

CLINICAL VIGNETTE

Thyroid Hormone Resistance: THR-B Mutation Presenting as Unexplained Tachycardia

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Introduction

Thyroid hormone receptors are widely distributed throughout the body, particularly in metabolically active tissues such as the heart, kidneys, brain, and skeletal muscles. They are found in two isoforms, alpha and beta, which together mediate thyroid hormone effects on metabolism and homeostasis. Resistance to thyroid hormone (RTH) due to a mutation in the THR-B gene, often termed “RTH-B,” is a genetic condition affecting the Beta isoform of the thyroid hormone receptor, resulting in a diminished response to thyroid hormone.

RTH-B is often detected initially as an elevated fT4 and fT3 in the absence of TSH suppression. This pattern reflects a compensatory increase in thyroid hormone production to maintain a clinically euthyroid state. However, the degree of resistance to thyroid hormone is highly variable and patients can present with tachycardia, goiter, and hyperactivity, which can lead to a misdiagnosis of hyperthyroidism. Use of antithyroid therapies can be extremely detrimental in these patients. Thus, although not common, it is important to consider RTH-B in the evaluation of abnormal thyroid function. We present a case of RTH-B in a hospitalized adult being evaluated for tachycardia.

Case Presentation

A 36-year-old male with a history of Medulloblastoma, Schizophrenia, and Hearing Loss presented for a scheduled resection of a recurrent Meningioma.

The patient was diagnosed with Medulloblastoma at age 10 and underwent treatment with surgical resection, chemotherapy, and radiation. Cranial radiation therapy was complicated by Growth Hormone deficiency requiring GH replacement, Hypogonadotropic Hypogonadism, and multiple recurrent meningiomas. He had significant hearing loss attributable to cisplatin ototoxicity and requires use of assistive devices or interpretation by family members to communicate. Of note, the patient and his family were not aware of any history of thyroid abnormalities, and report that the patient had not been given any hormone replacement other than growth hormone. Documentation of prior endocrine evaluation were not available. Family history did not identify any familial endocrine issues. He has a longstanding diagnosis of schizophrenia treated with multiple

agents, currently controlled on Clozapine. He does not take any other chronic medications.

The patient’s meningioma resection was completed as planned, but his post-procedural hospital course was complicated by altered mental status and aspiration pneumonia requiring intubation. He was treated with antibiotics and eventually extubated with apparent resolution of his infection and recovery to his baseline mental status. However, the patient had persistent sinus tachycardia up to 137 bpm despite negative evaluation for thrombotic, infectious, psychologic or hypovolemic etiologies. He denied any post-op pain or discomfort. He remained normotensive and afebrile without need for oxygen supplementation. Review of clinic visits during the months preceding his admission, noted documentation of his baseline heart rate the ranging 100-116 bpm. Current physical exam revealed normal reflexes, and was negative for gynecomastia, edema, rash, goiter, or lid lag. He was 5 feet 2 inches in height, 45 kg with BMI 18, and without craniofacial abnormalities. Thyroid function tests were drawn as part of the tachycardia evaluation and revealed a TSH of 5 mIU/L (normal 0.3 – 4.7 mIU/mL) and a free T4 of 2.2 ng/dL (normal 0.8-1.7 ng/dL). Concurrently elevated TSH and fT4 was confirmed on a repeat draw six days later with TSH of 3.9 mIU/mL and free T4 of 3.0 ng/dL, along with elevated fT3 433 pg/dL (normal 222-383 pg/dL). TPO ab and Thyroid Stimulating Immunoglobulins were negative. Thyroid ultrasound showed homogenous echotexture with several small intermediate suspicion nodules without increased color doppler flow, the largest measuring 8 mm. MRI brain did not reveal any pituitary abnormality other than empty sella. Further testing to exclude antibody interference and TSH-oma, with measurement of TSH with Human Anti-Mouse Antibody treatment, and TSH alpha subunit concentration. These studies were both unremarkable. SHBG was low at 9 nmol/L. Assessment of his HPA axis confirmed hypogonadotropic hypogonadism but was otherwise normal with IGF-1 Z -0.2, Total Testosterone 44 ng/dL (with inappropriately normal FSH and LH), ACTH 25 pg/mL, and AM cortisol 14 mcg/dL. The patient was started on Propranolol 5 mg TID which controlled his heart rate to 80-95 bpm and he was discharged home with outpatient endocrine follow up. Suspicion was high for a mutation in the Thyroid Hormone Receptor Beta gene and a sample was sent for

