

**THE SYNDROME OF RESISTANCE TO THYROID
HORMONE, MISDIAGNOSED AS THYROTOXICOSIS**

Abdelaziz Elamin, MB, MD, FRCP, PhD, FRCPCH

Professor of Child Health

College of Medicine

Sultan Qaboos University, Muscat, Oman

Hashim Jawad, MB, MRCPCH

Registrar, Department of Child Health

Sultan Qaboos University Hospital, Muscat, Oman

ABSTRACT

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

CORRESPONDENCE TO:⁴

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.

⁴) Dr. Elamin A, E-mail: azizmin@gmail.com

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 thyrotoxicosis⁶⁻⁷.

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 goiter 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 goiter 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 goiter 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 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

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 resistant 8. Genetic studies have localized the underlying defect to mutations of the thyroid hormone receptor- β (TRB) gene, which is a ligand-dependent transcription factor 9. TRB regulates the rate of transcription by binding to thyroid hormone response element located in promoter region of genes regulated by thyroid hormone 10. Mutation in most subjects with RTH result in reduction in affinity of TRB for T3 11. 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-gene 12. 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 sensorineural, conductive, or mixed, may occur in patients with RTH 13. 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 far 14.

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 inheritance 15. 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 family 16-17. Because of these latter features, in addition to the association with attention-deficit disorder, patients with RTH were often misdiagnosed and treated for thyrotoxicosis 7. 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 excluded 18. 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 hormone ⁹.

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 ferritin 19. 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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