

Reports

Psychiatric Admission Leading to Diagnosis of Thyroid Hormone Resistance Syndrome: An Adolescent Case Report

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Introduction

Resistance to thyroid hormone (RTH) is a rare congenital condition characterized by thyroid hormone resistance at target tissues. The syndrome results from a mutation in the thyroid hormone receptor beta (THR- β) gene and affects approximately 1 in every 40,000 live births (Rivas AM, Lado-Abeal J. Thyroid hormone resistance and its management. *Proc (Bayl Univ Med Cent)*. 2016;29(2):209–211). RTH has well-known psychiatric manifestations, but it is not often considered when a patient presents for acute or subacute psychiatric treatment.

Case

This article details the case of a 13-year-old adopted male with new auditory hallucinations and increased aggression toward family and self. Thyroid function screening revealed laboratory abnormalities consistent with RTH; subsequent review of systems revealed clinical hyperthyroidism. The diagnosis of RTH was ultimately confirmed through genetic testing, and symptomatic treatment with a beta-blocker proved successful.

Discussion and Conclusion

This case underscores the importance of proper thyroid screening in patients whose family history is unknown or suggestive of hereditary thyroid abnormalities. It also highlights the utility of genetic testing as a diagnostic tool for complex behavioral presentations. Proper diagnosis and treatment of this patient required collaboration between multiple pediatric specialties, demonstrating the value of interdisciplinary care. Early identification of RTH benefits patients and their families in many regards, allowing them to better contextualize their symptoms and avoid unnecessary thyroid interventions.

BACKGROUND

Thyroid hormone resistance syndrome, also known as Refetoff syndrome or resistance to thyroid hormone (RTH), is a rare congenital condition affecting approximately 1 in every 40,000 live births.¹ The most common form of this syndrome is caused by an autosomal dominant mutation in the thyroid hormone receptor beta (THR- β) gene, which encodes for the ubiquitous beta variant of thyroid hormone receptor. The mutated receptors have decreased affinity for thyroid hormone, which leads to impaired thyroid hormone

action at target tissues such as the brain, heart, musculoskeletal tissues, and pituitary gland.

The clinical manifestations of RTH vary significantly depending on the mutation severity and affected target tissues. Neurocognitive and psychological pathologies are among the most frequently reported symptoms, with attention-deficit/hyperactivity disorder (ADHD) showing a particularly strong association.² Nevertheless, RTH is rarely considered in the differential diagnosis for psychiatric presentations.

In this report, we detail the case of an adolescent patient who presented with aggression and auditory hallucinations and was admitted for acute psychiatric care. Medical



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workup during this admission revealed an abnormal thyroid panel. The patient was referred to pediatric endocrinology and ultimately diagnosed with RTH. To our knowledge, this is the first reported case of a child or adolescent patient being diagnosed with RTH as the direct result of laboratory abnormalities on psychiatric workup.

CASE

“Jeremy,” a 13-year-old adopted male, presented to the psychiatric hospital for acute-on-chronic aggression toward family, intrusive thoughts of self-harm, and new-onset auditory hallucinations. His psychiatric history was remarkable for fetal alcohol syndrome, autism spectrum disorder, ADHD, and posttraumatic stress disorder. His medical history included asthma, intellectual disability, and speech delay.

According to his adoptive mother, Jeremy’s aggressive behavior was prompted by his biological brother being temporarily out of the home for several days. The patient described harming himself using a knife and becoming physically aggressive toward his adoptive mother and sister. He broke windows in his home and made several attempts to elope. He endorsed a history of sleeping difficulties and nightmares, sometimes seeing monsters or hearing the voices of “monster friends.” Upon admission, Jeremy’s home risperidone dose was uptitrated (0.25 mg in the morning was added to his nighttime 0.5 mg dose) and all other home medications (clonidine, fluoxetine, hydroxyzine, and dexamethylphenidate) were continued. He responded favorably to inpatient interventions and was discharged home after 3 days.

Prior to discharge, a basic thyroid panel was collected. Thyroid-stimulating hormone (TSH) levels were unremarkable (2.0 mU/L, normal range 0.4–5.0 mU/L), but free T4 concentrations were double the normal upper limit (2.4 ng/dL, normal range 0.6–1.2 ng/dL). Repeat labs were collected after a follow-up visit with outpatient psychiatry, which demonstrated a similarly normal TSH, elevated free T4, and elevated total T3 (246 ng/dL, normal range 87–178 ng/dL). Jeremy was subsequently referred to pediatric endocrinology for further workup.

Review of systems at the initial endocrinology appointment revealed “jitteriness,” heat intolerance, poor sleep, occasional palpitations, and increased appetite. Additionally, a goiter was appreciated on the physical examination. A more comprehensive thyroid panel was ordered, which showed consistently normal TSH (2.8 mU/L), elevated free T4 (2.5 ng/dL), and elevated total T3 (253 ng/dL) as well as positive thyroid peroxidase antibodies (>1000 IU/mL) and TSH receptor antibodies (2.9 IU/mL total, with 0.9 IU/mL attributable to thyroid-stimulating immunoglobulin). These positive antibodies, in combination with hyperthyroidism symptoms, were suggestive of Hashitoxicosis vs Graves’ disease; as such, methimazole was trialed. On repeat laboratory testing, however, the patient’s previously normal TSH became elevated (26.6 mU/L) without any clinical improvement. Methimazole was discontinued and atenolol was started for symptomatic relief. Genetic testing

for RTH revealed a heterozygous pathogenic variant in the *THROB* gene (R338W), confirming the suspected diagnosis. He continues to follow up with both treatment teams and has exhibited steady symptomatic improvement—most notably in his hyperphagia, per caregiver report.

