

RESISTANCE TO THYROID HORMONE DUE TO A NOVEL THR- β MUTATION IN A PATIENT WITH THYROID AGENESIS

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ABSTRACT

Refetoff Syndrome is a rare disorder characterized by resistance to thyroid hormone (RTH). The coexistence of RTH and thyroid dysgenesis is a rare event. Up to now, only four cases of ectopic gland and RTH have been reported. We report the first case with both thyroid agenesis and RTH. The patient was referred to our center because of a high level of thyroid-stimulating hormone (TSH) at newborn screening. Laboratory analysis and thyroid ultrasound confirmed diagnosis of congenital hypothyroidism caused by athyreosis. Therefore, treatment with levothyroxine was started. During the follow-up, despite persistent mild elevation of serum free thyroxine concentrations, TSH level remained at the upper limit of the reference range. Direct sequencing of the thyroid hormone receptor β (THR- β) gene identified a new intronic variant (c.1144+9G>A). RTH may occur in presence of thyroid dysgenesis and this association suggests a hypothetical role of the THR- β in thyroid organogenesis.

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1. Introduction

The incidence of congenital hypothyroidism (CH) is 1 in 3,500 newborns, of which thyroid dysgenesis constitutes about 85% of cases [1]. Resistance to thyroid hormone (RTH) is a rare genetic disorder characterized by decreased responsiveness to thyroid hormone. Most RTH cases are caused by mutations in the thyroid hormone receptor β (THR- β) gene [2].

The coexistence of RTH and thyroid dysgenesis is an extremely rare event. When primary hypothyroidism coexists with RTH, the evaluation of thyroid status is difficult and this association is often not diagnosed. Up to now, only four cases of ectopic thyroid gland and RTH have been reported [3-6].

Here, we report the first case with both thyroid agenesis and RTH caused by a new intronic variant of THR- β gene.

2. Case presentation

The patient was an Italian girl born at 38 weeks gestation. She was the third child of unrelated healthy parents.

Gestational period was uneventful with the exception of CMV infection during the first trimester of pregnancy. At birth, she had breathing problems caused by inhalation of meconium necessitating supplementary oxygen (APGAR score 1° 7, 5° 8). Her birth weight was 3080g and her birth length was 50 cm. Newborn screening was performed and revealed a high level (338 mIU/ml) of thyroid-stimulating hormone (TSH). At ten days old, the patient was referred to our center. She had no dysmorphic features and physical examination showed signs of hypothyroidism, including mottled skin, prolonged jaundice, hypotonia, wide anterior fontanel and tongue protrusion. Her weight was 2890g (10-25th centile), length 50 cm (25th centile) and head circumference 34 cm (25th centile).

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On laboratory analysis her serum TSH level was >150 $\mu\text{IU/ml}$ (normal range: 0.60-10 $\mu\text{IU/ml}$), free thyroxine (FT4) level was 0.23 ng/dl (normal range: 0.7-1.7 ng/dl), free triiodothyronine (FT3) level was 0.8 pg/ml (normal range: 2.3-4.2 pg/ml). There was no family history of thyroid disorders and both parents had normal thyroid function without goiter. Thyroid ultrasound did not identify the thyroid gland. These data resulted in a diagnosis of congenital hypothyroidism and levothyroxine (L-T4) replacement was given (11.7 $\mu\text{g/Kg/die}$). Treatment with L-T4 lowered the serum TSH, but it could not maintain FT4 in the normal range.

For the following years, despite persistent mild elevation of serum FT4 concentrations, TSH levels remained at the upper limit of the reference range during L-T4-therapy (0.5-2.5 $\mu\text{IU/ml}$) (Fig.1). Noncompliance treatment has been excluded. She showed no signs of hypothyroidism or hyperthyroidism, her physical and intellectual development was unremarkable and her growth curve was normal for her age. At 6 years of age, after L-T4 withdrawal, a $^{99\text{m}}\text{Tc}$ -pertechnetate scintigraphy was performed confirming the thyroid agenesis. A TSH-releasing hormone (TRH) stimulation test showed an exaggerated serum TSH response.

With the suspicion of RTH in addition to thyroid agenesis, molecular analysis of THR- β and ALB genes was requested. The patient's parents provided informed consent for the genetic analysis. Genomic DNA was extracted from leukocytes of the patient and THR- β gene direct sequencing identified a new intronic variant (c.1144+9G>A).

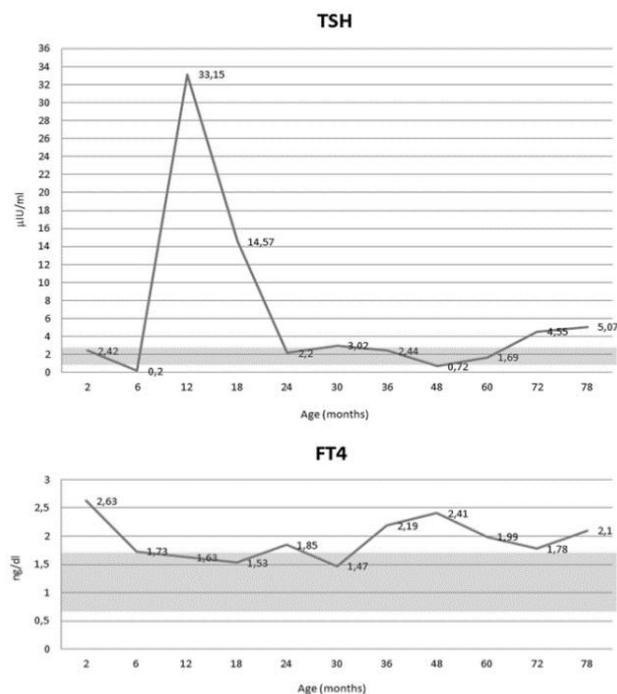


Figure 1 - Biochemical course of the levels of TSH and FT4 during the follow-up.

