Growth hormone treatment of a patient with X-linked hypophosphatemic rickets caused by PHEX mutation: effects on linear growth

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OBJECTIVES

Hypophosphatemic rickets (HR) stands for a heterogeneous group of rare disorders in which excessive renal phosphate wasting is observed. The main characteristics of X-linked HR (XLHR) (OMIM #307800) caused by mutation in PHEX (phosphate-regulating endopeptidase) gene (OMIM *300550) include bone deformities, disproportionately short stature, dental anomalies and hypophosphatemia with coexisting low renal phosphate reabsorption. The patient’s growth may be improved by early treatment with vitamin D, phosphate, as well as recombinant human growth hormone (rhGH) which acts on growth cartilage directly, and increases renal phosphate reabsorption and serum phosphate levels. Recently, the new treatment option is burosumab, a monoclonal antibody which attaches to the FGF23 protein.

AIM OF STUDY

The aim of the study was to investigate the clinical phenotype and molecular background of HR in a patient in which XLHR was suspected as well as to analyze the effects of rhGH treatment on growth.

CASE PRESENTATION

A girl aged 13 years and 2 months was diagnosed with HR at the age of 7 years and then treated with alfalcacidol (40 ng/kg/d) and phosphorus (33 mg/kg/d). Because of severe bowing of lower limbs the girl underwent several orthopedic operations. Mother of the girl is also affected. Due to the diagnosis of growth-hormone deficiency (max GH after stimulation was 7.4 ng/ml; N>10) rhGH therapy was initiated at the age of 10.5 years (current dose of rhGH is 0.029 mg/kg/d).

<table>
<thead>
<tr>
<th>Age (years/month)</th>
<th>Dental/pediatric problems</th>
<th>Ear problems</th>
<th>Other clinical features</th>
<th>Max GH levels after stimulation</th>
<th>Current /at last visit treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 4/12</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>7.4</td>
<td>mG1 0.029 mg/kg/d</td>
</tr>
</tbody>
</table>

Biochemical characteristics of the patient. S – serum, U – urine, ALP – alkaline phosphatase, PTHR – parathyroid hormone, TRP – Tubular reabsorption of phosphate. The presented laboratory results are at the time of the HR diagnosis or during the first stay at the Department of Pediatric Endocrinology and Rheumatology, Poznan University of Medical Sciences. Additionally, current concentration of ALP and TRP during pharmacologic therapy are given.

CONCLUSIONS

- Molecular analysis was performed using total genomic DNA isolated from whole blood. PHEX and FGF23 genes were analyzed using standard PCR and direct sequencing method.
- The dominant clinical signs in a patient were bowing of legs, short stature, and lumbar hyperlordosis. HS5D at the time of diagnosis was -2.6. Current HS5D is -2.2 and the height gain during rhGH therapy was 0.4 SD.
- Molecular analysis of PHEX gene revealed the presence of a known heterozygous mutation c.1645+1G>A in 5’ splicing site of intron 15 (HGMD ID: C5992468) as well as a known polymorphism c.1769-10C>T (rs3752433) in intron 17.
- Both DNA changes, which may cause aberrant splicing of the PHEX transcript, were also found in the girl’s affected mother.

METHODS AND RESULTS

- Early clinical and molecular diagnosis of HR, and early implementation of vitamin D and phosphorus is crucial to prevent severe bone deformities and to improve final height.
- rhGH therapy in patients with XHLHR may be very effective in those with coexisting growth hormone deficiency.
- Genetic counseling in families with HR patients should be proposed.

References


There is no conflict of interest.

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Bone, growth plate and mineral metabolism

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