Resistance to Thyroid Hormone

Heba Al-Saad, MB BCh BAO*
Naji Alamuddin, MB BCh BAO** Dalal Alromaihi, MD***

Resistance to thyroid hormone (RTH) is an inherited syndrome caused by a genetic mutation, which leads to a decreased response of thyroid hormone at the peripheral tissues. It could be a challenge to diagnose because patients can be asymptomatic or present with symptoms of hyperthyroidism. The biochemical hallmark of this syndrome is an elevated FT4, FT3 with a non-suppressed thyroid-stimulating hormone (TSH).

We report a case of thirty-five-year-old male who presented with palpitations. A thyroid uptake scan (using intravenous Tc-99m pertechnetate) was highly suggestive of Graves' disease. THRβ gene showed a heterozygous c.1009A>G, p.(Thr337Ala) variant. The result supports the clinical diagnosis of THR caused by a mutation in the THRβ gene. He was treated with propranolol and Rivaroxaban (Xarelto) 15 mg twice daily, the ECG demonstrated controlled atrial fibrillation.

Bahrain Med Bull 2019; 41(3): 182 - 183

Resistance to thyroid hormone (RTH) is referred to as Refetoff syndrome; it is a rare condition where peripheral tissues have a decreased response to thyroid hormone. It occurs in 1 in 40,000 live births in an autosomal dominant pattern[1].

RTH is caused mostly by a mutation of the β (beta) form of the thyroid hormone receptor (THRβ) gene (90%) protein[2-4]. In some cases, it can also be associated with a mutation in the MCT8 transporter protein and SECISBP2 binding protein[2-4].

The aim of this report is to present a rare case of RTH, with emphasis on diagnosis and management.

THE CASE

A thirty-five-year-old male presented with palpitations at rest.

On physical examination, the patient appeared anxious. Vitals were as follows: blood pressure 170/80 mmHg, respiratory rate 22 breaths/minute, temperature 37°C. ECG showed sinus tachycardia with a rate of 94 beats per min. He did not have a goiter. There were no palpable thyroid nodules, and there was no evidence of an orbitopathy.

Propranolol (Inderal) 40 mg was started twice daily for symptomatic relief of palpitations. However, he developed paroxysmal atrial fibrillation. He was then started on carbimazole 10 mg once a day. A thyroid uptake scan (using intravenous Tc-99m pertechnetate) was reported as follows: the thyroid gland is enlarged; diffused uniform enhancement, no dominant hot or cold nodule; the thyroid uptake is increased = 5.6%. High thyroid uptake was highly suggestive of Graves' disease, see figure 1 (A-B) and table 1.

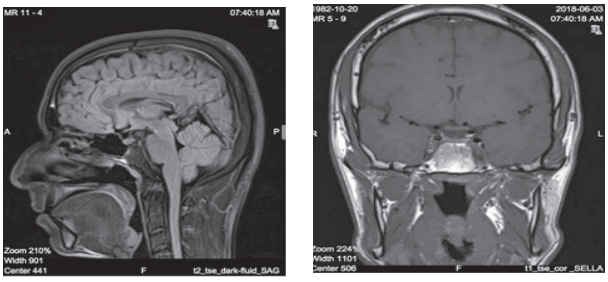

Figure 1 (A **Figure 1 (B)**

Figure 1 (A-B): Pituitary MRI Sagittal and Axial View, Demonstrating No Abnormalities of the Pituitary Gland

Table 1: Thyroid Function

Tests	Results	Reference Range
TSH	6.45	1.6-5.1 pg/ml
FT4	2.55	0.47- 1.99 ng/dL
FT3	3.44	0.35-5.5 uiu/ml
Anti-TSH Receptor Antibodies	< 1.1	< 1.75 UI/L
Thyroglobulin	15.6	3.5- 77 ng/ml

THRβ gene showed a heterozygous c.1009A>G, p.(Thr337Ala) variant, see figure 2. The result was suggestive of THR caused by a mutation in the THRβ gene. The variant affects a highly

* Intern
** Consultant Endocrinologist
King Hamad University Hospital
Senior Lecturer in Medicine
Royal College of Surgeons in Ireland-Medical University of Bahrain
*** Consultant Endocrinologist
Program Director of Internal Medicine Training
Department of Internal Medicine
King Hamad University Hospital
Kingdom of Bahrain
E-mail: heba.al.saad.94@gmail.com

conserved amino acid, located in the ligand-binding domain of the thyroid hormone receptor B.

