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(3.6-6.8pmol/L) and vitamin D insufficiency 37nmol/L (25-50) with low corrected calcium 2.05nmol/L (2.2-2.7), high ALP 1845IU/L (25-100).
- Parents were unrelated of Malaysian origin. The infant’s father died aged 31 years, 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), FT4(10.8-22.9mU/L), FT3 12.4(3.6-6.8pmol/L),)
- Thyroid hormone resistance (RTH): 80% autosomal dominant, 20% sporadic
- Incidence ~1 per 50000 live births
- Thyroid hormone receptor mutation in either α-receptors (TRα) or β-receptors (TRβ)
- Most are clinically silent and are referred to as echenocardiogram is normal to date
- Vitamin D insufficiency and hypocalcaemia were treated but did not improve poor cardiac indices

Mechanism of Disease

Thyroid hormone resistance (RTH):
- Is characterised by high T3 and T4 with inappropriately elevated TSH, which can lead to pituitary hyperplasia and subsequent increased TSH levels.
- Most common thyroid receptor mutation is the α-receptor (TRα)
- Thyroid hormone receptors (TR) are constitutively expressed in cardiac tissue, whilst tissues with normal thyroid receptors (TR) are functionally silent.

Table of characteristics

<table>
<thead>
<tr>
<th>Week of inpatient</th>
<th>1</th>
<th>4</th>
<th>8</th>
<th>13</th>
<th>16</th>
<th>18</th>
<th>23</th>
<th>32</th>
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<tbody>
<tr>
<td>Age (months)</td>
<td>9</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>8.2</td>
<td>8.19</td>
<td>8.3</td>
<td>8.5</td>
<td>9.07</td>
<td>8.9</td>
<td>9.5</td>
<td>9.8</td>
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<tr>
<td>Carbimazole dose (mg/kg/day)</td>
<td>0</td>
<td>0.6</td>
<td>0.9</td>
<td>0.9</td>
<td>0.8</td>
<td>0.8</td>
<td>0.75</td>
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<tr>
<td>TSH (mU/L)</td>
<td>7.27</td>
<td>4.15</td>
<td>19</td>
<td>17.36</td>
<td>9.97</td>
<td>5.8</td>
<td>1.56</td>
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<tr>
<td>Free T4 pmol/L</td>
<td>98.5</td>
<td>27</td>
<td>41</td>
<td>37.9</td>
<td>46.7</td>
<td>48.5</td>
<td>31.2</td>
<td>41</td>
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<tr>
<td>Free T3 pmol/L</td>
<td>25.6</td>
<td>10.1</td>
<td>18.9</td>
<td>14</td>
<td>15.1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TBIAB am pmol/L</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>175</td>
<td>175</td>
<td>350</td>
<td>350</td>
<td>175</td>
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<tr>
<td>Echocardiogram</td>
<td>Left ventricular dysfunction</td>
<td>EF 15%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heart rate (bpm)</td>
<td>170-200</td>
<td>130-150</td>
<td>140</td>
<td>121-140</td>
<td>130-150</td>
<td>120-140</td>
<td>110-140</td>
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</table>

Progress and Outcome
- Over ensuing months, our patient had persistent cardiomyopathy with reduced cardiac function (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 cardiac hypertrophy or directly secondary to cardiac failure.
- Carbimazole was commenced (0.6mg/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).
- TBIAB am pmol/L 175 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 TBIAB 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 THRβ is a clinical entity that requires ongoing active monitoring and management.

References