Resistance to thyroid hormone in a Turkish child with A317T mutation in the thyroid hormone receptor-beta gene

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Resistance to thyroid hormone (RTH) syndrome is a rare disorder usually inherited as an autosomal dominant trait. The combination of elevated serum levels of free thyroid hormones with elevated thyroid-stimulating hormone (TSH) suggest differential diagnoses of RTH, thyroxine-binding globulin abnormalities, familial dysalbuminemic hyperthyroxinemia and TSH-secreting pituitary tumors. We report a patient with RTH in a Turkish family. The diagnosis was confirmed by the identification of a known disease-causing mutation in the thyroid hormone receptor-beta (THRβ) gene, but is the first published in the Turkish population. Genetic analysis of the mother and the patient yielded a mutation in the THRβ gene, A317T, due to a base pair substitution of an adenine for a guanine.

Key words: thyroid hormone resistance, A317T mutation.

Thyroid hormone secretion and release are stimulated by thyroid-stimulating hormone (TSH), which in turn is controlled by thyroid hormones by negative feedback. Resistance to thyroid hormone (RTH) is a syndrome of impaired tissue responsiveness to thyroid hormone. Since the first description of RTH in 1967[1], more than 600 cases have been reported[2,3]. The biochemical hallmarks of RTH are increased circulating thyroid hormones and elevated or normal TSH levels caused by loss of the negative feedback. The genetic studies have shown that most mutations are found in three exons in the thyroid hormone receptor-beta (THRβ) gene on chromosome 3, coding for hormone-binding domain in the receptor[3,4]. About 10% of individuals with classic RTH do not have mutations in the THRα or THRβ genes. Most of the disease-causing mutations are clustered in the ligand-binding domain of THRβ, residues 310-353 (cluster 1), 429-461 (cluster 2), and 234-282 (cluster 3)[4]. Mutations in clusters 1 and 2 impair thyroid hormone binding directly, increase the dissociation of T3 from its binding site, inhibit the formation of heterodimers, or selectively inhibit coactivator binding[5,6], while mutations in cluster 3 affect receptor function indirectly by defective corepressor release[7]. The clinical picture varies from no symptoms, indicating generalized resistance, to overt thyrotoxicosis, as would be seen in selective pituitary resistance.

We report the clinical and genetic investigation of an infant and her mother with RTH caused by a mutation in the THRβ gene.

Case Report

S.O. (date of birth 10.07.2000), a female patient, was referred to our Unit at the age of 23 months for further investigation of high thyroid hormone and normal TSH levels. She was the first child of nonconsanguineous parents. The mother, who had a goiter, was started on propylthiouracil for hyperthyroidism three years before pregnancy and had been on therapy during pregnancy. The patient was born at term weighing 3540 g. Because of the mother's thyroid dysfunction, thyroid hormone levels of the patient were measured postnatally on several occasions. Although the patient was clinically euthyroid during the first week of life, TSH and T3 levels were high and T4 level was normal, as seen in Table I. Thyroid ultrasonography showed diffuse hyperplasia.

Table I. Thyroid Hormone and TSH Levels of the Patient

Age	TSH (mU/L) (N: 0.4-4.0)	T4 (ng/dl) (N: 0.8-1.9)	T3 (pg/dl) (N: 1.8-4.8)
Prior to presentation to our Unit			
2 days	70.3	1.7	9.1
7 days	75	1.1	10
1 month	3.3	3.9	6.4
3 months	2.9	4.8	6.2
6 months	1.6	4.9	8.1
9 months	2.1	4.9	6.3
11 months	2.3	5.4	6.4
13 months	1.6	4.7	6.3
15 months	1.3	4.2	5.7
20 months	1.8	4.3	9.5
At presentation to our Unit 22 months	1.5	4.6	7.9

TSH: Thyroid-stimulating hormone.

She was started on levothyroxine for presumed hypothyroidism, but it was discontinued after 1 month of age. Thyroid hormone measurements done at that age and on several occasions afterwards revealed high thyroid hormone and normal TSH levels (Table I).

Physical examination of the patient at presentation to our unit at 23 months of age was normal. She was clinically euthyroid. Height (89.2 cm) and weight (11.7 kg) expressed as standard deviation scores (SDS) were 1 SDS and -0.38 SDS, respectively, according to age- and sex-specific Turkish standards[8,9]. Thyroid hormones were high and TSH normal as seen in Table I. TSH-secreting tumor was ruled out by normal brain magnetic resonance imaging (MRI). After TRH stimulation tests (basal and after using 37.5 microgram L-T3 daily for 3 days according to Chicago protocol), no TSH suppression occurred (Table II). Possible effects of high thyroid hormone levels at the periphery were investigated. Echocardiography was normal. Serum alkaline phosphatase, sex hormone binding globulin (SHBG), thyroxine-binding globulin (TBG) levels and serum lipid levels were normal. Denver developmental test was normal. Thyroid hormone and TSH levels of the parents are shown in Table III.