DISCUSSION

As this case clearly illustrates, psychiatric symptoms are not exclusive to psychiatric pathologies. Because thyroid dysfunction is known to present with emotional and behavioral symptoms, thyroid function testing is frequently performed upon psychiatric admission. However, while isolated TSH testing is typically sufficient to identify underlying thyroid disorders, RTH represents a notable exception to this general rule.

In patients with thyroid hormone resistance, the affected tissues have impaired thyroid hormone sensitivity. To overcome tissue resistance and allow for adequate feedback at the level of the pituitary gland, free thyroid hormone levels are typically elevated. However, while the excess thyroid hormone concentrations are sufficient to counteract the insensitivity of pituitary tissue, they are typically not high enough to cause suppression of TSH levels. As a result, elevated free thyroid hormone levels with normal or slightly elevated TSH concentrations are hallmarks of this condition. Unfortunately, because isolated TSH testing is often within normal limits, RTH can go undiagnosed unless further thyroid hormone concentrations are obtained. In at least one previously reported case, a patient with RTH was admitted for psychiatric care but went undiagnosed for years due to normal TSH screening results.²

RTH presents a diagnostic challenge due to its significant overlap with other hyperthyroidism etiologies (see [Table 1](#)). Like RTH, toxic adenoma and autoimmune hyperthyroidism (eg, due to Graves’ disease or Hashitoxicosis) can present with symptoms of irritability, hyperactivity, sleep disturbances, tachycardia, goiter, and tremor. Similarly, both RTH and autoimmune hyperthyroidism can independently present with positive thyroid antibodies. However, in Jeremy’s case, treatment with antithyroid medication failed to improve symptoms and resulted in elevated TSH concentrations, further pointing to the diagnosis of RTH.

There are several historical factors that should raise a psychiatrist’s suspicion of RTH. A known family history of thyroid dysfunction should lower the threshold for a more comprehensive thyroid workup. Furthermore, adopted patients with an unknown family history should be treated with heightened suspicion for such inherited conditions. Considering that 40% to 60% of patients with RTH meet criteria for ADHD, a history of ADHD—especially with predominant hyperactivity—should raise concern for RTH in the presence of other suggestive symptoms (eg, Jeremy’s intellectual disability and tachycardia).² Other psychiatric comorbidities such as anxiety and psychosis have also been reported in patients with RTH, and these presentations should prompt screening for thyroid hormone resistance in the appropriate clinical context.³

Table 1. Select Diagnoses for Clinical Hyperthyroidism and Their Associated Laboratory Findings

Condition	Free T4	Total T3	TSH	Antibodies ^a
Normal thyroid function	Normal	Normal	Normal	Not present
Toxic adenoma	High	High	Low	Not present
Graves' disease	High	High	Low	Anti-TSH receptor (eg, thyroid-stimulating immunoglobulin)
Hashimoto's thyroiditis				
Toxicosis phase	High	High	Low	Antithyroglobulin
Hypothyroid phase	Low	Low	High	Antithyroid peroxidase
RTH ^b	High	High	Normal	Any of the above

^aThe antibodies are listed alongside the conditions with which they are most classically associated; however, they are not exclusive to a particular autoimmune disease.

^bAntibodies are present in a subset of patients with RTH but are not a classic feature of the disease.

Targeted genetic testing remains the gold standard in diagnosing RTH. More than 100 unique mutations in the THR- β gene have been reported, and the R338W missense mutation present in Jeremy's case is among the most common variants.

Once the diagnosis is confirmed through genetic testing, treatment should prioritize symptomatic relief rather than correction of laboratory abnormalities. To date, there is no definitive cure for RTH; however, as in Jeremy's case, beta-blockers can be useful in relieving tachycardia, tremor, and, to some degree, anxiety. Monitoring TSH levels (using a widened normal range of 0.1–6 mU/L) can be a useful tool to detect thyrotoxicosis, as TSH will become fully suppressed if thyroid hormone levels become excessively elevated. Importantly, patients with RTH should never undergo radioablation or surgical removal of the thyroid gland as this complicates future management and introduces unnecessary risks.

The benefits of diagnosing and treating thyroid hormone resistance syndrome extend beyond the individual patient. A confirmed genetic diagnosis can inform other family members of their potential risk and alert them to symptoms that warrant further workup. Additionally, receiving an underlying diagnosis can help contextualize previously unexplained symptoms for the patient and their family.

CONCLUSION

In patients like Jeremy with complicated psychiatric histories, it can be difficult to disentangle primary psychiatric disease from organic etiologies. Thoughtful utilization of screening tests (eg, a simple thyroid panel in the case of RTH) is the first step in clarifying the clinical presentation. Genetic testing can then be used to identify whether congenital conditions are contributing to the psychiatric picture. By leveraging genetic testing and interdisciplinary collaboration with other pediatric experts, child and adolescent psychiatrists can play an important role in catching RTH and other organic mimics of psychiatric disease.

PLAIN LANGUAGE SUMMARY

Resistance to thyroid hormone can initially present with psychiatric symptoms. Thyroid-stimulating hormone is often normal, so free T4 and/or total T3 should be included

on screening labs. After confirming the diagnosis with genetic testing, treatment should focus on symptomatic relief rather than lab normalization. Thyroid ablation or surgical removal should be avoided in all cases.

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