

The Syndrome of Resistance to Thyroid Hormone, Misdiagnosed as Thyrotoxicosis Elamin A¹, Jawad H²

Abstract

Objective: to report two cases of resistance to thyroid hormone to increase the awareness of this syndrome, which is frequently misdiagnosed and incorrectly treated.

Methods: we described two siblings, both of whom were diagnosed as having thyrotoxicosis and one of them was treated with carbamazole and subsequently developed hypothyroidism. Both patients showed features of resistance to thyroid hormone and required additional L-thyroxine to normalize the thyroid stimulating hormone level while remaining clinically euthyroid.

Results: Laboratory evaluation revealed increased serum thyroxine and tri-iodothyroxine levels as well as increased thyroid stimulating hormone (TSH) levels. The free alpha subunit/TSH ratio was normal, and CT of the pituitary gland showed no tumour. Metabolic studies using graded doses of tri-iodothyroxine supported the diagnosis.

Conclusion: The two patients have resistance to thyroid hormone but were erroneously diagnosed as thyrotoxic and one of them inappropriately treated. Patients with elevated plasma levels of thyroid hormones with high or normal TSH level need careful evaluation of the hypothalamic-pituitary function & peripheral action of thyroid hormones.

Key words: Thyroid function, hypothyroidism, TSH, goitre

Introduction

Resistance to thyroid hormone (RTH) is an inherited condition that is being recognized and reported more frequently now than in the past. More than 700 cases have been identified since Refetoff described the first reported patient in 1967¹. However, very few cases were reported in patients below the age of 15 years². Awareness need to be increased about this condition because it has frequently been misdiagnosed and inappropriately treated³. Variability in the responsiveness of tissues to thyroid hormones explains the different clinical presentations of RTH (hyper, hypo and euthyroid states)^{4,5}. The association of RTH with persistent tachycardia and hyperactivity has frequently resulted in erroneous diagnosis of thyrotoxicosis^{6,7}.

Clinical Findings

Two siblings, Moza a 15-year-old girl and Salim a 12-year-old boy were detected during a school health survey for goitre and familial thyroid disorders in the south Batna region in the sultanate of Oman. They were born to consanguineous parents after uneventful pregnancy and normal delivery. A family history of goitre was noted in their mother and a paternal grandmother, but none of them neither complained of any symptom nor was on any medication. Both teenagers were diagnosed as having hyperthyroidism at Sohar teaching hospital and the girl was

started on carbamazole treatment. Three weeks after this treatment the patient developed symptoms of hypothyroidism, so the drug was discontinued and both siblings were referred to our pediatric endocrinology clinic at the university hospital in Muscat.

Case 1: Moza was diagnosed as suffering from attention deficit and hyperactivity disorder at the age of 5 years and at the age of 15 years a goitre was noticed during school health examination. Hyperthyroidism was diagnosed at the regional hospital on the basis of high level of free thyroxine (free T4) in the serum (24 pmol/L) and she was started on carbamazole treatment despite a normal level of thyroid stimulating hormone (TSH) 4.5 mU/L (reference range 0.4-5.0). Her free T4 dropped to 3.1 pmol/L (reference range 10-22) and she showed clinical features of hypothyroidism. The anti-thyroid medication was then stopped and she was referred, together with her sibling, to the pediatric endocrinology clinic of the university hospital in the capital. Physical examination in our clinic showed a blood pressure of 110/70 mm Hg, heart rate was regular at 80 beats/minute, height on the 5th percentile and weight on the 75th percentile for age. Eye examination showed no exophthalmos, lid lag, lid retraction, or periorbital edema. Neck examination revealed a small non-nodular goitre without tenderness or bruit. She had no tremors or nail problems and her skin was normal. There were also no signs of hypothyroidism, but the patient complained of frequent constipation and fatigue.

Case 2: Salem, a smart and pleasant boy, was found during a school health survey to have small goitre. He had no past history of any significant medical problem and was asymptomatic. He was investigated by serum thyroid function test and

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referred, together with his elder sister Moza, to the regional hospital for evaluation and management. His TSH was 4.7 mU/L and his free T4 was 25 pmol/L. Hyperthyroidism was diagnosed, but he was not given anti-thyroid medication. Physical examination in our clinic showed a blood pressure of 110/66 mm Hg, heart rate was regular at 78 beats/minute, height on the 10th percentile and weight just above the 50th percentile for age. There were no signs of hypo or hyperthyroidism.

The two patients were thoroughly investigated using same tests. Because the results of the siblings were almost identical, we will only present and discuss the results of the elder sibling, Moza. Routine investigations, complete blood count, serum chemistry, urinalysis, and a chest x-ray film showed normal findings. A CT imaging of the pituitary gland excludes structural malformations and tumours. Free T4 & TSH serum levels were elevated above reference values in both siblings, but the molar ratio of the alpha subunit of pituitary glycoproteins over TSH was less than 1.0. The microsomal and thyroglobulin antibodies were negative and thyroid-binding globulin was normal. Radio-isotope thyroid scan showed increased uptake in both lobes.

