PITUITARY RESISTANCE TO EXOGENOUS LEVO-THYROXINE IN HUMANS

N Lacámara 1, A Escribano2, J Guerrero3, AC Barreda3, I Navarro4, I González-Casado5, JC Moreno 1

1Thyroid Molecular Laboratory, Institute for Medical Genetics (NGEMM). La Paz University Hospital (HULP). Madrid, Spain.; 2Virgen de la Arrixaca University Hospital, Murcia. 3La Paz University Hospital, Madrid. 4Manises Hospital, Valencia.

INTRODUCTION

• The pituitary set-point for TSH synthesis and secretion is known to be an individual characteristic with a strong genetic influence.

• Type II iodothyronine deiodinase is a pituitary enzyme involved in local deiodination of T4 to T3 and therefore in the negative feed-back loop for TSH secretion.

• Defects in DIO2 gene have not been reported in humans; however, Dio2 knockout mouse has pituitary resistance to (exogenous) T4 with elevated TSH, T4 and TSH/T4 ratio, and normal T3, when challenging the thyroid gland with anti-thyroid drugs (shown below).

OBJECTIVE

To identify human thyroid hormone phenotypes consistent with type 2 deiodinase defects.

RESULTS

From an initial cohort of 14 patients, 6 patients (43 %) were identified fulfilling our two inclusion criteria (TABLE 1).

Remarkably, all patients presented with the characteristic hormonal phenotype only after the occurrence of a thyroid disease leading to absence of functional thyroid tissue.

• 4/6 (3 males) had severe thyroid hypoplasia on ultrasound and/or scintigraphy, detected at neonatal screening

• 1 girl had euplastic hypothyroidism detected at 8 months of age.

• 1 girl had destructive thyroiditis at 13 years old.

No mutations in DIO2 coding region including the SECIS element in 3'-UTR were identified (Figure 2).

Table 1. Hormonal and clinical findings.

<table>
<thead>
<tr>
<th></th>
<th>TSH mL/L</th>
<th>FT4 pmol/L</th>
<th>FT3 pmol/L</th>
<th>TSH/FT4</th>
<th>SNP (rs225014)</th>
<th>Thyroid disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.1</td>
<td>24.8</td>
<td>5.9</td>
<td>0.49</td>
<td>AA</td>
<td>hypoplasia</td>
</tr>
<tr>
<td>2</td>
<td>20.8</td>
<td>25.1</td>
<td>5.4</td>
<td>0.83</td>
<td>AG</td>
<td>hypoplasia</td>
</tr>
<tr>
<td>3</td>
<td>9.8</td>
<td>21.5</td>
<td>6</td>
<td>0.46</td>
<td>GG</td>
<td>hypoplasia</td>
</tr>
<tr>
<td>4</td>
<td>8.3</td>
<td>22.1</td>
<td>3.7</td>
<td>0.37</td>
<td>AG</td>
<td>euplastic</td>
</tr>
<tr>
<td>5</td>
<td>9.2</td>
<td>23.9</td>
<td>2.2</td>
<td>0.38</td>
<td>AG</td>
<td>hypoplasia</td>
</tr>
<tr>
<td>6</td>
<td>9.17</td>
<td>24.8</td>
<td>4.9</td>
<td>0.37</td>
<td>AA</td>
<td>thyroiditis</td>
</tr>
<tr>
<td></td>
<td>11.6</td>
<td>4.7</td>
<td>1.5</td>
<td>4.9 (5/6)</td>
<td>0.48</td>
<td>0.18 MAF 0.42</td>
</tr>
</tbody>
</table>

No mutations in DIO2 coding region including the SECIS element in 3'-UTR were identified. Furthermore, 3/6 were heterozygous and 1 homozygous for the frequent DIO2 polymorphism (rs225014, Thr92Ala). This SNP has been associated with a lower enzyme stability, but its presence in some but not all patients indicated is not the major driving factor causing this novel human phenotype.

6 Bay Bjorn et al J Clin Endocrinol Metab, July 2009, 94(7); 2478-2481

CONCLUSIONS

• In a case-finding study we identified a homogeneous group of patients characterized by persistently elevated/difficult to normalize TSH despite exogenous L-T4 treatment. This hormonal pattern fully overlaps that described in Dio2 KO mice.

• Defects in TSH feed-back regulation may not be infrequent, but they may remain silent/compensated until the loss of thyroid tissue co-occurs.

• The phenotype is recognizable by high TSH/FT4 ratio and represents an aberrant set-point for TSH secretion and feedback whose genetic determinants need to be investigated (SECIS element at non-coding DIO2, DIO2 deubiquitinas)