Thyroid Hormone Resistance Due to a Novel THRβ Mutation

Dear Editor,

Resistance to thyroid hormone (RTH) is a syndrome of reduced responsiveness of target tissues to thyroid hormone. Patients with thyroid hormone resistance have elevated free triiodothyronine (fT3) and/or free thyroxine (fT4) with inappropriately normal or elevated thyroid stimulating hormone (TSH). It is a diagnosis to consider in newborns presenting with abnormal thyroid function. We report a case of a 1 year 8 months old boy with RTH who had a novel mutation of the THR β gene. This mutation is, to the best of our knowledge, the first such mutation reported in Singapore.

Case Description

Our patient is a Chinese boy who first presented with persistently elevated free T4 and TSH levels since birth. He was born at term with birth weight of 2.82 kg. There was no family history of thyroid disorders. He had persistently elevated free T4 and TSH levels since birth (Table 1). Serial dilution of the TSH in our service lab showed a linear trend, and thus it is unlikely that there are heterophile antibodies which interfered with the TSH assays. His parents' thyroid function tests were normal.

Table 1 Serial Thyroid Function Related Tests at Various Time Points



Fig. 1. Mutation analysis by direct sequencing of DNA from blood leucocytes.

The high fT4, fT3, inappropriately normal or elevated TSH, and high thyroglobulin are consistent with the diagnosis of thyroid hormone resistance. Clinically there were no overt symptoms of thyroid disorder or thyrotoxicosis. There was no goitre and pulse rate was 150 to 160/min. X-ray of the knees at 6 weeks of life showed the presence of distal femoral epiphysis which is expected to be present at birth. The proximal tibial epiphysis is also present, which normally appears at 1 to 3 months of age. Thus it is unlikely the baby has suffered significant delay in skeletal maturation in-utero due to this thyroid hormone (TH) resistance state.

Age	Birth (cord)	Day 4	Day 21	5 weeks	7 weeks	5 months
FreeT4 (pmol/L)	32.47 (12 – 22)	46.98 (19.35 – 33.41)	46.13 (19.35 – 33.41)	45.14 (14.45 – 23.99)	42.8 (10 – 23)	38.6 (10-23)
TSH (mIU/L)	10.04 (2 - 25)	20.598 (0.5 - 10)	10.294 (0.5 – 10)	6.561 (0.4 - 7)	5.75 (0.5 - 4)	4.1 (0.5 – 4)
T3 (nmol/L)				5.39 (1.23 - 3.48)		
FreeT3 (pmol/L)					13 (4.3 – 8.3)	
TSH Receptor Ab (IU/L)				<1 (<1.8)	1.1 (<1.8)	
Anti-TPO					<10 (0-50)	
Anti-TG					<20 (0-40)	
Thyroglobulin (g/L)					128 (0 - 110)	

The normal ranges are provided in brackets.

Direct sequencing of the thyroid hormone receptor beta gene (THR β) was performed for the proband and his parents (details available on request) using peripheral blood samples. The proband was heterozygous for a novel mutation His435Pro due to a single nucleotide substitution A>C at nucleotide 1304 which resulted in a change of histidine to proline at residue 435 (Fig. 1). The mutation likely represents a de novo mutation as it was not found in his parents, and was also not found in 50 Chinese controls.

PolyPhen-2 (polymorphism phenotyping) web service (available at http://genetics.bwh.harvard.edu/pph2/ index.shtml) was used to predict the effect of amino acid substitution on the structure and function of THR β .¹ PolyPhen-2 predicted that the H435P mutation is probably damaging with a score of 1.000 (sensitivity 0.00, specificity 1.00).

The patient remained clinically asymptomatic despite the TH excess and did not require any treatment. At 1 year 8 months, his development and growth has been appropriate, with weight on the 25th percentile and height 50th percentile (local chart).

Discussion

RTH is a rare cause of abnormal thyroid function test. It is a syndrome of reduced responsiveness of target tissues to TH.^{2,3} It is characterised by inappropriately normal or slightly elevated serum TSH in the presence of elevated serum fT4 and fT3 levels which are present in our patient.

The precise incidence is unknown. A limited neonatal survey by measuring blood T4 concentration, suggested the occurrence of one case per 40,000 live births.^{4,5} RTH has been found with equal frequency in both genders and prevalence vary among different ethnic groups. Familiar occurrence of RTH has been documented in approximately 75% of cases, and about 20% are de novo cases.²

Humans have 2 subtypes or isoforms of thyroid receptors (TR), namely TR α and TR β .² The expression and distribution of the 2 TR subtypes vary among tissues and during different stages of development. TR α and TR β are interchangeable, but the compensation in the absence of one isoform is incomplete. Differences in the degree of hormonal resistance in different tissues are due to the relative TR β and TR α expression. Compensation for hyposensitivity to thyroid hormones varies between individuals, and also between tissues, where features of TH excess and deficiency can co-exist in the same patient. A patient can have tachycardia and hyperactivity (thyrotoxicosis), but also delayed growth, bone maturation, and learning disability (hypothyroidism). The difference in degree of TH resistance in different tissues is due to relative levels of TR α and TR β expression. The hypothalamus and pituitary gland usually express more of and therefore are dependent on TR β , thus exhibiting features of TH deficiency when there is TR β defect. The heart is more dependent on TR α , and thus will manifest features of TH excess in the presence of high circulating TH in patients with TR β defect.

