A RARE CASE OF FAMILIAL HETEROZYGOUS THYROID HORMONE RECEPTOR BETA (THRβ) MUTATION PRESENTING WITH DILATED CARDIOMYOPATHY

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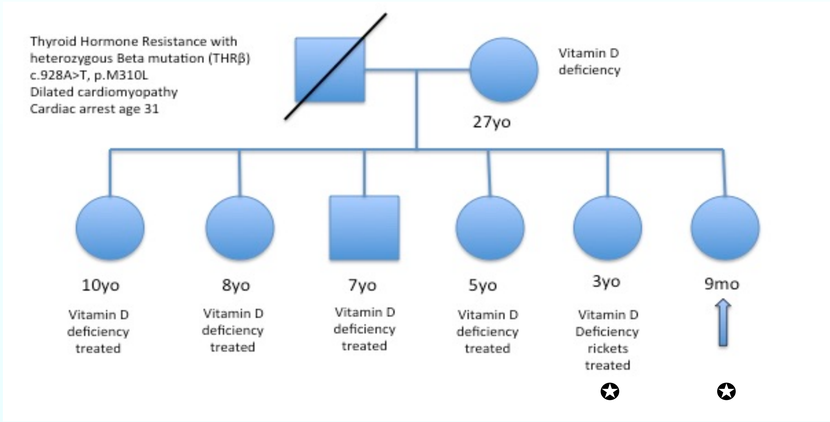
Background

Resistance to thyroid hormone beta (THRβ) is a clinical spectrum which varies in presentation even between individuals with the same mutation. Life-threatening cardiac dysfunction is recognized in homozygous THRβ but has not previously been reported in cases of inherited heterozygous THRβ defects. We report the first case of familial inherited heterozygous beta mutation presenting with severe dilated cardiomyopathy.

Presenting illness

- Previously well, 9-month-old girl presented with one-week history of lethargy, respiratory distress and resting tachycardia (HR 170-200bpm).
- Chest X-ray identified cardiomegaly. Echocardiogram confirmed heart failure with dilated cardiomyopathy
- Clinical investigations revealed markedly abnormal thyroid function tests with no goitre: **TSH 4.81(0.5- 3.8mU/L), fT4 50.6(10.8-22.9mU/L), fT3 17.2(3.6-6.8 pmol/L)** and vitamin D insufficiency 37nmol/L (25-50) with low corrected calcium 2.05nmol/L (2.2-2.7), high ALP 1845IU/L (80-330) and high PTH 646ng/L
- Parents were unrelated of Jamaican origin. The infant's father died aged 31years, from sudden cardiac arrest with underlying untreated hyperthyroidism and severe dilated cardiomyopathy of unknown etiology
- Genetic screening confirmed inheritance of the paternal THRβ mutation in our patient and her older sister aged 3yrs [TSH 2.26(0.5-3.8mU/L), fT45(10.8-22.9pmol/L), fT3 12.4(3.6-6.8pmol/L)], whose echocardiogram is normal to date
- Vitamin D insufficiency and hypocalcaemia were treated but did not improve poor cardiac indices

Family Pedigree



✪ indicates affected individuals carrying the paternally inherited THRβ mutation

Mechanism of Disease

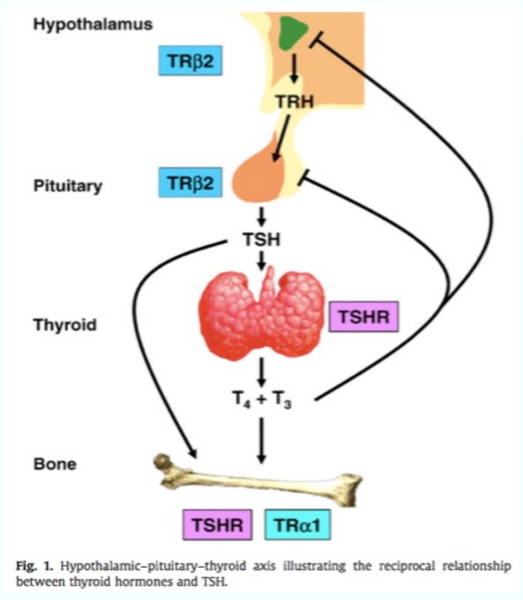


Fig. 1. Hypothalamic–pituitary–thyroid axis illustrating the reciprocal relationship between thyroid hormones and TSH.

