

Thyroid Hormone Resistance due to a Novel De Novo Mutation in Thyroid Hormone Receptor Alpha: First Case Report from the Middle East and North Africa

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ABSTRACT

The physiological actions of thyroid hormone (TH) are mediated through TH alpha and TH beta receptors. Resistance to TH (RTH) is characterized by a lack of peripheral tissues' response to the active form of TH. TH receptor beta has been extensively studied. Mutations in this receptor were considered the main reason for TH resistance for some time up until the discovery of mutations in TH receptor alpha (TR α) that has attained more focus and interest in recent years. A 13-year-old child with classic hypothyroidism features (coarse facies, growth and developmental delay, skeletal dysplasia, generalized muscular hypertrophy, and severe constipation) associated with near-normal thyroid hormone levels, which did not support the diagnosis of hypothyroidism biochemically. Therefore, progressing with whole-exome sequencing had revealed a de novo heterozygous mutation in a gene encoding TR α that establishes a diagnosis of RTH α . This case report demonstrates a rare form of TH resistance due to mutation of TR α . It also emphasizes that THs act through distinctive receptor subtypes in different target tissues. Moreover, this report aims to raise awareness about this genetic mutation, which is thought to be more common than expected. However, due to its subtle features and insidious presentation, many cases remain undiagnosed; hence, the disorder's exact incidence is unknown.

Thyroid hormones (THs), thyroxine (T₄) and triiodothyronine (T₃), regulate skeletal growth, maturation of the central nervous system, energy homeostasis, positive chronotropic and inotropic cardiac effects, and gastrointestinal functions. The hypothalamic pituitary thyroid axis accomplishes this process. These physiological effects are mediated through TH nuclear receptors (TR),¹ which have been classified into α and β receptors.

TR α (TR α 1, TR α 2) and TR β (TR β 1, TR β 2) have different tissue distributions. TR α 1 is the predominant subtype in bone, the gastrointestinal tract, central nervous system, and cardiac and skeletal muscles, while TR α 2 location and role are not yet clear. TR β 1 is the primary subtype in the liver and kidney, while TR β 2 dominates in the hypothalamus, pituitary, cochlea, and retina.²⁻⁴

Various genetic conditions of partial insensitivity to THs have been described. The resulting defects

can cause either an alteration of the β or α nuclear receptors, a disruption of an intracellular transporter (monocarboxylate transporter 8), or a defect in their activation in the peripheral tissues due to failed activation of deiodinases by selenoproteins (selenocysteine insertion sequence binding protein 2).⁵

The reported incidence of resistance to thyroid hormone beta (RTH β), which is a dominantly inherited disorder due to TR β gene mutations is 1 in 40 000.⁶ Most patients with RTH β are clinically euthyroid, but they can present with various symptoms and signs as summarized in Table 1. Biochemically, they manifest with high serum free T₄ (fT₄), fT₃, and thyroid-stimulating hormone (TSH).⁷

However, clinical features of resistance to thyroid hormone alpha ((RTH α) (OMIM 614450) which was first reported in 2012, including dysmorphic facies, skeletal dysplasia (macrocephaly, epiphyseal

Table 1: Comparison between the clinical features of resistance to thyroid hormone β (RTH β) versus resistance to thyroid hormone α (RTH α).

Features	RTH β	RTH α
Clinical features		
Thyroid gland	Goiter	No goiter
Dysmorphism	Nil	Dysmorphic facies
Skeletal changes	Nil	Macrocephaly, epiphyseal dysgenesis, Wormian bones
Hematological	Nil	Anemia
Heart	Tachycardia	Bradycardia
Nervous system and behavior	Emotional disturbances, hyperkinetic behavior, attention deficit hyperactivity disorder, learning disability, mental retardation (intelligence quotient < 70)	Autistic spectrum disorder, dyspraxia, learning disability, intellectual deficit
Growth and development	Short stature (< 5%), delayed bone age > 2 standard deviation, low body mass index (in children), hearing loss (sensorineural)	Short stature, delayed bone age, high body mass index, delayed mile stones
Gastrointestinal		Chronic constipation
Recurrent ear and throat Infections	Yes, 55%	No
Biochemical profile		
free T4	High	Low/low-normal
free T3	High	High/high-normal
Thyroid-stimulating hormone	High	Normal
Reverse T3	-	Low
Creatinine kinase	-	High

dysgenesis), growth retardation, constipation, dyspraxia, and intellectual deficit.

