Clinical phenotype and molecular studies in patients with hypophosphatemic rickets

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DISCLOSURE STATEMENT: The authors have nothing to disclose.

BACKGROUND

Hypophosphatemic rickets (HR) is a group of rare disorders caused by excessive renal phosphate wasting. The dominant form of HR is X-linked HR (XLHR) caused by mutation in the phosphate-regulating endopeptidase gene PHEX. There is also autosomal dominant form of HR caused by mutation in FGF23 gene or rare autosomal recessive form caused by DMP1 mutation. The phenotype can vary from very delicate to severe bone disease.

The aim of the study was to investigate the clinical and molecular background of HR in 5 patients.

Patients and Methods: 5 patients aged 2-8 years (2 girls and 3 boys) diagnosed with HR due to clinical and biochemical picture. In each of these patients three exons of the FGF23 gene were directly sequenced after polymerase chain reaction amplification of the entire coding region. Additionally, in one patient PHEX gene was also analyzed by direct sequencing (in the four remaining the analyses are ongoing).

RESULTS

1. Bowing of legs was the dominant symptom in all patients.
2. All patients presented hypophosphatemia, increased alkaline phosphatase concentration with normal levels of serum calcium and 25OHD3. In all children with the time the increased loss of phosphorus with urine and decrease of tubular reabsorption of phosphate (TRP) was observed.
3. In one patient analysis of the FGF23 gene revealed the presence of one polymorphism c.C716>T, p.T239M. The remaining four patients were FGF23 mutation-negative. In one patient the already known PHEX gene deletion was found encompassing exons 17-22.

CONCLUSIONS

1. The early diagnosis of HR is very important for proper treatment and to prevent bone deformities.
2. The molecular analysis of FGF23 and PHEX gene is very important for the confirmation of clinical diagnosis of hypophosphatemic rickets and highlights the role of further genetic counselling in families with HR patients.

Table 1. Chosen parametres in the studied group.

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Long bone deformities</th>
<th>Dental/oral problems</th>
<th>Other clinical problems</th>
<th>S-Ca (mg/dL)</th>
<th>S-P (mg/dL)</th>
<th>25(OH)D (ng/ml)</th>
<th>ALP (U/L)</th>
<th>TRP (%)</th>
<th>TRH (%)</th>
<th>PHEX</th>
<th>FGF23</th>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>3/12</td>
<td>bowing of lower limbs, short stature</td>
<td>no</td>
<td>no</td>
<td>9.76 3.13</td>
<td>8.22 11.65</td>
<td>3.96 6.4</td>
<td>21.8</td>
<td>0.4</td>
<td>1.3</td>
<td>6.4</td>
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<tr>
<td>2</td>
<td>F</td>
<td>7</td>
<td>bowing of lower limbs, short stature, lumbar hyperlordosis</td>
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<td>no</td>
<td>8.0 11.25</td>
<td>17.2 11.65</td>
<td>3.96 6.4</td>
<td>21.8</td>
<td>0.4</td>
<td>1.3</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>3</td>
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<td>3/12</td>
<td>bowing of lower limbs, short stature, frontal bowing, widening of distal parts of forearms</td>
<td>yes</td>
<td>no</td>
<td>9.76 3.13</td>
<td>8.22 11.65</td>
<td>3.96 6.4</td>
<td>21.8</td>
<td>0.4</td>
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<td>4</td>
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<td>bowing of lower limbs, short stature</td>
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<td>immunodeficiency (hypogammaglobulinemia)</td>
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<td>27.7 21.8</td>
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<td>1.3</td>
<td>5</td>
<td>91</td>
<td>72</td>
<td>not tested</td>
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<td>5</td>
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<td>bowing of lower limbs, short stature, widening of distal parts of forearms</td>
<td>yes</td>
<td>immunodeficiency suspected</td>
<td>10.6 8.0 12.3</td>
<td>27.7 21.8</td>
<td>2.4</td>
<td>1.3</td>
<td>5</td>
<td>91</td>
<td>72</td>
<td>not tested</td>
</tr>
</tbody>
</table>

*Fig 1. The characteristic bowing of legs of one of the patients.*