Discussion

In this report, we describe a newly identified THR- β mutation (c.1144+9G>A) in a unique case of RTH associated with a thyroid agenesis.

RTH, first described in 1967 by Refetoff (Refetoff Syndrome), is a rare condition (prevalence of 1:40,000) characterized by decreased tissue responsiveness to thyroid hormone. In most cases it is caused by mutations in the THR- β gene which encodes for the thyroid hormone receptor beta unit.

More recently, thyroid hormone receptor α (THR- α) gene defect has also been reported [2]. THR- β and THR- α are members of the nuclear receptor family. Alternative splicing and promoter usage produce 2 major THR- α ($\alpha 1$, $\alpha 2$) and 2 major THR- β ($\beta 1$, $\beta 2$) isoforms, of which three isoforms bind thyroid hormone (THR- $\alpha 1$, THR- $\beta 1$ and THR- $\beta 2$) [7]. A subgroup of individuals presents the cardinal features of RTH (high FT4 level in presence of nonsuppressed TSH) but no mutation in the THR- β and THR- α genes, and this is likely due to defects in the factors (cofactors, transporters, deiodinases, binding protein) that may affect the actions of thyroid hormone [8].

Numerous reports have documented inappropriately elevated serum TSH concentrations in 20-50% of L-T4-treated infants with CH. This phenomenon has been attributed to an abnormal maturation of the feedback control of TSH secretion which may persist into adulthood in approximately 10% of cases [3,9]. The coexistence of RTH would also lead to TSH elevation, but this eventuality, often undiagnosed, has rarely been described (Tab.1). In 2005, Grasberger et al. described the first case of a patient with sublingual ectopy of the thyroid gland and RTH due to a heterozygous mutation (R320H) in the THR- β gene [3]. After a few years, Nakajima et al. reported the first case of a R316C THR- β mutation in a patient with an ectopic sublingual thyroid [4]. Heather et al. described the case of a 2-year-old girl with dysmorphic features and developmental delay who presented ectopic sublingual gland and RTH due to a heterozygous mutation (p.Arg243Trp) in the THR- β subunit gene [5]. Finally, Man-Li Guo et al. report a patient with a large sublingual thyroid gland and clinical and biochemical criteria for RTH, but no mutation in THR- β , THR- α , thyrotropin receptor (TSHR) and GNAS1 genes [6].

In our patient, the THR- β genomic sequencing revealed a new intronic variant (c.1144+9G>A). The G>A mutation insists on canonical sequence cccccccGA in the acceptor site and might have effects on transcript splicing and then most probably on protein product. Further studies are needed to confirm this finding.

Our patient was even more unusual because she had severely reduced circulating thyroid hormones at birth due to thyroid dysgenesis. A severe congenital hypothyroidism at birth was also reported in the child described by Nakajima et al. [4].

The association between RTH and thyroid dysgenesis suggests that the thyroid hormone receptor may also have a role in thyroid organogenesis. Heather et al. postulated a possible, though speculative, hypothesis to explain this.

CASE REPORT	SEX	INITIAL TSH LEVEL	INITIAL FT4 LEVEL	TYPE OF DYSGENESIS	GENETIC MUTATION	SYMPTOMS OF DYSTHYROIDISM	OTHER CLINICAL FEATURES
Grasberger et al. 2005	F	350 µU/ml	6.8 ng/dl	Sublingual gland	R320H (THR-β)	No	No
Nakajima et al. 2010	F	177 µU/ml	0.36 ng/dl	Sublingual gland	R316C (THR-β)	No	No
Heather et al. 2012	F	44 µU/ml	/	Sublingual gland	p.Arg243Trp (THR-β)	No	Dysmorphic features, psychomotor development retardation
Guo et al. 2016	F	36.9 µU/ml	0.70 ng/dl	Sublingual gland	None	No	No
Present case	F	>150 µU/ml	0.23 ng/dl	Agnesis	C1144+9G>A (THR-β)	No	No

Table 1 - Reports of patients with both thyroid dysgenesis and RTH.

According to these authors the mechanism for an association between RTH and thyroid dysgenesis would be a dominant negative interaction, during thyroid organogenesis, between the mutant THR-β and another members of the nuclear receptor superfamily (retinoid X receptors, RXRs) that have a key role in embryonic development and organogenesis [5].

Clinical presentation of the patients is heterogeneous ranging from subclinical to highly symptomatic phenotypes. The main symptoms described are poor attention and concentration, fatigue and disturbed sleep. Furthermore, signs of thyroid hormone deficiency, sufficiency and excess may coexist depending on the level of THR-β gene expression in different tissues. Decisions regarding the initiation and modification of treatment are difficult. Reduction of TSH levels can guide therapy, as can other markers (sex hormone binding globulin, cholesterol, creatine kinase, ferritin) which are influenced by thyroid hormone [10].

In conclusion, RTH may occur in association with CH and this coexistence should be ratified when serum TSH and FT4 remain persistently elevated even when suboptimal treatment and noncompliance have been excluded. It is important to consider this diagnosis in young children with CH, because unrecognized tissue hypothyroidism may have a negative impact on growth and development.

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