RTH can be classified into generalised, pituitary and peripheral resistance on the basis of tissue resistance. In generalised TH resistance, patients are usually clinically euthyroid with normal stature, though some may have low IQ. The euthyroid state is due to sufficient compensatory rise in TH concentration. In pituitary TH resistance, patients have features of thyrotoxicosis due to lesser TH responsiveness at the pituitary gland compared to peripheral tissues, and thus there is inappropriately high pituitary TSH secretion which results in overproduction of T4 and T3. In peripheral TH resistance, patients have features of hypothyroidism, as peripheral tissues are less sensitive to TH than the pituitary, and thus TSH is usually in the normal range.²

About 90% of RTH patients carry mutations in their TR β gene and more than 100 mutations have been reported.^{2,3} RTH is not simply the consequence of a reduced amount of functional TR but is usually caused by the interference of the mutant TR with the function of the wild type TF (dominant negative effect).⁶ The mutation we found was a new mutation which has not been described in literature in a Singaporean.

Mutations in the same codon 435 was previously reported in 2 unrelated Japanese patients with RTH.⁷ One patient with generalised TH resistance had histidine to leucine substitution (CAT \rightarrow CTT) while the other patient with pituitary selective TH resistance had histidine to glutamine(CAT \rightarrow CAA) substitution. Although the mutations were at the same codon, the patients had different clinical phenotype, with the first patient having generalised resistance while the second patient having pituitary-selective resistance.⁷ It is increasingly clear nowadays that the spectrum of presentation may be a continuum, and the distinction is less clear as a variable degree of resistance can be found in pituitary and peripheral tissues of the same individual.²

Characteristics of the RTH syndrome is the paucity of specific clinical manifestations.² When present, they varied from one patient to another. Presenting symptoms and signs are goitre, hyperactive behaviour, learning disabilities, developmental delay and sinus tachycardia. The majority of subjects maintain a normal metabolic state at the expense of high TH levels. As discussed earlier, this compensation for the hyposensitivity to TH is variable not only among individuals but also in different tissues.² As a consequence, evidence of TH deficiency and excess often coexist.

Fortunately, in most subjects with RTH, the partial tissue resistance to TH is adequately compensated for by an

increase in the endogenous supply of TH and thus, treatment is not required. It is important not to intervene with the sole purpose of normalising TH levels. Sinus tachycardia can be controlled with the β-adrenergic blocking agent such as atenolol. Rarely, the compensation is incomplete and requires the judicious administration of supraphysiologic doses of the hormone. Since the dose varies greatly among cases, it should be individually determined by assessing tissue responses. In children, particular attention must be paid to growth, bone maturation and mental development.^{2,3} Also, prenatal diagnosis and counselling are particularly important in families whose affected members show evidence of growth or mental retardation. Cindy WL <u>Ho</u>, ¹*MBBS*, *MMed Paediatrics*, *MRCPCH*, Raymond ME Chan, ²*BSc*, Yvonne YJ Lim, ¹*MBBS*, *MMed*

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REFERENCES

- Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, et al. A method and server for predicting damaging missense mutations. Nat Methods 2010;7:248-9.
- Dumitrescu, AM and Refetoff, S: Reduced sensitivity to Thyroid Hormone: Defects of Transport, Metabolism and Action (Chapter 58). In Werner & Ingbar's The Thyroid: A Fundamental and Clinical Text. Braverman, L.E., and Cooper D.S. (eds.), Wolters Kluver / Lippincott, Williams & Wilkins Publications, Philadelphia, PA.
- Refetoff S, Weiss RE, Usala SJ. The syndromes of resistance to thyroid hormone. Endocr Rev 1993;1:348-99.
- LaFranchi SH, Snyder DB, Sesser DE, Skeels MR, Singh N, Brent GA, et al. Follow-up of newborns with elevated screening T4 concentrations. J Pediatr 2003;143:296-301.
- Tajima T, Jo W, Fujikura K, Fukushi M, Fujieda K. Elevated free thyroxine levels detected by a neonatal screening system. Pediatr Res 2009;66:312-6.
- Yen PM, Chin WW. Molecular mechanism of dominant negative activity by nuclear hormone receptors. Mol Endocrinol 1994;8:1450-4.
- Tsukaguchi H, Yoshimasa Y, Fujimoto K, Ishii H, Yamamoto T, Yoshimasa T, et al. Three novel mutations of thyroid hormone receptor beta gene in unrelated patients with resistance to thyroid hormone: two mutations of the same codon (H435L and H435Q) produce separate subtypes of resistance. J Clin Endocrinol Metab 1995;80:3613-6.