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Patients Homozygous for Mutations in the Thyroid Hormone Receptor Beta Gene Have More Severe Symptoms of Thyroid Hormone Resistance

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SUMMARY

Background

Patients who have persistently high thyroid hormone levels but whose TSH values are persistently normal (or high) may be resistant to thyroid hormone. After ruling out other possible diagnoses, most cases of resistance turn out to be due to a single nucleotide mutation in one copy of the thyroid hormone receptor beta (THRB) gene. The mutations differ widely in their dominant negative effects and in the degree of resistance observed in different tissues. The same mutation can be associated with very different clinical manifestations, even in members of the same family. Some patients are unaware of symptoms or merely have a long-standing goiter, while others may be nervous, or have tremor, palpitations, insomnia, heat intolerance, weight loss, or increased appetite, suggesting hyperthyroidism, while in children, delays in neurologic and skeletal development can suggest hypothyroidism.

Methods

Three children from two families were noted to have tachycardia, goiter, deafness, defective speech, and delays in growth and intellectual development. Thyroid-function tests strongly suggested resistance, so THRB was analyzed in family members.

Results

Neonatal TSH levels in the first child were very high; her thyroid was normal in size but its 99mTc uptake was increased. She was treated with beta-blockade for tachycardia at 1 week of age, and by the age of 3 years, deafness, goiter and delayed skeletal and gross motor development had appeared. The consanguineous parents both had mild hearing defects. The putative father was taking L-T_4 for an unknown thyroid problem, but he did not undergo testing. The patient's mother, uncle, grandmother, and great grandmother had high total T_4, T_3, and FT_4 index (FTI) levels, yet their TSH levels were normal to high. They all had some degree of deafness and were found to be heterozygous for a point mutation (G347E) in thyroid receptor beta (TRβ), whereas the child was homozygous.

The G347E mutation had previously been found in a 36-year-old man who had undergone thyroidectomy and had started L-T_3 therapy to suppress his TSH; he was mildly mentally retarded, and his resting pulse was under 80. In vitro studies on the T_3-binding activity of the mutant receptor showed it to be 1/20 of the wild type receptor (1).

A girl and boy in a second family had birdlike faces and were deaf. At 3 years of age, the girl was noted to have a goiter with thyroid-function tests consistent with thyroid hormone resistance, and she was treated with propranolol for tachycardia. At 7 years of age, her FT_4 and T_3 levels were immeasurably high, yet her TSH was 14 μU/ml. She was given increasing doses of triiodothyroacetic acid (Triac), but her goiter continued to grow, necessitating a thyroidectomy before she was 9. Her skeletal and mental development were retarded. Her younger brother was deaf and had a goiter and developmental delays, but he did not have tachycardia. His TSH was 91 μU/ml despite having an elevated serum T_4. These two siblings were homozygous for a point mutation in TRβ (R316C), while the consanguineous parents

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were heterozygous, as were the paternal grandfather and maternal uncle. The father had undergone thyroidectomy at age 28, and his TSH was 37 μU/ml despite an elevated FTI. The mother did not have a goiter or tachycardia, but her FT_4 was high; she also had a positive TPO antibody titer [interestingly, autoimmune thyroiditis is more common in patients with thyroid hormone resistance, which can further complicate evaluation of their thyroid status (2)]. A girl who had hypothyroidism at birth with only a lingual thyroid was found to be heterozygous for R316C (3). L-T_4 at 350 μg/day eventually normalized her TSH levels. In vitro studies on the mutated receptor showed its affinity for T_3 to be about one third of that of the wild type; it was also unable to form homodimers and it impaired the transcription of T_3-responsive genes.

Conclusions

The greater severity of laboratory and clinical abnormalities in the homozygous members of these two families with point mutations in TRβ resembles what was previously reported in the homozygote of a family bearing a 3-base-pair deletion in THRB (4). The lesser biochemical and clinical severity in the heterozygotes, who have one normal allele, suggests that the mutant protein has less opportunity to disturb the function of TRα1,which predominates in the conduction system of the heart, and with which TRβs commonly heterodimerize.

ANALYSIS AND COMMENTARY

The single-point mutations found in these two families are known to affect the affinity of the receptor for T_3, but many THRB mutations that do not affect T_3 binding still cause resistance. Some disturb heterodimerization between TRs, RARs, or RXRs, or interactions with coactivators or coinhibitors. The TRβ1 isoform predominates in many peripheral tissues, whereas the TRβ2 isoform predominates in the hypothalamus and pituitary. However, there are several other splice variants from both the TRα and β genes that do not bind T_3 but do form dominant negative heterodimers and are expressed at varying levels in certain tissues (5). Covalent modifications such as phosphorylation also influence the activity, subcellular distribution, and stability of the TRs, and also need to be included in assessing mechanisms of resistance. However, TR mutations are not the whole story. Thyroid hormone responsiveness is also influenced by nongenomic actions of thyroid hormones, and the activity of thyronine transporters and deiodinases in different cell types, so unraveling all the players involved will be an arduous undertaking. In the case of the pituitary, thyrotroph sensitivity can be estimated by the product of the TSH and the FT_4 levels, but no simple tests for resistance in other organs are available yet.

Severe cases of resistance are unusual, but there may be more subtle patients in one's practice whose diagnosis of hyperthyroidism needs to be reassessed. Such patients may have had a goiter, palpitations, and a high T_4 level in the days before the TSH assay was sensitive enough to be meaningful at low levels. Those patients may have received "definitive treatment" and then were given enough thyroid hormone to make them "clinically euthyroid." If their TSH is in the normal range, and their FT_4 is only slightly high, what should be done? We recognize that TSH should be undetectable if the FT_4 is high, but we also know that the FT_4 test can give questionable results, and that TSH levels can vary by 40% on repeat testing. However, if the two tests disagree consistently, shouldn't one reassess the diagnosis? Before proceeding to a muta-

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tional analysis of THRB, the possibility of interfering human antimouse antibodies should be ruled out. However, in their absence—and particularly if other family members have similar histories—establishing the diagnosis of thyroid hormone resistance could avert surgical or radioiodine ablations in future generations. In about 15% of cases, no mutation is found in THRB. In such cases, it may be reasonable to determine the ratio of the level of the alpha subunit of pituitary glycoprotein hormones to the level of TSH, since TSH-secreting pituitary adenomas, although very rare, can occur. In such a case, a formal test of TSH sensitivity using increasing doses of T_3 may be in order. The test can provoke hyperthyroid symptoms or have cardiac effects, although cautious use of beta blockade may be somewhat protective.

— Stephen W. Spaulding, MD

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