sequencing, which was eventually confirmed a heterozygous missense mutation of Proline to Alanine at codon 453 in exon 10 of the THRB gene.

Discussion

Thyroid hormone levels are normally under tight regulation by TSH, which is produced by the anterior pituitary and stimulates thyroidal secretion of thyroid hormones (T4 and T3). These thyroid hormones then act through negative feedback on the anterior pituitary to modulate further TSH secretion. Small changes in T4 concentrations produce large reciprocal changes in TSH in a negative log-linear relationship. Thus, normal to elevated thyroid hormone levels without suppression of TSH are usually caused by one of three etiologies: assay interference, central hyperthyroidism, or thyroid hormone resistance. These can generally be elucidated using a small number of serum studies.

Assay Interference

TSH is commonly measured using an automated chemiluminescence assay utilizing sandwich antibodies.¹ In this assay, TSH molecules are bound by two different fluorescently labelled mouse anti-TSH antibodies. TSH is then quantified through measurement of these doubly-bound chemiluminescent units. However, the presence of Human anti-mouse antibodies (HAMA) can also bridge these labelled antibodies independently of TSH and thus result in a falsely elevated TSH measurement. Prevalence of these antibodies in patients is cited to be as high as 10%.² This problem can be avoided by repeating the assay using a treated sample in which these HAMA are either quantified or removed by adding mouse IgG to aggregate the HAMA to avoid detection by the assay. A serial dilution of TSH can also be performed to confirm that the measured TSH dilutes linearly in the expected fashion. If the TSH is normal after correcting for HAMA, the patient can be reassured that their initial test was an artifactual error.

Familial Dysalbuminaemic Hyperthyroxinemia (FDH) is a genetic mutation in the albumin gene that increases its affinity to thyroid hormone by five to ten-fold. This can cause assay interference by artifactually increasing fT4 and fT3 measurements. Prevalence is cited as 1:10,000 among Caucasians. This can be avoided by measuring fT4 and fT3 by equilibrium dialysis or ultrafiltration.³

Patients should also be advised to stop biotin supplements 3-5 days prior to thyroid function testing.⁴ Most immunoassays utilize a biotin – streptavidin binding platform to link antibodies and capture targets. Thus, excess biotin can cause false elevation in competitive assays (usually T4 and T3) and false depression in sandwich assays (usually TSH).⁵

Central Hyperthyroidism

TSH-secreting pituitary adenomas are a rare cause of hyperthyroidism, cited in less than 1% of all cases.⁶ These adenomas are

characterized by unregulated TSH secretion not responsive to feedback inhibition from elevated thyroid hormone levels or to TRH stimulation. About 20-25% of TSH-secreting pituitary adenomas co-secrete growth hormone or prolactin, thus the HPA axis should be fully assessed.⁷ There is also potential for hypopituitarism if there is significant compression of normal pituitary tissue. Wild-type TSH is a glycoprotein comprising of an alpha subunit (which shares homology with FH and LSH) and a beta subunit that is unique. The TSH – alpha subunit is preferentially secreted in 50-85% of TSH producing adenomas, thus an elevation in serum alpha subunit can point towards this diagnosis.⁸ The biological activity of adenoma-secreted TSH can vary significantly. If active, a hyperthyroid state results with the typical symptoms of hyperthyroidism such as palpitations, heat intolerance, and tremor. Increased thyroid hormone results in increased SHBG production as well. This may cause symptoms of hypogonadism and gynecomastia in men as SHBG binds more avidly to testosterone than estrogen, resulting in a relative deficiency in free testosterone.⁸ Additionally, patients should be assessed for neurological symptoms such as headache, vision loss, and cranial nerve palsies. An MRI of the pituitary should be done if suspicion is high for central hyperthyroidism. Treatment is generally with a somatostatin analogue to achieve euthyroidism followed by surgical resection of the pituitary adenoma.⁹