The biochemical features are typically borderline normal thyroid function tests with low/low-normal fT4 and high/high-normal fT3 concentrations, a subnormal fT4/fT3 ratio, reduced reverse T3, raised muscle creatinine kinase, and mild anemia.⁸

To date, 31 patients have been reported in the literature carrying 20 missense and frameshift mutations.^{9,10} None of the described patients are from Arab countries. The authors searched the EMBASE, Medline, and PubMed databases using 'thyroid hormone resistance alpha' as search words, and none were reported from the Middle East and North Africa (MENA) region.

CASE REPORT

A 13-year-old male was referred at the age of three months to our center for evaluation of anemia. He was found to have hypochromic microcytic anemia diagnosed as iron deficiency anemia. However, his anemia persisted after correction of the iron deficiency by a therapeutic dose of ferrous sulfate, evidenced by persistent normochromic normocytic anemia and

normal bone marrow iron stores. Reduced activity, excessive sleepiness, and chronic constipation were also reported since early infancy. The child was on regular follow-up with a hematologist; subtle dysmorphism was reported. Later, during his follow-up, his growth was suboptimal, and there was a delay in achieving the age-appropriate developmental milestones.

His developmental delay manifested as an impairment of his gross motor, coordination, language, and cognitive abilities. He started to walk independently at the age of eighteen months but with imbalance. His speech was slow and monotonous, with no major receptive or expressive deficit. His school performance was suboptimal in almost all subjects and required extra teaching sessions.

The child's growth was slow from two and a half years of age. At the age of three years, his height was 83 cm below the third percentile (-3.5 standard deviation (SD)) for his age. He was obese, weight for age was 14 kg at 41st percentile (-0.2 SD), and he had a body mass index of 20.1 kg/m² above the 99th percentile (+3.2 SD). He had disproportionate short stature, with an upper/lower segment ratio > 1.7, predominantly affecting the

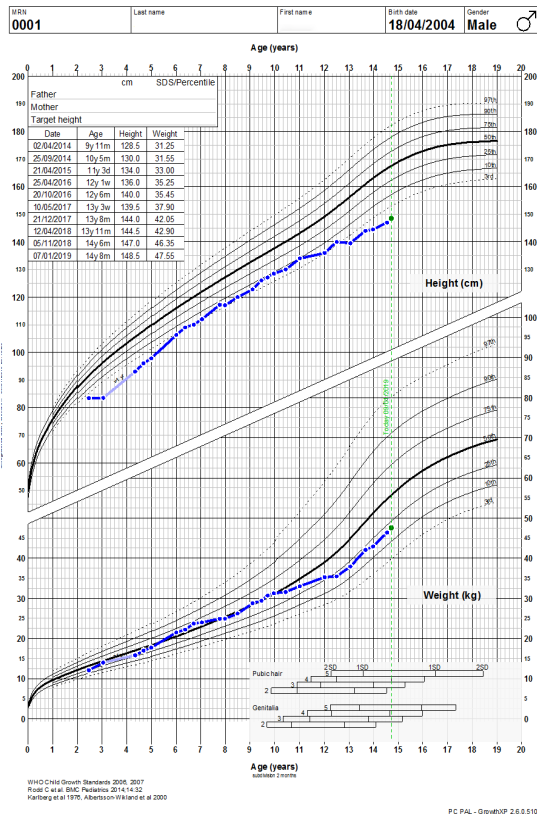


Figure 1: Growth charts of the patient.

lower segment. Furthermore, he had macrocephaly; his head circumference was $> 97^{\text{th}}$ percentile ($+2.0$ SD) [Figure 1]. He had thick dry myxedematous skin with generalized hypertrichosis and muscle hypertrophy. Dysmorphic features including coarse facial features, low anterior and posterior hairline, periorbital fullness, telecanthus and hypertelorism, epicanthic folds, broad and flat nasal bridge, midface hypoplasia, splayed out nasal base with flat nasal tip, anteverted nares, thick prominent lips, low set ears with thick and prominent ear lobes, brachydactyly, and broad hands [Figure 2]. He has a mild increase in joint laxity. His teeth were small and widely spaced with multiple dental caries. He had generalized muscular weakness with a wide-based and waddling gait. Gower's sign was negative. Muscle tone and power were normal with brisk reflexes.

