**TITLE PAGE**

**Type of article:** Case report

**Title-** Resistance to thyroid hormone α (RTHα): a rare form of resistance to thyroid hormone - First report from India

**Running title-** RTHα diagnosis in a case of enigmatic thyroid function test

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**TEXT**

**Abstract**

Thyroid hormone receptor alpha (THRA) gene mutation is a thyroid hormone resistance syndrome characterized by non-responsiveness of peripheral tissues to the active form of thyroid hormone (T3). We describe a heterozygous missense variant in exon 8 of THRA gene detected at mutation analysis in a 3 month old female with clinical phenotype of hypothyroidism, low free thyroxine, elevated free triiodothyronine but normal levels of thyroid stimulating hormone. THRA gene mutation should be considered in patients with features of clinical hypothyroidism and increased/moderately elevated free T3, decreased/ normal free thyroxine, normal thyroid-stimulating hormone levels.

**Keywords**

Thyroid hormone receptor α, hypothyroidism, THRA gene

**Introduction**

Thyroid hormones (TH) affect target tissues via specific nuclear receptors encoded by the TH receptor α (THRA) gene and TH receptor β (THRB) gene. THRA is a gene located on chromosome 17q11.2 . TR α1, and TR α2 are mainly located in the bones, cardiac and skeletal muscle, digestive tract and central nervous system.[1] Resistance to TH (RTH) is characterized by non-responsiveness of peripheral tissues to the active form of TH (T3). Two forms of inheritable RTH have been described—RTH β and RTH α.[2] The first case of THRA mutation was reported in 2012 in a 6-year-old girl with growth retardation.[1]

**Case Report**

A 3 month old female born full term of third degree consanguineous union was referred to us with a presumptive diagnosis of central hypothyroidism (FT4 < -2SD, normal TSH levels) and normal serum cortisol and IGFBP3 levels. Her length & OFC were at the 1st & 50th centile for age on the WHO growth chart respectively. She had pallor, broad face and nasal bridge, macroglossia, umbilical hernia and axial hypotonia and there was history of infrequent passage of stools.

Further evaluation suggested presence of normocytic normochromic anaemia, higher FT3 ( > + 2SD) & low rT3 (< -2SD), low FT4 (< -2SD), normal TSH and elevated creatinine kinase CK levels. Based on the clinical phenotype and this typical biochemical profile, thyroid hormone resistance with mutation in Thyroid Hormone Resistance Alfa (THRA) was suspected.

L-Thyroxine supplementation in a dose of 25 mcg/day was initiated & periodic titration thyroxine dose, initially at 4 weeks then at 8-12 weeks intervals to ensure optimal FT4 levels ( ~ + 1SD) was performed (Table 1). Clinical exome analysis was sent which yielded a heterozygous novel missense variant c.871G>A in exon 8 of THRA gene. Parental analysis for the variant were negative. This missense variant was not found in the Ensembl, dbSNP, and ClinVar variation databases nor in the Exome Sequencing Project (ESP), 1000 Genomes Project and Exome Aggregation Consortium (ExAC) population databases and was predicted to be deleterious by bioinformatics algorithms such as Polyphen-2, SIFT and Mutation Taster 2.We evaluated this variant as likely pathogenic according to the ACMG Standards and Guidelines recommendations.

Catch up in length to just above the 3rd centile, improvement in axial tone albeit not total, improvement in the stool frequency, normalisation of Ft4 & rT3, persistently elevated FT3, suppressed TSH and decrease in CK levels have been noted over the 6 months duration of follow up subsequently on thyroxine though the results of evaluations using BSID 4 indicate neurodevelopmental delay

**Discussion**

The spectrum of resistance to thyroid hormones (RTH) characterized by non-responsiveness of peripheral tissues to T3, comprises of THRA and THRB mutations, of which the latter is widely studied whereas the 1st patient with THRA mutation was reported in 2012.[1]

The clinical as well as biochemical profile of the two mutations are quite different from another, albeit the spectrum of severity ranging from mild to severe.[2] This discrepancy is most likely due to the differences in tissue expression of THRA and THRB; organs expressing a dysfunctional receptor will respond in a tissue-specific way. THRA(TRα1, TRα2 isoforms) is expressed in the cardiac and skeletal muscle, digestive tract, bones and brain, while THRB is found in the liver, hypothalamus, hypophysis and thyroid gland. And thus, despite the deprivation of thyroid hormone (TH) stimulus on peripheral tissues, the concentration of TSH in these individuals is found within the normal range in THRA mutants.[1]

Various clinical disorders such as developmental retardation, growth impairment, macroglossia, changes in bone ossification, and chronic constipation have to date been detected in THRA patients, similarly to cases of untreated congenital hypothyroidism.[3] Reports of some cases support the hypothesis of phenotype and genotype correlation with intellectual disability being more common in cases with nonsense mutations.[4] Normocytic normochromic anaemia as in our case is a common characteristic in THRA patients.[5] Inactivating mutations in TRα affect balance between proliferation and differentiation in human erythroid progenitor cells. Elevated CK levels similar to those observed in hypothyroidism may be seen in patients with THRA mutation. Increased parasympathetic activity and consequently reduced colonic motility have been described in previously reported RTHα patients.[6] Improvement, albeit not total, in metabolic status, increased motor coordination, and accelerated growth as well as improvement in constipation have been reported with Na-L thyroxin therapy in THRA cases but insufficiencies in cognitive and fine motor skills may remain.[2]

**Conclusion**

THRA mutations may be more common than currently thought. THRA gene mutation should therefore be considered in patients with features of clinical hypothyroidism and increased/moderately elevated free T3, decreased/ normal free thyroxine, normal thyroid-stimulating hormone levels. The diagnosis can easily be missed when only TSH and (Free)T4 are analysed, since these may be normal. When THRA mutations are suspected, serum T3 and rT3 should be measured as well.

**SUMMARY**

Resistance to thyroid hormone is evident by a lack of response of peripheral tissues to the active form of thyroid hormone (triiodothyronine, T3). In majority of cases described in literature till now, a mutation in THRB, the gene coding for thyroid receptor β (TRβ), was described. Recently, reports described the first patients with thyroid hormone receptor α gene (THRA) defects, first published in 2012. We identified a novel missense mutation in the THRA gene in our patient using whole exome sequencing and subsequent Sanger sequencing. This is the first case report from Indian subcontinent described. She presented with features of hypothyroidism with low T4 levels. Laboratory investigations revealed anaemia and complete thyroid profile showed low free thyroxine (fT4) levels coupled with high free T3 (fT3), leading to an altered T4 : T3 ratio, along with normal thyroid-stimulating hormone levels. THRA gene mutation should therefore be considered in patients with features of clinical hypothyroidism but enigmatic thyroid function test results.

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**TABLE**

Table1- Serial Thyroid function tests pre treatment and post treatment

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Pre-Thyroxine | 1 month on treatment | 3 months on treatment | 6 months on treatment |
| Thyroxine (ng/dl) (Free)  |  0.72  |  1.02 | 1.27 | 1.41 |
| TriiodothyronineFree (pg/ml)  |  5.97 |  5.83 | 5.67 | 5.75 |
| Reverse T3(ng/dl) |  11 |  - |  - |  32 |
| Thyroid-stimulating hormone(mIU/l) |  3.11 | 1.12 | 0.47  | 0.34 |
| Creatinine Kinase (CK) |  389 | 259 | 200 | 191 |