Alder Hey Children's NHS
NHS Foundation Trust

Thyroid Hormone Receptor β (THRB) mutation: two new cases of heterozygous mutation with significant family history

James Blackburn[1], Dinesh Giri[1], Senthil Senniappan[1]

BACKGROUND

- Resistance to thyroid hormone (RTH) is a relatively uncommon disorder that is usually associated with mutations in thyroid hormone receptor (*THR)* beta, although rarely *THR* alpha mutations have been described.
- RTH beta (RTHB) is often inherited in an autosomal dominant pattern.

CASE 1

A two year old patient presented with a three week history of diarrhoea, weight loss and lethargy.

- On examination the patient was tachycardic, dehydrated and had evidence of faltering growth (weight 8.95kg, SDS -2.8).
- Thyroid function taken at the time of admission showed:
  - Raised TSH of 6.35mu/L [0.3-3.8mu/L].
  - Raised Free T4 of 29.1pmol/L [9-19pmol/L].
  - Raised triiodothyronine (FT3) of 8.1pmol/L [4.29-6.79pmol/L].
- Detailed evaluation revealed a family history of failure to thrive and childhood thyroid illness in the father and paternal aunt (who had previously undergone thyroid surgery).
- The patient underwent genetic analysis that revealed M334R mutation in *THR* confirming a diagnosis of RTH (beta).
- The patient was initially commenced on carbimazole and propranolol prior to genetic confirmation but treatment was subsequently discontinued. On further follow-up she was symptom free and gaining weight adequately.

CASE 2

A five year old patient was referred to the endocrine clinic with poor weight gain (weight 13.8kg, SDS -2.37).

- On examination, the patient was euthyroid and asymptomatic.
- Thyroid function tests revealed:
  - Raised TSH of 5.93mu/l [0.3-3.8mu/L]
  - Raised FT4 of 28.6pmol/l [9-19pmol/L]
  - Raised triiodothyronine (FT3) of 7.4pmol/L [4.29-6.79pmol/L].
- Further investigations revealed that the patient's mother had an elevated T4 of 21.3pmol/L [9-19pmol/L] and elevated T3 of 8.8pmol/L [4.29-6.79pmol/L] with the TSH in the normal range.
- Patient's 8 year old sister had a T4 of 24pmol/L[9-19pmol/L] and T3 of 12pmol/L [4.29-6.79pmol/L] with a normal TSH.
- Subsequent genetic analysis of the patient and family showed a single base change in Exon 10 [c.1357C>T Pro453Ser] of *THR* confirming RTH (beta).
- The patient did not require any treatment and remains under regular follow-up with good weight gain.

DISCUSSION

We describe two cases of RTHBeta to highlight the variations in both clinical presentation and family history.

These cases demonstrate the highly variable presentation of RTHB. The combination of elevated serum levels of free T4 and TSH should suggest a diagnosis of RTHB. The inheritance pattern highlights the importance of thorough family history. Timely genetic analysis helps confirm the diagnosis and avoid any unnecessary treatment.

Thyroid hormone resistance is associated with mutations of TSH alpha and TSH beta which have distinct clinical phenotypes[1]:

- **TSH beta mutations are associated with raised TSH/T4 and clinically patient are often euthyroid, with a goitre, although presentations are highly variable.**
- **TSH alpha are associated with normal TFTs but clinically present with features of hypothyroidism.**

Inspired by Children

INSTITUTIONS
1 Department of Paediatric Endocrinology, Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom.

REFERENCES
1. Tânia M. Ortiga-Carvalho, Aniket R. Sidhaye & Fredric E. Wondisford Thyroid hormone receptors and resistance to thyroid hormone disorders Nature Reviews Endocrinology volume 10, pages 582–591 (2014)

57ESPE 385--P2
Thyroid
James Blackburn
Poster presented at: 57th ESPE 2018 Meeting ATHENS GREECE 27-29 September 2018
PosterSessionOnline.com