Discrepant Thyroid Function Test Results in a 44-Year-Old Man
Julio Leey1* and Philip Cryer2

CASE DESCRIPTION

A 44-year-old Caucasian male was transferred to our hospital for increased concentrations of thyroid hormones and constitutional symptoms, including fatigue and muscle tenderness of 6 weeks’ duration. Four weeks before admission, the patient’s primary care physician found a diffuse goiter and ordered thyroid hormone testing (Table 1). Two weeks later, the patient developed generalized muscle pain and began a weight loss of 10 pounds until the day of admission. One day before admission, he had fever and diarrhea. The patient was then transferred with the suspicion of severe hyperthyroidism.

The patient’s medical history included “hyperthyroidism” and goiter diagnosed at age 24 years. Since then, he has intermittently taken propylthiouracil several times for short periods. At age 34 years, the patient experienced anxiety, tachycardia, and spells of muscle pain. He underwent radioiodine therapy at that time but experienced no improvement in the symptoms or goiter. A few months later, the patient underwent a repeat radioactive iodine treatment with the same unsuccessful result. He has experienced anxiety and tachycardia spells, which were intermittently treated with propylthiouracil for short periods with no relief. He also experiences chronic cluster migraine headaches.

At admission, the patient’s vital signs were as follows: temperature, 37 °C; pulse, 94/min; blood pressure, 140/70 mmHg. There was a diffuse goiter, with the thyroid gland approximately 4 times normal size. The patient had no eye bulging, eyelid lag, tremor, or brisk reflexes. His skin texture was normal. The following day, his pulse was 80/min, and his blood pressure was 120/70 mmHg. The patient’s fever and diarrhea had resolved, and he remained afebrile.

An investigation of the discordant results in thyroid function tests was initiated.

DISCUSSION

DIFFERENTIAL DIAGNOSIS

The combination of goiter and increased concentrations of free thyroxine (T4) and free triiodothyronine (T3) with unsuppressed thyroid-stimulating hormone (TSH) is suspicious for 4 conditions: (a) hyperthyroidism with a false increase in TSH due to antibody interference; (b) euthyroidism with a false increase in thyroid hormone due to antibody interference or abnormal binding to carrier proteins; (c) a TSH-secreting pituitary tumor; and (d) resistance to thyroid hormone.

QUESTIONS TO CONSIDER

1. List some causes of goiter, increased free T4 and free T3 values, and a normal TSH result.
2. What laboratory tests could be done to help determine the cause of these laboratory values?
3. What is the role of clinical findings in confirming the diagnosis?
4. Is there a molecular test that can help to confirm the diagnosis?

Nonstandard abbreviations: T4, thyroxine; T3, triiodothyronine; TSH, thyroid-stimulating hormone.
measurement). Measurement of free thyroid hormones by equilibrium dialysis and measurement of TSH by another manufacturer’s assay are approaches that can rule out immunoassay interference (1, 2). The presence of the symptoms and goiter in this patient, however, suggest another cause for the discrepant results.

Familial dysalbuminemic hyperthyroxinemia presents with an increased total T4 concentration, owing to an increased binding of albumin to T4; however, these patients are usually asymptomatic and have a normal thyroid gland (3).

Patients with TSH-secreting pituitary tumors have clear features of hyperthyroidism and often have an enlarged thyroid. These very rare tumors are usually larger than 10 mm and cause dysfunction of other pituitary hormones due to tumor enlargement and compression of surrounding structures (4). An MRI evaluation of the pituitary is indicated to rule out this uncommon condition. This approach has one caveat, the presence of incidentalomas. Incidentalomas of the pituitary are detected in 10%–20% of patients undergoing MRI of the brain for unrelated reasons. The majority of them are smaller than 10 mm, and they do not cause symptoms of hyperthyroidism unless they are secreting TSH (4). If the suspicion of a TSH-secreting pituitary tumor is high, a measurement of the free α subunit of TSH would support this diagnosis. The concentration of serum sex hormone–binding globulin is increased in hyperthyroid states such as TSH-secreting pituitary tumors, whereas normal concentrations of this globulin are expected in patients with resistance to thyroid hormone (5).

