

Case of Resistance to Thyroid hormones (RTH) with relatively rare mutation in Thyroid Hormones Receptor (THR)

Hind Ahmed¹, Khalid Khamis¹, and Mohanad Ahmed²

¹Hamad Medical Corporation

²Affiliation not available

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Abstract

This is an article that share clinical manifestation and diagnosis of patient with THR mutation, who found to have very rare mutation in THR-beta.

Introduction

Thyroid hormones are produced in response of the thyroid gland to thyroid stimulating hormone (TSH) secreted from anterior pituitary gland. Circulating thyroid hormones in forms of T4 and T3 enter cells by diffusion and, in some tissues, such as the thyroid and brain, by active transport [1]. T3 is the active form of thyroid hormones which will also be available to cells from local conversion of T4 into T3 in side cells them self. This locally produced T3 can leave the cell and binds to T3 receptors in other tissues. In humans, approximately 80 percent of extrathyroidal T3 produced from T4 is produced intracellularly [2,3]. Intracellular T3 binds to nuclear receptor called Thyroid Receptor (TR). T3-TR complexes then bind to regulatory regions contained in the genes that are responsive to thyroid hormone and exerts its action [4].

There are two TRs, alpha (THRa) and beta (THRb) [4,5]. THRa is mainly found in bones, intestine nervous system and heart while THRb is found mainly in retina, ear, heart, nervous system and it's the main regulator of the negative feedback on pituitary thyroid axis [6].

Most patients diagnosed with RTH are found to have mutations in THRb with variant mutations had been described. However, recently some patients are found to have mutations in THRa [6]. Clinical manifestation depends on the receptor affected and the magnitude of the resistance. There is no specific treatment for RTH and multiple modalities of treatment have been found in reviewing the literature.

In this article we are reporting case of RTH, confirmed with genetic testing and found to have sequence variant mutation that is not well described due to absence of genetic conclusive evidence.

Case Report/Case Presentation

Our case is 35 years old female known to have type 2 Diabetes Mellitus on metformin 1 gm daily. In 2014, the patient presented with fatigue and weight gain. Work up showed TSH 23 Miu/l (0.5 to 5.5 Miu/l) and T4 of 15 Miu/l (9 to 21 Miu/l). The patient was diagnosed with subclinical hypothyroidism and started on levothyroxine treatment. Starting dose was 25 mcg daily and the patient was followed to monitor her symptoms and TSH level.

In next follow up appointments, the patient reported some improvement in her symptoms. however, her TSH level was persistently elevated. Thyroxin dose was gradually built up till a dose of 100 mcg was reached over

4 years period but TSH level wasn't inhibited. Other labs including complete blood count, renal function, liver function and lipid profile were within normal limits.

Appointment in November 2018, TSH was 20 mIU/L. levothyroxine dose was subsequently increased to 150 mcg daily. Few weeks later, the patient reported hyperthyroid symptoms including insomnia, tremors and palpitation. Repeated thyroid function test showed TSH of 6.6 mIU/L and T4 level was significantly high (30 mic/L). the dose was reduced to 100 mcg and antibodies were requested.

Next appointment following reduction of levothyroxine dose, her insomnia and palpitations improved. Repeated labs showed TSH 34 mIU/L, T4 17 mIU/L, antithyroid peroxidase antibody > 600 IU/ml (0 to 34 IU/ml), antithyroglobulin antibody 489 IU/ml (0 to 115 IU/ml) and TSH receptor antibody 0.8 IU/L (0 to 1.7 IU/L).Figure 1 showed TSH, T4 and T3 throughout treatment with various doses of levothyroxine from time of diagnosis (2013) till 2020,

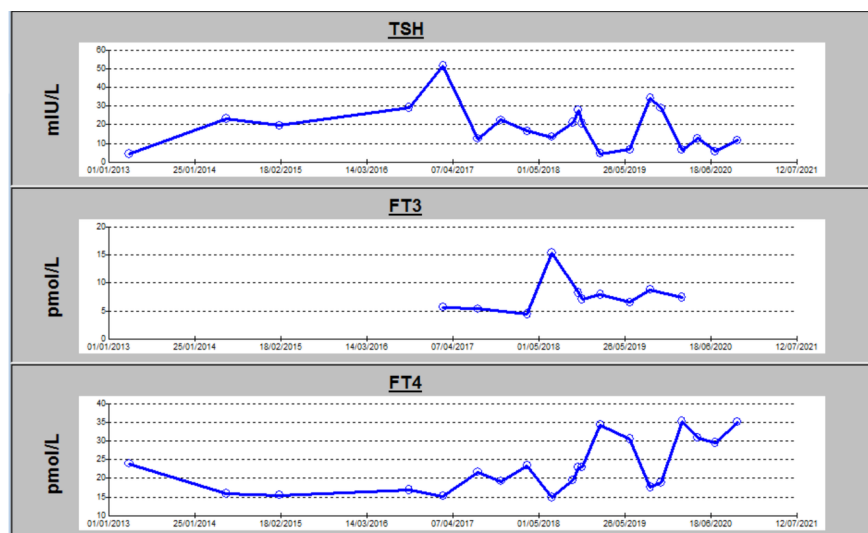


Figure 1. TSH, T4 and T3 level from diagnosis throughout various thyroxin treatment doses till 2020.

Given the values of high TSH not suppressed by levothyroxine treatment, we started to think about alternative diagnosis that leads to persistent elevation of TSH for example TSH secreting tumor and TSH resistance. Magnetic Resonance Images (MRI) of the pituitary gland was ordered to exclude TSH secreting pituitary tumor which revealed normal pituitary gland size. See figure 2.



