Nutrient X2-2 human mutation causes neonatal diabetes followed by severe infantile obesity associated with paradoxical upregulated ghrelin levels – do beta-cells secrete ghrelin?

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Background:

*NKX2-2 gene mutation was only once reported (3 cases worldwide) as a cause of neonatal diabetes(1).

*Beta-cells of Nkx2-2 (-/-) mice were recently shown to convert into cells producing ghrelin instead of insulin (2) (figure 1).

*Classically, ghrelin secretion is stimulated during fast and suppressed by nutrients (glucose) ingestion in all age groups.

*In obese children OGTT causes up to 40% suppression in serum ghrelin levels 60 minutes following glucose ingestion(3).

Objective:

To characterize the rare clinical phenotype of a patient homozygous for the c.356delG (p.P119fs64*64*) NKX2.2 mutation and examine the ghrelin response to OGTT in this patient

Clinical characteristics and laboratory tests:

A 3.5 years old girl with NKX2-2 mutation born very small for gestational age (1080g at 38 weeks) with a challenging neonatal diabetes and developmental delay developed severe obesity since 1y of age (figure 2) and at 3.5 y of age weighed 19.5Kg (BMI SDS +4.32).

During a standard OGTT (1.75 gr/kg) - Glucose, insulin and total ghrelin levels were measured at 0,30,60 minutes time points.

Ghrelin levels were compared to reported data(4) of healthy obese and non obese prepubertal children and to our data of age matched healthy children.

Results:

During the OGTT-while glucose increased from 19.4 mmol/l at baseline to 30.8 mmol /l after 60 minutes insulin levels dropped from 101.36 pmol/l to 31.11 pmol/l with constantly undetectable C-peptide levels.

Interestingly, total ghrelin levels paradoxically increased from 303.3 Pmol/l at baseline (similar to baseline values in obese children) to 404.7 pmol/l after glucose ingestion (table 1 A, B).

Table 1A: Ghrelin and insulin levels during OGTT. 1B: Ghrelin change during OGTT

<table>
<thead>
<tr>
<th>Time</th>
<th>Glucose (mmol/L)</th>
<th>Insulin (pmol/L)</th>
<th>C-peptide (pmol/L)</th>
<th>Total Ghrelin (pmol/L)</th>
<th>Father Ghrelin (pmol/L)</th>
<th>Mother Ghrelin (pmol/L)</th>
<th>Control-Age matched female (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0’</td>
<td>19.4</td>
<td>101.36</td>
<td>&lt;43</td>
<td>303.3</td>
<td>162.9</td>
<td>36</td>
<td>295.98</td>
</tr>
<tr>
<td>30’</td>
<td>24.9</td>
<td>57.03</td>
<td>&lt;43</td>
<td>370.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60’</td>
<td>30.8</td>
<td>31.11</td>
<td>&lt;43</td>
<td>404.7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1B: Ghrelin

<table>
<thead>
<tr>
<th>Patient</th>
<th>Normal weight prepubertal girls (Bacha F at el*) (mean ± SEM)</th>
<th>Overweight prepubertal girls (Bacha F at el*) (mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline ghrelin (pmol/l)</td>
<td>303.3</td>
<td>589.9 ± 55.6</td>
</tr>
<tr>
<td>Absolute ghrelin change 60 min after OGTT (pmol/l)</td>
<td>+101.4</td>
<td>-139.1 ± 12.2</td>
</tr>
<tr>
<td>%Ghrelin change 60 min after OGTT</td>
<td>+33.4</td>
<td>-25.2 ± 1.8</td>
</tr>
</tbody>
</table>

Conclusion:

NKX2-2 mutation phenotype includes severe early childhood obesity in addition to neonatal diabetes. During OGTT, our obese diabetic patient showed a paradoxical increase in ghrelin but no increment in insulin levels. This results suggest that human beta cells with NKX2-2 mutation- may mimic Nkx2-2 (-/-) mice’s beta cells that pathologically differentiate into ghrelin instead of insulin producing cells; Thus, contributing to the clinical severe hyperphagia and obesity.

References: