A Rare Mutation in Patients With Resistance to Thyroid Hormone and Review of Therapeutic Strategies

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Abstract: *Background:* Resistance to thyroid hormone (RTH) is a rare syndrome characterized by elevated thyroid hormone (TH) along with nonsuppressed thyroid-stimulating hormone (TSH). The clinical symptoms can vary considerably, and no definite treatment has been established thus far. *Methods:* A family with RTH harboring a TH receptor (THR)-β gene mutation (A234T) is described, the therapeutic strategies for RTH are reviewed, and optimization of the treatment strategies was attempted. *Results:* Gene sequencing revealed a point mutation (A234T) in the THR-β gene of the proposita, her elder brother and her mother. During the 20-month follow-up period, it was found that the proposita experienced apparently higher TSH level and normal TH level on taking antithyroid medication. However, on discontinuing the medication, her thyroid function returned to the baseline of elevated FT3, FT4 level along with inappropriately normal TSH. Thus far, there is no guideline regarding the treatment strategies for the RTH. Antithyroid drugs are effective for patients with thyrotoxic symptoms but pose an increased risk of thyrotroph hyperplasia. The efficacy and safety of D-T4 and bromocriptine still remains debatable, TRIAC may be the most promising drug, as it is effective and can reduce both TH and TSH level. However, L-T3 or L-T4 may be necessary for some RTH patients who exhibit massive goiter or hypothyroid symptoms. *Conclusions:* It is demonstrated in this article that the A234T mutation in the THR-β gene can cause the RTH. Treatment of this condition is challenging, and individualized therapy is required because of the variable clinical features.

Key Indexing Terms: Resistance to thyroid hormone; Thyroid hormone receptor; Gene mutation; Treatment strategies. **[Am J Med Sci 2015;350(3):167–174.]**

The concept of decreased target responsiveness to hormone stimulation was first introduced to medicine by Albright et al in 1942,[1] and has now been extended to most of the endocrine systems. Later, a selective tissue resistance to thyroxin was postulated by Refetoff et al[2,3] to account for the findings of apparently elevated thyroid hormone (TH) levels in 3 siblings who did not present symptoms or signs of hormone excess, but rather hormone sufficiency and even deficiency, and he designated this special situation as resistance to thyroid hormone (RTH). More than 1,000 subjects[4] with RTH from different families have been reported since its first description by Refetoff et al[2] in 1967, and the incidence of THR is estimated to be 1 in 40,000 live births. Biochemically, the RTH syndrome is defined by persistent increased serum TH levels including FT3 and FT4, along with inappropriately normal or elevated level of thyroid-stimulating hormone (TSH). The clinical features of RTH are highly variable, as even the manifestations of various tissues within the same individual or family members who carry identical mutations vary considerably.[5] The clinical spectrum ranges from isolated biochemical abnormalities to the classic features related to hyperthyroidism and hypothyroidism, including goiter, hyperactivity, attention-deficit hyperactivity disorder, growth delay and tachycardia.[6,7] However, other features such as frequent ear nose and throat infections, hearing deficit and decreased bone mass have recently been recognized in RTH patients.[8,9] Clinically, RTH can be divided into general resistance to thyroid hormone and pituitary resistance to thyroid hormone (PRTH), or a combination of both. Most of the RTH patients belong to the general resistance to thyroid hormone class presenting with asymptomatic goiter, whereas PRTH patients tend to exhibit hypermetabolic symptoms as mentioned above.

The most common cause of RTH is the dominantly inherited THR-β gene (THR-β) mutations located on the chromosome 3. These mutations cluster in 3 hot spots of the THR-β ligand-binding domain including residues 310 to 353 (cluster 1), 429 to 461 (cluster 2) and 234 to 282 (cluster 3).[10] Most of the THR-β gene mutation can interfere with the binding affinity for T3 in a dominant-negative manner,[11] although a subset of mutations impairs the function of transcriptional factors including the coactivators and corepressors despite near-normal T3 binding.[12] The dominant-negative mutation is characterized inhibition of function of the normal counterparts by mutant receptor in the heterozygous mutation; this kind of mutation can cause the hypofunction of the whole receptor. Accurate diagnosis of RTH is important to avoid the misdiagnosis with primary hyperthyroidism and to avoid inappropriate treatment of the abnormal thyroid function. Majority of the RTH patients are asymptomatic, with adequate compensation through an increase of T4 production and do not require medical intervention although treatment may be necessary in a subset of patients to improve their hypothyroid or thyrotoxic symptoms.[13,14] Numerous studied have been reported, wherein it was attempted to relieve the thyrotoxic or hypothyroidism symptoms with multiple medications including antithyroid drugs,[15–17] bromocriptine,[18] dextrothyroxine(D-T4)[19] and triiodothyronine analog 3,5,3′-triiodothyroacetic acid (TRIAC).[20,21] However, the effects of the above treatment strategies varied considerably among patients and even for those with the identical mutation. Moreover, there are no definite guidelines regarding the treatment for RTH until now.

In this study, the clinical findings and laboratory data from 2 generations of a family harboring a THR-β mutation (A234T) was demonstrated, and the thyroid functional profile of this mutant THR-β gene was evaluated. The data suggested that the mutant A234T THR-β led to a clinical picture of RTH. In addition, the therapeutic strategies for RTH patients were reviewed, and optimization of the treatment strategies was attempted.

