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Case Report
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Thyroid Hormone Resistance in a Family due to a Mutation in the Receptor Beta Gene (p.M313V)

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Abstract

Context: Resistance to Thyroid Hormone (RTH) is a rare disease characterized by reduced Thyroid (TH) hormone sensitivity due to a defect at the site of hormone action at the receptor level.

Case Description: We are reporting a mutation in the β receptor gene that presented with RTH in 3 generations of family members with variable symptomatology within family members.

Introduction

Resistance to Thyroid Hormone (RTH) is a disease characterized by reduced Thyroid Hormone (TH) sensitivity due to a defect at the receptor level for TH. This disorder, inherited in an autosomal dominant fashion, is caused by a mutation in the isoform β of the thyroid hormone receptor (THRβ) causing this receptor to be resistant to TH [1]. The syndrome is represented by an increase in TH concentration in association with normal or elevated Thyroid Stimulating Hormone (TSH). The clinical presentation is variable due to the different spectrum of the same entity as there is an overlap in the clinical features within family members with the same mutation [2].

Case Presentation

A 3-month-old male presents with growth delay and vomiting. He was a former late preterm newborn with adequate weight for gestational age. The extensive gastro-enteral evaluation was significant for Gastrointestinal Reflux (GER) and protein-calorie malnutrition. Thyroi Function Testing (TFT) showed an elevated thyroxine (T4) level of 20.3 ug/dl (7.1-15), elevated triiodothyronine level (T3) of 322 ng/dl (0.87-1.67), elevated Free T3 of 760 pg/ml (337-506) and slightly elevated TSH of 6.27 uIU/ml (0.41-4.67).

Furthermore, family history was consistent with end-organ RTH in the patient's mother, elder sister, and maternal grandmother. Patient's mother had a low Body Mass Index associated with palpitations. She was initially treated for hyperthyroidism before being diagnosed with RTH. Maternal grandmother was clinically diagnosed with RTH during adolescence. Three of maternal grandmother's sisters and maternal great grandfather were diagnosed with thyroid disease, and they were treated with thyroxine (exact etiology unknown); however, none of the mother's three sisters had ever been diagnosed with a thyroid problem.

Because of the strong family history, genetic testing was undertaken in our index patient and family members with and without RTH. Direct sequence analysis of the entire coding region and splice-sites of the THRβ gene in the commercial lab (Quest Diagnostic) revealed a novel heterozygous variant caused by A>G change at nucleotide position c.937 in exon 9 of the THRβ gene leading to the replacement of methionine by a valine at position 313 (p.M313V) of the translated TRHβ protein. Since this change had not been described in the literature upon diagnosis, its clinical significance was unknown

Analysis by the online tool polyphen, (http://genetics.bwh.harvard.edu.pph/), used for the prediction of the effect of amino acid changes on the protein structure, indicated that the M313V change is probably damaging. However, as polyphenis not fully validated we could not predict the effect on the activity of the THRβ

Family members who were positive for p.M313V mutation include the patient's mother, maternal grandmother younger sister and eldest sister (previously diagnosed with RTH). Another genetic change was also noted which is a copy of c.735>T. This polymorphic single nucleotide substitution in

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exon sevendoes not alter the amino acid coding and thus is a benign variant. Patient's mother, elder sister and younger sister diagnosed with RTH and another older sister negative for RTH had this mutation. To the best of our knowledge, the p.M313V mutation has never been described in multiple family members with different symptomatology.

Sex Hormone Binding Globulin (SHBG) and Angiotensin-Converting Enzyme (ACE) assays were requested to assess clinical status as markers of thyroid function and both were within normal limits. As expected with RTH, free T4 has always been above the normal limit with TSH varying between normal to slightly elevated. Our index patient weight and height improved with hydrolyzed formula and GER medical treatment. His speech is slightly delayed, but his motor development is normal at four years of age.

The older sister with RTH was also born as late preterm newborn, required phototherapy, and had similar feeding intolerance. The younger sister, who is asymptomatic, was diagnosed with RTH based on TFT and genetic testing.

Results and Discussion

The THR has two isoforms, THRα and THRβ. Most RTH are caused by abnormalities in the THRβ. Approximately 100 missense mutations have been reported, which are located in the T3-binding domain (exons 8-9-10) [3], same location of p.M313V mutation.

RTH has a great range of symptomatology, varying from increased serum level of T4 and T3 with non-suppressed TSH and with the relative normal metabolic state to variable manifestations of hyperthyroidism or hypothyroidism. Family members can have a significant phenotype difference with the same mutation [4]. This variability could be a difference in the degree of disease expression by selective pituitary resistance to TH or differential distribution of the mutated receptor in different tissues

Most of the neonates are euthyroid since the increase in TH level is enough to overcome the hormonal resistance. However, jaundice and hyperkinetic state may be present. Newborn Screen (NBS) screening by TSH or T4 is used in different programs around the world [5], so there are cases diagnosed on NBS [6]. None of our patients had abnormal NBS.

Children may present with growth delay, hearing loss, ADHD, palpitations, and learning disability [7]. In our report, ADHD and learning disability was present in the 10-year-old female, while the other siblings are still young for such a diagnosis.

Most adult patients are clinically asymptomatic except for elevated TH with apparently normal TSH, which complicates the diagnosis [8]. Various patients may be misdiagnosed with hyperthyroidism, which put them at risk for inappropriate treatment, as happened to this mother. However, in the absence of positive family history, a pituitary tumor with inappropriate secretion of TSH must be ruled out [9].

Limited treatment options are available for RTH, although most patients do not require treatment since they can compensate for the resistance by an increase in TH. Symptomatic patients may benefit from beta-blockers or exogenous TH to overcome peripheral resistance [10].

In conclusion, RTH involves different genetic mutations with variable clinical symptoms. Even in family members with the same mutation, as reported in this manuscript, the phenotype can vary which may complicate the diagnosis within family members.

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