After the initial workup, a provisional diagnosis of RTH was made and we started both siblings on Levo-thyroxine (LT4). Their compliance was adequate and the dose of thyroxine was gradually increased till the serum TSH level returned to normal. Moza became more energetic with better self esteem and normal bowel habits. Additional metabolic investigations were then performed on both siblings to confirm the diagnosis and to determine the peripheral tissue sensitivity to thyroid hormone. The serum levels of cholesterol, creatine kinase (CK), ferritin, and sex hormone-binding globulin (SHBG) were measured at baseline and repeated after the administration of graded dose of triiodothyronine (LT3) in the two patients and then compared with normal control subjects. The LT3 dosages were 50, 100 and 200 µg daily, each given in split doses every 12 hours for 3 days. The thyrotropin-releasing hormone test was performed at the termination of each LT3 dose, and the TSH response was determined and compared with baseline. These investigations reflect the peripheral tissues and central responses to the administration of LT3 in the patients and the normal subjects. The patients have demonstrated an attenuated response of SHBG, CK, and cholesterol to the administration of LT3 as well as

the need for higher doses of LT3 to suppress the serum TSH concentration. In the normal subjects, the responses of cholesterol and CK to administration of LT3 were negatively regulated, whereas the response of ferritin and SHBG were positively regulated. Further details on the interpretation of these metabolic studies are presented below.

Discussion

RTH is characterized by reduced responsiveness of target tissue to concentrations of thyroid hormone that would be excessive under normal conditions. The hormonal insensitivity is partial and is usually compensated for by increased hormone secretion. It is variable from tissue to tissue, with heart and metabolism being the least resistant and pituitary the most resistant⁸. Genetic studies have localized the underlying defect to mutations of the thyroid hormone receptor-β (TRB) gene, which is a ligand-dependent transcription factor⁹. TRB regulates the rate of transcription by binding to thyroid hormone response element located in promoter region of genes regulated by thyroid hormone¹⁰. Mutation in most subjects with RTH result in reduction in affinity of TRB for T3¹¹. Recently, a family was described with three members having a severe type of RTH in the absence of a mutation in the TRB or thyroid hormone receptor-α gene¹². An abnormal cofactor in the regulation of thyroid hormone action could explain the RTH in those subjects. TRB has been shown to be important in the development of the auditory apparatus, and severe hearing loss; which can be senso-neural, conductive, or mixed, may occur in patients with RTH¹³. Although RTH is a genetic disease with a defect that can be detected in utero, it rarely presents before the age of 20 years and only few cases have been described in children, so far¹⁴.

RTH affects boys & girls equally, but few studies had suggested female predilection. Most cases are familial, but sporadic cases due to new mutation have been reported. Although the first reported family with RTH showed autosomal recessive inheritance, most of the cases studied and documented after that have autosomal dominant mode of inheritance¹⁵. Patient with RTH are usually euthyroid and have goiters, although various degrees of hypothyroidism or hyperthyroidism may be noted among affected persons or within one family¹⁶⁻¹⁷. Because of these latter features, in addition to the association with attention-deficit disorder, patients with RTH were often misdiagnosed and treated for

thyrotoxicosis⁷. In RTH, thyroid function tests show increased levels of both total and free T3 and T4 in the presence of unsuppressed TSH, which may be either normal or slightly increased. In confirming the diagnosis of RTH, TSH-producing pituitary tumor, as well as other forms of euthyroid hyperthyrotoxinemia must be excluded¹⁸. The features favouring the diagnosis of RTH rather than thyrotoxicosis included the normal or elevated level of TSH, the mild elevation of free T4, the normal ratio of the alpha subunit of pituitary glycoproteins over TSH and the peripheral tissue response to the graded T3 administration or hormone⁹.

Once the diagnosis of RTH is suspected clinically and biochemically, simple metabolic studies can be performed to support the diagnosis. These studies include the demonstration of attenuated responses of thyroid hormone dependant markers to the administration of graded doses of LT3. Such markers include serum cholesterol, SHBG, CK, and ferritin¹⁹. No treatment is necessary in most patients of RTH because they are euthyroid, except in those with prominent features of hypothyroidism at the time of initial assessment or in those who had undergone thyroid ablative treatment. Supraphysiologic doses of LT4 are usually effective (approximately 1 to 5 mU/L). Preliminary results show that therapy with LT3 may be of value in patients with RTH who have attention-deficit hyperactivity disorder, but further studies are needed²⁰⁻²².

Conclusion

On the basis of the foregoing review, both of our patients (the girl and her brother) have RTH. The mode of inheritance couldn't be ascertained because of lack of essential parts of family and medical history, but it is apparently autosomal dominant. Both patients have the typical clinical and biochemical features of the syndrome, and the results of the metabolic studies support this diagnosis. We did not identify the TRB mutation in our patients because it was not important diagnostically or in the management. Such knowledge, however, could assist in prenatal diagnosis and genetic counseling. Neonatal screening is important and recommended; blood TSH and T4 levels should be measured for early diagnosis. Both patients described herein were, unfortunately, misdiagnosed as having thyrotoxicosis and one of them had received unnecessary and potentially harmful treatment. We hope that this report promotes awareness of

this condition among physicians, in order to help prevent unnecessary treatment.

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