Image from: J Duncan Bassett et al. **Bone** 43 (2008) 418-426

Thyroid hormone resistance (RTH):

- Is characterised by high T3 and T4 with inappropriately normal or high TSH (1-3)
- Is due to Thyroid hormone receptor mutation in either α-receptors (TRα) or β-receptors (TRβ)
- Most are clinically euthyroid (2)
- Incidence ~1 per 50000 live births (4)
- Variable tissue effects dependent on dominant receptor type (5)

RTHβ:

- 80% autosomal dominant, 20% sporadic (6)
- High T3/4 is required to overcome the 'resistance' in affected tissues (TRβ) including the hypothalamus and pituitary, whilst tissues with normal thyroid receptors (TRα) are excessively stimulated by the high fT3 and fT4
- normalisation of TSH and T3/4 can cause a hypothyroid state in β-receptor dominant tissues (deleterious to growth, development and neurocognition)

When to treat:

- Do not treat biochemical picture – only treat if clinically thyrotoxic
- Need to reduce the T3/4 without causing a chronically elevated TSH that can lead to pituitary hyperplasia (and risk of pituitary adenoma) (7)

Differential distribution of thyroid receptors in the body:

TRα	TRβ
Myocardium	Liver
CNS	Kidney
GIT	Hypothalamus, pituitary
Bone	Retina
Skeletal muscle	Cochlea

Typical clinical features in RTHα vs RTHβ:

RTHα	RTHβ*
Bradycardia	Goitre
Neurodevelopmental delay	Resting tachycardia
Anaemia	ADHD
Skeletal dysplasia	Short stature
Constipation	Osteoporosis

Reff: Brucker David, F. Ann Int Med. 1995. 123;572-583 * heterozygotes

Table of characteristics

Week of inpatient admission	1	4	8	13	16	18	23	32
Age (months)	9	11	12	13	14	14.5	16	17
Weight (kg)	8.2	8.19	8.3	8.5	9.07	8.9	9.5	9.8
Carbimazole dose (mg/kg/day)	0	0.6	0.9	0.9	0.8	0.85	0.8	0.75
TSH mU/L (reference range 0.5-3.8)	7.27	4.15	18	17.36	9.97	5.8	1.56	5.4
Free T4 pmol/L (reference range 10.8-22.9)	98.5	27.9	41	37.9	46.7	48.5	31.2	41
Free T3 pmol/L (reference range 3.6-6.8)	25.6	10.1	18.9	14	19.1			
TRIAC am dose (mcg) pm dose (mcg)	X	X	X	 175 0	 175 175	 350 175	 350 175	 350 175
Echocardiogram (cardiac function)		Left ventricular dysfunction EF 15%					Improved left ventricular function EF>15%	
Heart rate (bpm)	170-200	130-150	140	121-150	130-150		120-140	110-140

Progress and Outcome

- Over ensuing months, our patient had persistent cardiomyopathy with reduced cardiac function (ejection fraction (EF) 15-20%). She required respiratory and inotropic support and was listed for urgent cardiac transplant
- It was unclear if the tachycardia was secondary to cardiotoxic hyperthyroxinemia or directly secondary to cardiac failure
- Carbimazole was commenced (0.9mg/kg/day) to reduce hyperthyroid additive strain on the heart, despite which fT3/fT4 remained significantly elevated
- By week 6 of Carbimazole, tachycardia and clinical status improved, though with concurrent elevation in TSH 17.36 (0.5-3.8mU/L)
- To circumvent the elevation in TSH the patient was treated with TRIAC (3,5,3'-triiodothyroacetic acid), a centrally acting thyroid hormone analog with minimal peripheral bioactivity, effective in the management of childhood RTHβ (8,9)
- This was associated with improvement in cardiac function (EF ≧ 51%) over the ensuing months. The patient came off the cardiac transplant list after 5 months of inpatient care and was discharged home on oral feeds
- Genetic cardiomyopathy screens in affected cases were negative

Conclusions

- This is the first case-report of an infant with heterozygous RTHβ mutation requiring combined carbimazole and TRIAC treatment for concurrent life-threatening cardiac dysfunction
- The critical status of our patient at presentation, in-conjunction with the sudden death of her untreated father and potential risk of evolution of disease in her sister, demonstrates that heterozygous RTHβ is a clinical entity that requires ongoing active monitoring and management

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