he was thyrotoxic and he had raised free T4 and T3 but normal TSH and no response to TRH stimulation. He was considered to have pituitary resistance because of the increase in TSH following treatment with anti-thyroid drugs.

Patients with resistance to thyroid hormone, have other clinical features such short stature, tachycardia, increased systolic cardiac performance and valvular defects, increase frequency of ear, nose, and throat infections, significant hearing loss as thyroid hormone receptor beta is now known to be restricted to the cochlea, lower IQ as well as speech delay [3]. This patient had none of the above.

Treatment of PRTH is usually necessary because of the presence of clinical thyrotoxicosis. The first line of treatment of these patients should be symptomatic. Beta blocker is very effective in treating tachycardia and tremor without affecting the conversion of T4 to T3 and this patient was given propranolol. Since overproduction of TSH is the major abnormality, treatment with agents which have the potential to decrease the levels of thyroid hormone through suppression of TSH has received much attention. Dopaminergic drugs and somatostatin analogs have had limited use because of side effects and low success rate in maintaining TSH suppression.

Thyroid ablation with radioiodine in patients with PRTH appears, at present, to be the best compromise solution[2]. The benefit of correcting the thyrotoxicosis probably outweighs the unsubstantiated risk of pituitary enlargement. Close monitoring must be continued because of the possibility of thyrotoxicosis recurring. It may also be advisable to periodically monitor pituitary gland size by radiographic or magnetic resonance imaging.

References

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