Thyroid Hormone Resistance

Resistance to thyroid hormone occurs due to receptor mutations that reduce end-organ responsiveness to thyroid hormone. T3 acts upon thyroid hormone receptors at both the nuclear and intracellular level, regulating transcription, translation, and cell signaling. Thyroid hormone receptors are present in two major isoforms, alpha and beta. The alpha isoform is widely distributed in skeletal and cardiac muscle, as well as bone, brain, and kidney. The beta isoform is predominantly expressed in brain, liver, kidney, retina, and cochlea. Either of these isoforms can harbor an inactivating mutation, leading to thyroid hormone resistance. Thyroid hormone receptor Alpha mutation (THRA) is very rare and presents with normal to low fT4, high fT3, and normal TSH, along with abnormal physical characteristics.¹⁰ Mutation in the beta isoform (THR-B) is the most common cause of Resistance to Thyroid Hormone, cited at 1 in 40,000 live births.¹¹ RTH is typically inherited in an autosomal dominant manner but may be sporadic in about 15% of cases.¹² Over 120 different mutations in the THRB gene have been identified to be pathogenic, mostly occurring in the T3 binding domain. Patients are often minimally symptomatic as the elevated TSH and thyroid hormone represents a compensatory response to effect adequate downstream signaling in the setting of thyroid hormone receptor defect. Tachycardia is commonly noted in THR-B mutation as the increased levels of thyroid hormone stimulate the intact THR-alpha, which is the predominant isoform in cardiac tissue.¹³ A goiter can also be present due to the increased TSH stimulation. Other common clinical manifestations include hyperkinetic behavior, Attention Deficit Disorder, emotional disturbances, recurrent ear and throat infections, and sensorineural hearing deficits.¹⁴

Our patient was diagnosed with a P453A mutation. Most reported cases of this mutation are familial.^{15,16} However, one case of this mutation has been reported in a Japanese individual with a negative family history who also presented with isolated tachycardia.¹⁷ Interestingly, the degree of THR can vary significantly even among those sharing the same mutation. The cause of this variation is unknown, but may be related to variation in cofactors to thyroid hormone binding. One Turkish mother and son were described with the same mutation.¹⁸ The mother had symptoms of tachycardia, anxiety, weakness, while the son was asymptomatic except for ADHD. Our patient had growth delay, developmental delay, sensorineural hearing loss and mood disorders. Many of these conditions were previously attributed to GH deficiency secondary to medulloblastoma resection, schizophrenia, and cisplatin toxicity. In retrospect, his THR-B may have been contributory to some or all of these diagnoses.

This patient's TFT profile in conjunction with minimal hyperthyroid symptoms, normal SHBG, normal TSH alpha subunit, normal HAMA, and normal MRI brain pointed us toward THR-B mutation. We would also expect him to be responsive to TRH stimulation as opposed to lack of response in TSH-oma, but this assay is not currently available in the United States.

Most patients with RTH-B do not require treatment as they are adequately compensated for their degree of peripheral tissue resistance. Resolution of clinical symptoms should be the goal of treatment rather than targeting specific thyroid hormone levels. This can often be achieved with beta blockers, anxiolytic agents, or standard treatments for Attention Deficit Disorder. However, a minority of patients with normal TSH sometimes do need supplemental doses of thyroid hormone replacement to achieve adequate symptom control. This is particularly important in children to ensure appropriate bone maturation, growth, and cognitive development. Long term outcomes data are lacking for RTH-B patients, but we would not expect any particular complications to develop for the compensated RTH-B patient in this case. The most important intervention will be educating the patient and his family members on the diagnosis and avoiding any unnecessary thyroid treatment.

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