The child has been investigated and seen by different specialties, including a hematologist, general pediatrician, endocrinologist, neurologist, geneticist, cardiologist, developmental pediatrics specialist, and speech and occupational therapists.

The child was thoroughly investigated, and his initial workup showed a microcytic, hypochromic



Figure 2: The patient aged 10. Note the characteristic facial features such as macrocephaly, coarse and flat face, periorbital fullness, hypertelorism, flat broad nasal bridge, upturned nose, anteverted nares, thick prominent lips, generalized muscular hypertrophy, and puffy, short, broad hands with rough and doughy texture skin.

anemia. He was evaluated for inborn errors of metabolism. His urine screening was negative for glycosaminoglycans and oligosaccharides. Skeletal survey showed that both femoral epiphysis were small with shallow acetabulum and minimal anterior beaking of lumbar vertebrae. Genetic workup showed a normal karyotype, with normal array comparative genomic hybridization and negative fluorescence in situ hybridization for 7q11.23 microdeletion which ruled out Williams Beuren syndrome (OMIM 194050). Sequencing for polymerase I and transcript release factor mutation for congenital generalized lipodystrophy type 4 (CGL4; OMIM 61337) was also negative.

He had repeated normal levels of fT_4 and TSH, persistent mild elevation of creatine kinase (CK) around 788 U/L (39–308), low insulin-like growth factor (IGF1) 68 $\mu\text{g/L}$ (115–498), with failure to respond to two growth hormone (GH) stimulation tests as the peak of provoked growth

Table 2: Biochemical profile of the patient before and during treatment.

Laboratory test	Age, years							
	2 2006	4 2008	11 2015	12 April 2016	12 May 2016	12 Aug 2016	12 Oct 2016	13 2017
Dose of Levothyroxine, µg					25	50	75	100
Free T4 (9.7–14.2 pmol/L)	8.8	8.7	11.1	12.2	13.3	14.3	18.3	10.9
Free T3 (3.8–6 pmol/L)	7.6			7.8	8.0	8.1	9.6	7.9
TSH (0.8–3.9 mIU/L)	2.70	2.30	1.66	1.68	1.42	0.47	0.01	0.02
Free T4:Free T3 (2.0–4.5 pmol/L)	1.2			1.6				
CK (39–308 U/L)		713	327	264				
CK, Mb			19.4					
Hb (11.5–15.5 g/dL)	9.6	9.5	10.3					10.9
MCV (78.0–96.0 fL)	71.8	72.7	77.3					78.0
MCH (26.0–33.0 pg)	23.7	24.5	25.0					23.7
MCHC (31.0–35.0 g/L)	33.1	33.7	32.4					30.4
IGF1, µg/L	30 (75–260)	68 (115–498)						

TSH: thyroid-stimulating hormone; CK: creatine kinase; Hb: hemoglobin; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; IGF1: low insulin-like growth factor.

hormone was only 15 mIU/L (our lab's cut off is 20 mIU/L). We opted for the “wait and see” approach initially, and then he was started on GH therapy after four years of age. He initially showed a good response but later went suboptimal, which was thought to be due to poor adherence to GH therapy and/or the underlying pathology related to the genetic mutation. His height before GH therapy was -2.9 SDs, which gradually improved to -1.4 SD at 11 years old but later deteriorated to -2.4 SD [Figure 1].

Skeletal radiographic study showed delayed bone age by two years at chronologic age of six years. His neurological evaluation showed normal brain magnetic resonance imaging (MRI). MRI of thigh muscle showed only muscular hypertrophy. His muscle biopsy showed normal morphology with a negative caveolin stain. Nerve conduction study showed bilateral delay in both motor and sensory divisions of his median nerve. An echocardiogram showed mild left ventricular trabeculations. His brainstem auditory evoked potentials were normal. His IQ assessment was found to be below-average intelligence (IQ 87). Although initial THs levels were normal, subsequent measurements revealed persistently elevated levels of fT3 and normal levels of fT4 and TSH [Table 2].

In 2016, TRIO whole-exome sequencing detected that the patient was heterozygous for a novel, de novo mutation in the TH receptor α

(THRA) (NM-001190910) gene, (c.871G>A, p.Gly291Ser), which was absent in his parents.

Our institutional ethics committee approved the genetic study. The patient's parents provided written informed consent. We performed whole-exome sequencing for the patient and his parents. Bioinformatics analysis of the sequence data identified a novel de novo mutation that is linked with the patient's phenotype.