Thyroid Hormone Assays

Serum TSH, T4, T3, prolactin, TBG and SHBG were measured by chemiluminescent microparticle immunoassay (Architect System, Abbott Ireland Diagnostic Division, Lisnamuck, Longford, Co. Longford, Ireland). Serum alkaline phosphatase and lipid levels were measured in the hospital clinical chemistry laboratory by automated assays. The normal values of thyroid hormones and TSH are depicted in the Tables.

Table II. TSH Responsiveness to TRH Stimulation Test on Incremental L-T3 Dose

	0 minute	30 minute	60 minute	90 minute
Basal TSH (mU/L)	2.03	24.2	17.4	13.9
Prolactin (ng/ml)	14.7	–	–	11.4
After 3 days of L-T3 25 μg				
TSH (mU/L)	0.7	9.3	7.5	4.8
Prolactin (ng/ml)	31.7	–	–	11.1
50 μg				
TSH (mU/L)	0.4	6.8	5.1	4.4
Prolactin (ng/ml)	10.8	–	–	18.8
100 μg				
TSH (mU/L)	1.0	3.4	2.6	2.7
Prolactin (ng/ml)	16.7	–	–	21.3

TSH: Thyroid stimulating hormone. TRH: Thyroid releasing hormone.

Table III. Thyroid Hormone and TSH Levels in the Parents of the Patient

	Father	Mother
TT4 μg/dl (N: 5-12 μg/dl)	9.4	22.1
TT3 ng/dl (N: 90-180 ng/dl)	116	282
TrT3 ng/dl (N: 6.0-10.5 ng/dl)	28.0	114.6
FT4 I (N: 0.4-3.6)	11.8	29.2
TSH μU/ml (N: 1-25 μU/ml)	4.0	1.7

TSH: Thyroid stimulating hormone.

Mutational Analysis

Informed consent was obtained from the family. Genetic analyses of the patient and her parents were performed in the Thyroid Study Unit-Department of Medicine, University of Chicago. Genomic DNA was extracted from circulating white blood cells of family members and used for direct sequencing of the TRβ gene. Polymerase chain reaction (PCR) amplification of the last 3 coding exons (8, 9, and 10) of TR was carried out using 100 ng of genomic DNA as the template and 10 pmol each of an appropriate pair of primers, as described previously[8]. Genetic analysis of the mother and the patient yielded a mutation in the THRβ gene, A317T, due to a base pair substitution of an adenine for a guanine.

Discussion

Most patients with RTH are heterozygous, with only one mutated THRβ gene, and the clinical symptoms are mild[3]. Only one patient homozygous for mutant THRβ has been reported[3]. The clinical picture varies from no symptoms, indicating generalized resistance, to manifest thyrotoxicosis, as would be seen in selective pituitary resistance. Variable resistance in different organs due to differences in the distributions of THRα or THRβ can cause a mosaic of hyper- and hypothyroid signs in the same patient. The most common findings are growth retardation, attention deficit and hyperactivity disorder, goiter and hyperthyroid cardiac symptoms[2,3]. Severe mental retardation is quite uncommon in RTH[10]. Patients with RTH are usually euthyroid but can occasionally present with signs and symptoms of thyrotoxicosis or rarely with hypothyroidism[3].

We report a relatively common mutation that has been previously described in other populations[11-13]. Parilla et al.[12] reported a patient with the same mutation with significant articulation problem. The clinical manifestations vary between families with the same mutations and also between members of the same family with identical mutations[3]. Our patient was euthyroid and the only clinical symptom was goiter in the mother. This mutation has been described in different phenotypes, suggesting that the heterogeneity in RTH may be the result of multiple genetic factors[11-13].

Differential diagnosis of RTH is very important for therapeutic approach. RTH can be misdiagnosed in individuals with TBG abnormalities. Subjects with TBG excess present with elevation of both serum TT4 and TT3 but normal TSH levels[14]. Familial dysalbuminemic hyperthyroxinemia is the most common cause of euthyroid hyperthyroxinemia. It results in elevations of serum T4 and rarely T3 level[15]. TSH-secreting pituitary tumors (TSHomas) should always be considered in the differential diagnosis. TSHomas are sporadic and often co-secrete prolactin and growth hormone. LT-3 administration does not decrease serum TSH and administration of TRH does not stimulate TSH release. These patients are thyrotoxic and almost always have low SHBG[16]. Diagnosis of RTH confirmed by genetic studies prevents further investigation.

In conclusion, we present a common mutation in RTH, but the first published in the Turkish population, and we aimed thereby to point out the importance of the differential diagnosis of RTH. Furthermore, the wide clinical variability should be kept in mind when RTH is suspected.

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