Resistance to thyroid hormone lacks specific clinical manifestations. The manifestations are variable, and signs of hormone deficiency and excess often can coexist in the same patient. Relative common features of this syndrome include goiter (66%–95% of patients), tachycardia (33%–75%), hyperkinetic behavior (33%–68%), learning disabilities (30%), and short stature (18%–25%) (6). The disease has an autosomal dominant genetic basis, so the patient’s medical history is helpful: 80% of patients have a parent with the same condition. Further questioning of our patient revealed that his mother, grandmother, and daughter all had goiter and were treated for hyperthyroidism. Unfortunately, we were unable to obtain their medical records.

The presence of goiter, increased thyroid hormones (T4 and T3), and the absence of consistent clinical features of overt hyperthyroidism were important diagnostic clues for our patient. An MRI of the brain ruled out a TSH-secreting pituitary tumor. Evaluation for heterophile-blocking antibodies with the Scantibodies Heterophilic Blocking Tube in serum did not alter the TSH results, suggesting the absence of heterophile antibody interference. Quest Laboratories carried out a genetic analysis. Exons 3–10 of the THRB (thyroid hormone receptor, beta) gene were sequenced, and a mutation was detected. Further analysis revealed a mutation in the THRA (thyroid hormone receptor, alpha) gene, which was confirmed by sequencing.

<table>
<thead>
<tr>
<th>Table 1. Thyroid hormone values.</th>
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<tr>
<td>Analyte reference interval, conventional units (SI units)</td>
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<tr>
<td>Total T4</td>
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<tr>
<td>(72–176 nmol/L)</td>
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<tr>
<td>Total T3</td>
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<tr>
<td>(0.92–2.79 nmol/L)</td>
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<tr>
<td>Free T4</td>
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<tr>
<td>(10.3–24.7 pmol/L)</td>
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<tr>
<td>Free T3</td>
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<tr>
<td>(3.5–6.47 pmol/L)</td>
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<tr>
<td>TSH</td>
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* Analyte values above the upper reference limit are indicated (↑).
Clinic Case Study

Resistance to thyroid hormone receptor, alpha) gene were amplified from genomic DNA by the PCR, and the amplified DNA was sequenced. Our patient was heterozygous for a mutation in the THRB gene, with an Ala residue replaced by Thr at position 317 in the protein, confirming the clinical diagnosis of resistance to thyroid hormone.

Measuring the biochemical response to the administration of 3 incremental doses of L-T3 for 3 days is the best method to make the clinical diagnosis of resistance to thyroid hormone (6). Unfortunately, our patient did not show up in the endocrine clinic for follow-up.

MECHANISM OF ACTION

The signaling of thyroid hormone is complex and highly regulated, owing to the expression of cell- and tissue-specific thyroid hormone transporters, thyroid hormone receptor isoforms, and interaction with corepressors and coactivators. THRA (thyroid hormone receptor, alpha) and THRB encode thyroid hormone receptors THRA and THRB, and each has different patterns of gene expression and different splicing products. Many of the actions of thyroid hormone include potentiation of other signaling pathways, such as adrenergic signaling and metabolic-sensing nuclear receptors (7).

Mutations in the THRB protein explain 85%–90% of cases of resistance to thyroid hormone. The pathophysiology of the remaining 10%–15% of cases remains unknown, but it is plausible that mutations in cofactors that interact with the thyroid hormone receptor play a role (3). More than 1000 patients and more than 370 families with resistance to thyroid hormone have been described in the literature (8).

The mutant THRB molecules have either a reduced affinity for T3 or an impaired interaction with one of the cofactors involved in the mediation of thyroid hormone action. Our patient had a mutation in amino acid residue 317, which is located in a region involved in binding T3 and prevents appropriate binding. The replacement of Ala by Thr at position 317 has been reported in 29 families (8).