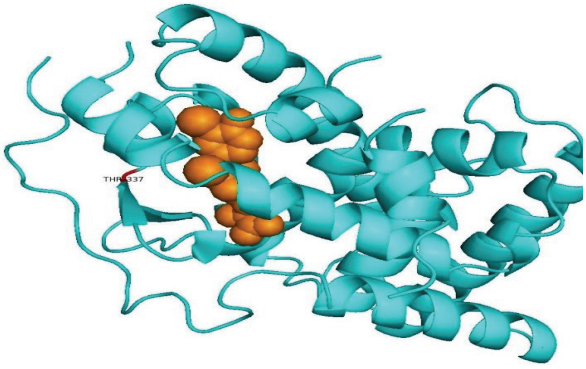

Figure 2: Structure of TRß with Localized T337. Position of THR (red) in 3D Structure (PDB Identifier: 1BSX) in Close Proximity with the Ligand 3,5,3'- Triiodothyronine (orange)

He was advised to continue propranolol and was treated for his atrial fibrillation with Rivaroxaban (Xarelto) 15 mg twice daily, as his ECG demonstrated controlled atrial fibrillation.

DISCUSSION

RTH could be diagnosed through the exclusion of all other etiologies, including familial dysalbuminemic hyperthyroxinemia, thyroxine-binding globulin excess, and TSH-secreting pituitary adenoma. Patients are usually undiagnosed for many years until the first symptoms appear. The main characteristic is the unsuppressed serum TSH and elevated free T4 level[5].

Thyroid function tests in RTH would show a normal or exaggerated level of serum TSH. Usually, a TSH-secreting pituitary tumor would have T4, T3 elevated and the serum TSH would be unsuppressed[6].

THRβ gene abnormality causes central and peripheral thyroid hormone resistance that increases T3, without manifesting all the hyperthyroid symptoms. The risk of transmission of the allele with the variant to the offspring is 50%.

The presentation of TRH differs, depending on the severity of the thyroid hormone receptor's mutation; patients may be asymptomatic or have symptoms of hyperthyroidism, which makes the diagnosis particularly challenging. In our case, the symptoms presented were palpitation and anxiety.

The management is symptomatic rather than based on the thyroid hormone testing results. Our patient was treated with a beta-blocker for his palpitations. Anti-thyroid drug is not recommended as it would lead to an increased risk of developing goiter or pituitary adenomas. The addition of anti-thyroid drugs would only be indicated if the TSH hormone was normal and the T4 level was high[7].

Failure to treat would result in hypothyroidism and thyroid hormone replacement would be needed.

CONCLUSION

TSH resistant is a very rare condition caused by a mutation in the THRβ gene, awareness must be made over the management of such condition where it is only managed symptomatically rather than laboratory based.

Author Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

Potential Conflicts of Interest: None.

Competing Interest: None.

Sponsor Ship: None.

Acceptance Date: 26 June 2019.

Ethical Approval: Approved by the Research and Ethics Committee, Bahrain Defence Force Hospital, Bahrain.

REFERENCES

1. Society for Endocrinology. You and Your Hormones. Resistance to Thyroid Hormone. http://www.yourhormones.info/endocrine-conditions/resistance-to-thyroid-hormone/ Accessed in March 2018.
2. Kammoun I, Bouzid C, Kandara H, et al. A Case of Resistance to Thyroid Hormone with Chronic Thyroiditis: Discovery of a Novel Mutation (I54V). Case Reports in Endocrinology 2011; 2011: 584930.
3. Weiss RE, Weinberg M, Refetoff S. Identical Mutations in Unrelated Families with Generalized Resistance to Thyroid Hormone Occur in Cytosine-Guanine- Rich Areas of the Thyroid Hormone Receptor Beta Gene. Analysis of 15 Families. J Clin Invest 1993; 91(6): 2408–2415.
4. Dumitrescu AM, Referoff S. The Syndromes of Reduced Sensitivity to Thyroid Hormone. Biochom Biophys Acta 2012; 1830(7): 3987–4003.
5. Patient like Me. Thyroid Hormone Resistance. https://www.patientslikeme.com/conditions/thyroid-hormone-resistance Accessed on 1 December 2018.
6. Wick JY. Treating Patients with Resistance to Thyroid Hormone. MD Magazine. https://www.mdmag.com/medical-news/treating-patients-with-resistance-to-thyroid-hormone Accessed on 1 October 2015.
7. Rivas AM, Lado-Abeal J. Thyroid Hormone Resistance and its Management. Baylor University Medical Center Proceedings 2016; 29(2): 209–211.