Neonatal Hyperparathyroidism with Homozygous Missense Mutation in the CASR Gene

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Introduction

Neonatal severe hyperparathyroidism is a rare disorder, caused by inactivation mutation of the CASR gene. These receptors expressed in parathyroid glands, renal cells, bone and thyroid glands. These receptors regulate and maintain calcium hemostasis.

Heterozygous loss of function in CASR give rise to familial (benign) hypocalciuric hypercalcemia in which the lifelong hypercalcemia is generally asymptomatic.

Familial hypercalcuric hypercalcemia (FHH) patients demonstrates inappropriately normal serum concentration of PTH despite hypercalcemia. Homozygous mutation in CaSR gene manifested as neonatal severe hyperparathyroidism in the first few weeks of life which characterized by severe hypercalcemia and bony demineralization in infancy, those infants exhibit polyuria, dehydration and hypotonia associated with a history of failure to thrive, irritability, constipation and delayed neuropsychological development. Parathyroidectomy is the mainstay of treatment (4).

Methods

Consent was obtained from one Libyan family with neonatal severe hyperparathyroidism with four affected siblings to perform familial genetic analysis, where clinical and biochemical data for parents and their siblings were collected, skeletal survey of affected siblings was interpreted and outcomes after parathyroidectomy was evaluated.

RESULTS

<table>
<thead>
<tr>
<th>Individual</th>
<th>Calcium</th>
<th>PTH</th>
<th>Gene</th>
<th>Clinical</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>12mg/dl</td>
<td>70 pmol/l</td>
<td>Heterozygote mutation (p.Arg680His;CGC&gt;CAC) in exon 7 des CaSR Gene</td>
<td>Carrier</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>M</td>
<td>9mg/dl</td>
<td>60pmol/l</td>
<td>Heterozygous mutation P(Arg 689 His, CGC&gt;CAC in exon 7 desCASR</td>
<td>Carrier</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>1♂</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>Died at 3 wks.</td>
<td>-----</td>
</tr>
<tr>
<td>2♀ PROBAND</td>
<td>18mg/d</td>
<td>1118 pmol/l</td>
<td>Homozygous mutation P(Arg 689 His, CGC&gt;CAC in exon 7 desCASR</td>
<td>Died at 3 yr</td>
<td>Pamidrunate &amp; Parathyroidectomy</td>
</tr>
<tr>
<td>3♂</td>
<td>20mg/dl</td>
<td>1501 pmol/l</td>
<td>Homozygous mutation P(Arg 689 His, CGC&gt;CAC in exon 7 desCASR</td>
<td>Alive</td>
<td>Pamidrunate &amp; Cincalcet Parathyroidectomy (at 1 yr)</td>
</tr>
<tr>
<td>4♂</td>
<td>28mg/dl</td>
<td>1221 pmol/l</td>
<td>Homozygous mutation P(Arg 689 His, CGC&gt;CAC in exon 7 desCASR</td>
<td>Alive</td>
<td>Pamidrunate &amp; Cincalcet Parathyroidectomy (8wks)</td>
</tr>
</tbody>
</table>

CONCLUSIONS

• Neonatal severe hyperparathyroidism (NSHPT) is a rare disease due to CASR gene mutation in homozygous state that requires a high index of suspicion and a very good history to make an early diagnosis and avoid complication. Genetic counseling for a family who have an affected sibling with CASR gene mutation.

• Medical treatment is helpful in stabilizing the patient and bridging him to definitive surgical treatment. Cincalcet may work in some mutations not all.

• Parathyroidectomy with auto-transplant on half a gland in the forearm remains the most effective intervention that associated with long term calcium level stabilization.

REFERENCES

1- OMIM: calcium sensing receptor ([http://omim.org/entry/601199]).