This is the first case report from Oman and the MENA region. At the age of 12, he was started on thyroxine treatment with gradual dose increment from 25 µg to 100 mcg with monitoring of his clinical and biochemical response. Close monitoring of his biochemical indices showed suppression of TSH. His fT3 level remained in the supra-physiological range. He showed some clinical response in terms of improved general wellbeing and some improvement in constipation. He went into normal puberty. He still suffers from significant learning difficulties. However, he continued attending a mainstream school with inclusion classes.

DISCUSSION

RTH β is extensively studied, however, it is likely that RTH α is more common than expected and may even be more common than RTH β . The difference in the presentation is most likely due to the differences in tissue expression of TR α and TR β .¹¹ Recently, several

patients with RTH α due to THRA mutations were identified. These patients' phenotype consists of varying degrees of growth impairment, delayed bone, mental and motor development, constipation, macrocephaly, and near-normal thyroid function tests.^{7,12–18} The phenotype of mice harboring different TR α mutations is not uniform, suggesting that the human disorder may also be variable.¹⁹

Our patient had many clinical features typical of congenital hypothyroidism, but that paradoxically was associated with normal levels of fT4 and TSH with elevated fT3 levels and low fT4/fT3 ratio. He had normochromic normocytic anemia and developmental delay; mainly impairing his gross motor coordination, language, and cognitive abilities. He also had disproportionate short stature with femoral epiphyseal dysgenesis, and delayed bone age, coarse facial features and generalized muscular hypertrophy with high CK (Kocher–Debré–Semelaigne Syndrome).

Molecular genetic study identified a novel heterozygous mutation in the THRA in a highly conserved amino acid that is likely to be the cause, which describes the phenotype and the endocrinopathy the patient has.

The patient was treated using GH therapy, for which he showed a good response in improving his linear growth with delta of +1.5 SD. Although treatment with thyroxine started late, marked improvement in his general wellbeing and some improvement in constipation noted, but that was not reflected on the linear growth or reducing the skin thickness, or minimizing the coarse facial features. Biochemically, starting thyroxine increased fT4, suppressed TSH, and maintained fT3 at supra-physiological levels. Furthermore, his anemia persisted. Reviewing the literature, the benefit of thyroxine replacement in patients with RTH α is not as effective but showed some benefits, especially if started early in life. In three patients described by Moran et al,¹⁵ starting thyroxine between the age of two to three years improved their resting energy expenditure with a subjective feeling of being more energetic. It also improved constipation, and growth and development. Furthermore, a case from the Netherlands treated at 18 months of age showed a marked improvement in growth and development over a period of 12 months.¹⁰ Other reported patients had no improvement, which may be related to the severity of the structural alteration of the

causative mutant TR α 1 so that the more severe the alteration, the less effective the thyroxine therapy.²⁰ It may also reflect the delay in initiating thyroxine treatment. Researchers have started thinking about alternative therapy for this cohort of patients. Histone deacetylases inhibitor like suberoylanilide hydroxamic acid was tried on mice model, but it showed no benefit on skeletal development.²¹ Other types of therapies might emerge soon as the discovery of this mutation had attracted the attention of researchers worldwide.

Our case highlights the need to maintain a high index of suspicion when the phenotype suggests hypothyroidism but with normal fT4 and TSH. The measurement of the levels of fT3 can help to reach the diagnosis of RTH α .

CONCLUSION

Although it was thought that RTH α is rare, improvements in molecular genetic testing have led to the discovery of more cases. TR α resistance secondary to a mutation in the THRA gene has distinct clinical features along with physiological features of hypothyroidism in specific tissues. Almost all patients will have subtle or no abnormalities in fT4. These cases are not usually detected by newborn screening, as they do not manifest with high TSH. It is important to consider resistance to TH α in children with refractory anemia, severe constipation, short stature, and subtle dysmorphism. Although many cases present with symptoms because of the subtle changes in the thyroid function tests, many patients remain undiagnosed for a long time, even in tertiary hospitals. In such cases, in addition to fT4 and TSH, other investigations, including fT3, CK should be considered. Clinical dysmorphism assessment and genetic testing is indicated. Thyroxine therapy can reverse some clinical and/or biochemical abnormalities. However, careful monitoring for excessive TH adverse effects in hormone-sensitive TR β tissues is recommended. Delayed treatment can result in lower neurocognitive outcomes.

Disclosure

The authors declared no conflicts of interest.

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