Figure 2. arrow pointing to normal pituitary gland size.

Alpha subunit of pituitary gland which is used as a tumor marker for anterior pituitary gland tumors was also ordered, it was found to be 0.2 ng/ml (normal < 1.8 ng/ml).

Then genetic test was ordered to establish a diagnosis of TSH resistance which confirmed TSH resistance through THRB gene. see figure 3.

MOLECULAR GENETICS REPORT: Thyroid Hormone Resistance via the <i>THRB</i> Gene						
SUMMARY OF RESULTS			Heterozygous for a Variant of Uncertain Significance in <i>THRB</i>			
Gene, Transcript	Mode of Inheritance, Gene OMIM	DNA Variations, Predicted Effects, Zygosity	ClinVar ID	Highest Allele Frequency in a gnomAD Population	In Silico Missense Predictions	Interpretation
<i>THRB</i> , NM_001252634.1	AD, AR, 190160	c.1147C>T, p.Arg383Cys, Heterozygous	619915	Not Present	Damaging	UNCERTAIN

Mode of Inheritance: Autosomal Dominant=AD, Autosomal Recessive=AR, X-Linked=XL.
 ClinVar ID: Variant accession (www.ncbi.nlm.nih.gov/clinvar)
 gnomAD: Allele Frequency registered in a large population database (gnomad.broadinstitute.org). Value listed is the highest allele frequency reported within one of seven population categories recognized in gnomAD v2.0 (The "Other" population is excluded).
 Missense Predictions: Summarized output (Damaging, Conflicting, or Tolerated) via PolyPhen-2, SIFT, MutationTaster, and FATHMM (PMID: 26555599).

RESULTS AND INTERPRETATIONS: This patient is heterozygous in the *THRB* gene for a sequence variant designated c.1147C>T, which is predicted to result in the amino acid substitution p.Arg383Cys.

Figure 3. Molecular genetic report confirming THS resistance via THRB gene.

The diagnosis was explained to the patient and levothyroxine dose was reduced gradually to maintain the lowest dose that is sufficient to prevent symptoms with subsequent follow up to depend on T4 level and the patient symptoms not on TSH level.

Discussion:

Resistance to thyroid hormone was first described as a clinical entity in 1967 [7]. Subsequent studies about the molecular pathogenesis of this syndrome identified mutations in the region of the gene that encodes the ligand-binding domain of THRb. Interestingly, patients with mutations in *THRa* were not identified until 2012 [6]. Our patient in this article was found to have mutation in THRb same as majority of the patients described in the literature.

Patients with RTHb may have some symptoms or signs of hypothyroidism or hyperthyroidism, but these are variable and, when present, often inconstant. They frequently have elevated thyroid hormones level, high or normal TSH and goiter which suggest the importance of THRb in feedback of hypothalamic pituitary axis [6]. In contrast, patients with RTHa present with musculoskeletal and gastrointestinal abnormalities. They usually have near normal thyroid function due to lack of *THRa* contribution in feedback on hypothalamic pituitary axis [8,9]. Our patient initially presented with symptoms of hypothyroidism including weight gain and generalized fatigability in addition to high TSH which is consistent to typical presentation found in the literature. However, she had normal T3 and T4 which is not usually typical in presentation of RTHb that made our initial impression to be subclinical hypothyroidism.

To date, more than 100 *THRB* mutations have been reported among RTH patients. Most mutations substitute a single amino-acid residue in the ligand-binding domain [10]. The most unique part in our case is found in genetic study, which confirmed that the patient is heterozygous in THRb gene for sequence variant designated **c.1147C>T**, which is predicted to result in amino acid substitution **p.Arg383Cys**. this variant appears to have been reported in French patient with thyroid hormone resistant [11]. It was also reported in another affected individual but was inherited from apparently unaffected father [10]. Another variant affecting the same amino acid have also been reported in patient with thyroid hormone resistance [12].

While we suspect this variant could be pathogenic, at this time clinical significance of this variant is uncertain due to lack of conclusive functional and genetic evidence.

Looking in literature about associations. We found that RTH-beta is associated with an increased risk for autoimmune thyroid disease [13]. Thus, the presence of antibodies to thyroid peroxidase and thyroglobulin should not detract from the investigation of RTH-beta if thyroid function tests suggest this possibility. Both antibodies were found to be positive in our patient, so now we are closely monitoring her for development of other autoimmune disease.

Conclusion;

Our case represent aid to other colleagues in clinical suspicion and diagnosing cases of RTH in addition to differentiation of RTH-alpha and RTH-beta. However the most interesting part in our case is the genetic study which revealed a rare mutation in thyroid hormone receptor beta which have been only reported in very few cases before (**heterozygous in THRb gene for sequence variant designated c.1147C>T, which is predicted to result in amino acid substitution p.Arg383Cys**). While we suspect this variant could be pathogenic, at this time clinical significance of this variant is uncertain due to lack of conclusive functional and genetic evidence.

Statements

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Statement of Ethics Case approved by HMC medical research center and Subjects have given his written informed consent to publish her case.

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Author Contributions

1. Mohanad Ahmed: Corresponding author, Case writing, patient clinical follow up , data collection and analysis , submission to journal.
2. Khalid Hassan: over all supervision, data collection patient clinical follow up.
3. Hind Ahmed: patient clinical follow up and contact with genetic lab.

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