A rare cause of hypophosphatemia: Raine Syndrome

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- A 9-month-old male was referred for hypophosphatemia
- Birth weight of 3800 g from non-consanguineous parents
- Prenatal USG demonstrated nasal bone agenesis
- Family history was unremarkable
- Tracheostomy at 48 days of age
- Percutaneous endoscopic gastrostomy at 5.5 months of age
- Ventriculoperitoneal shunt operation at 9 months of age
- At presentation, his height at -1.1 SDS, weight at -2.14 SDS, and head circumference at -0.62 SDS.

Physical examination:
- A large anterior fontanel (5x6 cm),
- Frontal bossing,
- Exophthalmos, corneal opacification
- Hypoplastic nose,
- High arched palate,
- Low set ear,
- Triangular mouth

The ophthalmological examination: Optic atrophy.

Skeletal X-rays (Figure):
- Diffuse osteosclerosis at birth
- Gradually resolved by the age of 5 months.
- Medullary space of long bone could be distinguishable with bone-in-bone appearance.
- At 9 month of age hand X-ray revealed cupping of ulna with loose radial bone margin with minimal fraying and osteopenia.

Cranial CT scan showed bilateral periventricular calcification with cerebral atrophy (Figure).

After an initial assessment, oral phosphate and calcitriol therapy were initiated.
- No significant improvement was observed in laboratory findings during the six-month follow-up despite of good compliance, gradual dose increase and close follow-up (Table)
- But, ALP decreased and rickets signs improved on radiographs

The clinical, laboratory and radiological examinations were consistent with RS.

Molecular analyses
- Compound heterozygous mutation in FAM20C gene
  (a known pathogenic mutation, c.1645C>T, p.Arg549Trp; and a novel mutation, c.863+5G>C)

Table. Laboratory follow-up of the patient

<table>
<thead>
<tr>
<th>First Evaluation (9 month-old)</th>
<th>15. Day</th>
<th>1 month</th>
<th>1.5 month</th>
<th>2 month</th>
<th>3 month</th>
<th>4 month</th>
<th>5 month</th>
<th>6 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>P (mg/dL) (4.5-6.5)</td>
<td>2</td>
<td>2.3</td>
<td>1.7</td>
<td>2.4</td>
<td>2.6</td>
<td>2.8</td>
<td>3.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Ca (mg/dL) (9-11)</td>
<td>9.6</td>
<td>9.9</td>
<td>8.6</td>
<td>9.9</td>
<td>9.4</td>
<td>10.1</td>
<td>9.4</td>
<td>9.2</td>
</tr>
<tr>
<td>ALP (IU/L) [116-450]</td>
<td>950</td>
<td>745</td>
<td>280</td>
<td>380</td>
<td>467</td>
<td>671</td>
<td>575</td>
<td>329</td>
</tr>
<tr>
<td>PTH (ng/L) (15-65)</td>
<td>84.47</td>
<td>142</td>
<td>119.1</td>
<td>86.04</td>
<td>86.97</td>
<td>58.15</td>
<td>95.48</td>
<td>-</td>
</tr>
<tr>
<td>25-OHD (µg/L) [30-100]</td>
<td>28.05</td>
<td>23.63</td>
<td>20.69</td>
<td>-</td>
<td>38.28</td>
<td>33.29</td>
<td>33.03</td>
<td>22.53</td>
</tr>
<tr>
<td>Spot urine Ca/Cr</td>
<td>0.22</td>
<td>0.06</td>
<td>0.007</td>
<td>0.06</td>
<td>-</td>
<td>0.3</td>
<td>0.06</td>
<td>0.007</td>
</tr>
<tr>
<td>TRP (µg/L) [145-100]</td>
<td>94</td>
<td>87.5</td>
<td>94.7</td>
<td>86.7</td>
<td>-</td>
<td>91.8</td>
<td>89.2</td>
<td>88.3</td>
</tr>
<tr>
<td>TnF/GfR [4.8-8]</td>
<td>2.31</td>
<td>2.02</td>
<td>2</td>
<td>2.04</td>
<td>-</td>
<td>2.9</td>
<td>3.09</td>
<td>2.26</td>
</tr>
<tr>
<td>Calciotriol[µg]/Phosphorus (mg/kg)</td>
<td>-</td>
<td>0.25/30</td>
<td>0.25/30</td>
<td>0.5/35</td>
<td>0.75/35</td>
<td>0.75/35</td>
<td>0.75/40</td>
<td>1.0/40</td>
</tr>
</tbody>
</table>

Learning Points:
- Although rare, RS should be considered in differential diagnosis of hypophosphatemia in patients with typical craniofacial abnormalities.
- Inactivating mutations of FAM20C gene may cause non-lethal RS and hypophosphatemia without typical craniofacial abnormalities.