The THRA gene is expressed in cardiac and skeletal tissues, THRB splice variant 1 is expressed in brain, liver, and kidney, and THRB splice variant 2 is expressed in the hypothalamus and the pituitary. The tissue-specific expression of the genes encoding the different receptors sheds light on the conflicting hyperthyroid and hypothyroid symptoms. A defect in THRB leads to excess hormone, activating THRA and leading to cardiac and skeletal manifestations. Studies have shown that THRB knockout mice have tachycardia and THRA knockout mice have a decreased heart rate (9). These findings are not consistent with those in humans, and even affected members of the same family show different patterns of symptoms and signs (7, 8).

The reduced affinity of the thyroid hormone receptor leads to a reduced feedback action of thyroid hormones, and this situation is compensated for by higher TSH secretion. In the steady state, the thyroid hormones are increased, but TSH is unsuppressed. In patients with resistance to thyroid hormone, TSH has increased biological activity, which can explain the presence of goiter (10).

CLINICAL ASPECTS

Goiter occurs as the thyroid attempts to produce more thyroid hormone to overcome the resistance. Tachycardia prompts 25% of adults with resistance to thyroid hormone to seek medical advice (6). From the laboratory point of view, increased T4 and T3 concentrations along with normal concentrations of TSH are typical, unless the patient had previous successful surgery or radioactive iodine therapy. In that case, symptoms of hypothyroidism will predominate, and the TSH concentration will be increased. Our patient had received 2 treatments with 131I several years earlier.

Surgery and radioactive iodine are ineffective. There is no specific treatment to correct the underlying defect; therapy is aimed at alleviating symptoms. The most common symptom is sinus tachycardia, which is present in 35%–75% of patients. If the disease is symptomatic, tachycardia can be treated with a β-adrenergic blocking agent such as atenolol. Other symptoms, such as tremor, heat intolerance, and sweating, can also improve with atenolol treatment (6). Treatment with L-T3 on alternating days has been effective in lowering TSH secretion and in reducing the size of the goiter.

POINTS TO REMEMBER

- Resistance to thyroid hormone is a rare autosomal dominant disease caused mainly by mutations in the β isoform of the thyroid hormone receptor.
- Diagnosis is based on increased thyroid hormone concentrations, a normal TSH concentration, and absent or mild symptoms of hyperthyroidism.
- Antibody interference needs to be considered after obtaining discordant results in thyroid function tests.
- A gene test is available and can identify up to 85% of patients with resistance to thyroid hormone.
The appropriate diagnosis of this condition prevents unnecessary therapy with radioactive ablation or surgery.

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Commentary

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Leey and Cryer (1) nicely discuss a patient with a heterozygous mutation in the THRB gene and review the differential diagnosis. A normal serum TSH value with increased total and free T4 and T3 concentrations should raise suspicion that the patient may not have typical thyrotoxicosis. Family members must be assessed for the mutation once the familial proband has been identified. It is important to identify patients with a T3 receptor mutation so that inappropriate treatments can be avoided. Immunoassays for TSH measure serum TSH concentrations only and do not assess TSH biological activity. In unusual circumstances, immunoactivity and bioactivity are discordant (2). For example, patients with pituitary or hypothalamic disorders may show a decreased ratio of TSH bioactivity to immunoreactivity. Patients with TSH-secreting pituitary tumors, conversely, may show enhanced TSH bioactivity (2). A mutation in the THRB protein is the most common form of thyroid hormone resistance; however, van Mullem et al. have recently described the syndrome of resistance associated with a THRA mutation (3). Furthermore, Visser (4) has described a different type of thyroid hormone resistance, in which the cellular membrane has a mutation in the monocarboxylate transporter 8 receptor, an important thyroid hormone transporter. Patients with mutations in this receptor may have severe neurologic and endocrine abnormalities. As Leey and Cryer (1) note, patients with TSH-secreting pituitary tumors have an increased molar ratio of α TSH to TSH (entire molecule). One caveat is that this ratio is a molar ratio and values for the α subunit (usually expressed in nanograms per milliliter) and TSH values (usually expressed in milliunits per liter) must be converted appropriately. A T3 suppression test is rarely performed, because it may cause hypothyroidism and the diagnosis of a T3 receptor mutation can usually be made on a genetic basis.

References


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