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SUBJECTS AND METHODS

Patients

The proposita, a 27-year-old Chinese woman, initially presented to another hospital with enlarged thyroid gland and mild palpitation. She had these symptoms for 6 months before the presentation, and the thyroid function test conducted in the hospital demonstrated slightly elevated FT4 and FT3 levels, along with normal TSH. Owing to the findings of elevated serum TH levels coupled with palpitation symptoms, the patient was presumed to have primary hyperthyroidism. Therefore, she was administered methimazole (MMI) therapy for several months. However, as the patient's free T3 and free T4 levels dropped and stayed at the upper limit of normal range, her TSH levels elevated dramatically after the antithyroid drug treatment. This raised a suspicion about the condition, and other disorders besides primary hyperthyroidism were considered.

The patient was then transferred to the authors' medical center. The thyroid function test revealed normal free T3 and free T4 levels, along with apparently elevated TSH; thyroid peroxidase antibody was slightly elevated. Physical examination revealed a well-developed euthyroid female experiencing normal menstrual cycle. The enlarged thyroid was firm on palpation. TSH-secreting adenoma was ruled out by magnetic resonance imaging of the pituitary gland. RTH was suspected, and so the MMI treatment was discontinued.

Blood samples were obtained from most of the patient's family members (except the son of her elder brother who refused to test); all of them except her mother, who also had the enlarged thyroid, were asymptomatic for thyroid diseases.

Thyroid Function Testing and Clinical Assays

Almost, all of the patient's family members who were present (except her sister who refused to test) were subjected to thyroid function tests. Serum FT4, FT3, T4, T3 and TSH were measured by chemiluminescence assay. Sex hormone-binding globulin and reverse T3 (rT3) were measured by chemiluminescence assay at the Guangzhou Kingmed Diagnostics Center.

DNA Isolation and THR-β Amplification

Informed consent was obtained from the patient and her family members before the study. Genomic DNA was extracted from peripheral whole-blood exons 7 to 10 of the THR-β gene were amplified by polymerase chain reaction.

Sequencing and Genotyping

The products of amplification were sequenced directly using automated fluorescence-based sequencing. To determine the presence or absence of nucleotide substitution, sequencing results were compared with the reference sequences NG_009159.1 and NM_000461.4.

RESULTS

Thyroid Function Test

The family pedigree is depicted in Figure 1. Elevated FT3, FT3 and T4 with inappropriately nonsuppressed TSH were found in the patient's elder brother (II-1) and her mother (I-2).

Subject II-3, the proposita, was a 27-year-old woman. She was on daily dose of 10 mg MMI for more than 2 months when she was transferred to the authors' medical center; the thyroid function test had revealed obviously elevated TSH and normal FT3 and FT4. Her antithyroid medication was discontinued on admission, and thyroid function test was monitored regularly (Figure 2), which showed that the patient's TSH level returned to normal range in 2 weeks. However, the FT4 increased dramatically, then decreased gradually, finally maintained a plateau, while the FT3 increased very slowly.

Subject II-1 was a 32-year-old man, the elder brother of the proposita. His thyroid function test was abnormal in the authors' medical center; however, he denied having any of the hyperthyroidism symptoms.

Subject I-2 was a 63-year-old woman, the mother of the proposita. Her enlarged thyroid was quite noticeable. Her thyroid function test conducted elsewhere showed elevated FT3 and FT4. Antithyroid drugs had been prescribed to her several years ago for suspected hyperthyroidism. She has discontinued the drug for 3 years before presented; she denied having any other hyperthyroidism symptoms besides enlargement of the thyroid gland.

THR-β Gene Sequencing and Genotyping

A missense mutation in exon 7 of the THR-β gene was found in the proposita, changing codon 234 from GCC to ACC, substituting residue 234 from alanine to threonine, ie, 700 G>A (Figure 3). This substitution was also identified in subjectI-2 and subject II-1, whereas the other family members did not have the mutation.

DISCUSSION

Clinical Features

The clinical manifestations of the 3 affected characters suggested that they were euthyroid except for palpitation and thyroid gland enlargement but were dissociated from the apparent thyroid dysfunction with elevated FT3 and FT4 and inappropriately normal TSH. The major differential diagnosis of RTH is pituitary TSH adenoma, which also presents as elevated FT3 and FT4 but with obviously elevated TSH in most instances. Moreover, the euthyroid clinical features and normal pituitary magnetic resonance imaging results helped to rule out the TSH adenoma in this family. The diagnosis of RTH was supported by identifying the heterozygous mutation at residue 234 of THR-β in the affected family members.

THRs have been shown to belong to a large super family of nuclear hormone receptors including the steroid, vitamin D and the retinoic acid receptors.[22] They share a similar domain organization with other family members as they all have a central DNA binding domain, a carboxy-terminal ligand-binding domain (LBD) and a hinge region. Previous studies have shown that there are 2 types of THRs, designated as THR-α and THR-β, which are encoded by genes located on chromosome 3 and 17, respectively.[23] The alternative splicing of the primary transcripts can result in several isotypes of THR. The 3 main isotypes of THR are THR-β1, THR-β2 and THR-α1. They can bind to T3 and fulfill a number of important functions in many different cell types, both during development and in adults. THR-α1 mRNA, being expressed from the very beginning of development, is nearly ubiquitous,[24] expressed mainly in the heart, bone and brain,[25] whereas the major expression sites for THR-β1 are the liver, kidney and thyroid. THR-β2 mRNA has a much more restricted distribution, limited to the pituitary, retina, inner ear and hypothalamus.[26] The variable phenotypes may be related to the variable distribution of the THR isotypes. Most of the RTH subjects have been proved to harbor mutations in the THR-β gene.[27] The long sought mutation in the THR-α gene was recently identified by exomic sequencing of DNA obtained from an 8-year-old girl with delayed growth and development.[28] Hyposensitivity to T3 with an identical