A Case Report of XLHR Caused by a PHEX Intron Variant Responsive to Burosumab: A Four-Year Follow-Up

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1. Abstract
1.1. Introduction: X-linked hypophosphatemic rickets (XLHR) is a dominant inherited disease characterized by renal phosphate wasting and impairment of vitamin D activation. We present a clinical case of a patient with XLHR as a consequence of an intron pathogenic variant in the PHEX gene.

1.2. Case Presentation: A 3.4-year-old patient presented with bilateral varus knee, gait disorders and severe short stature (84 cm, -2 SD). On the basis of clinical picture, biochemical findings (hypophosphatemia, hypovitaminosis D, high serum level of alkaline phosphatase, normal calcemia and PTH) and X-ray findings, diagnosis of hypophosphatemic rickets was suspected. Genetic analysis was conducted and it was detected a PHEX gene heterozygous variant c.1303-1G>A in intron 11, with consequent increased expression of FGF23, causing renal phosphate loss and reduced synthesis of the active form of vitamin D. The analysis of PHEX gene made possible the diagnosis of XLHR. Conventional treatment with phosphate and calcitriol was carried out up to May 2019, when it was started Burosumab twice a month. Currently, data from a 4-year follow-up from the beginning of Burosumab therapy show a normalization of vitamin D and alkaline phosphatase serum levels and an improvement of Rickets Severity Score (RSS) and linear growth, with complete resolution of varus knee and gait disorders, despite blood phosphate values constantly at the lower limits for age.

1.3. Conclusion: Identification of genetic defects is fundamental for genotypic and phenotypic characterization of hereditary hypophosphatemic rickets in order to identify the correct therapy.

2. Introduction
Rickets is a bone metabolism pathology typical of the pediatric age and characterized by a mineralization defect of the bone matrix [1]. The most frequent forms are nutritional rickets caused by vitamin D and calcium deficiency [2]. There are also rarer forms, genetically transmitted, represented by hypophosphatemic rickets [3]. Among these, the most frequent form is X-linked hypophosphatemic rickets (XLHR), with an incidence of 1:20,000 in males and females [4]. XLHR is caused by inactivating mutations in the “X-linked Phosphate Regulating Endopeptidase” (PHEX) gene, which controls the expression of “Fibroblast growth factor 23” (FGF23), the major regulator of phosphorus homeostasis [5-7]. Exposure to a state of chronic hypophosphatemia causes the onset of signs and symptoms resulting by an inadequate mineralization, such as skeletal deformities especially in the long bones of the lower limbs, growth retardation, gait disorders, dental abscesses and chronic pain with a consequent reduction in the quality of life of young patients. For this reason, it is important to perform an early diagnosis and correctly identify the etiopathogenesis of the pathology in order to begin the appropriate therapy [8]. Hereafter we report the clinical case of a little girl who came to our observation in the Pediatric Clinic of Chieti in March 2018, whose diagnosis of XLHR has also been confirmed genetically.

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Citation:
3. Case Report

A 3.4-year-old child comes to our observation in March 2018 for short stature, gait disorders and progressive onset of bilateral varus knee and lower extremity pain since the age of 1 year. She was born from term pregnancy characterized by gestational diabetes treated with insulin. At birth her body weight was 3700 g (94th percentile, SD 1.4), body length 48 cm (27th percentile, SD -0.6), head circumference 34 cm (55th percentile, SD 0.12). Through the first year and afterwards the patient regularly assumed the daily dose of vitamin D. Her motor development was characterized by failure to crawl and delayed acquisition of independent walking. Since maternal family history was positive for bilateral varus knee and short stature, the child’s problems were attributed to harmless inherited disorder, so that she was under orthopedic follow-up, performing regular physiotherapy sessions and using orthopedic braces. Physical examination at admission documented a harmonic short stature, bilateral varus knee with anserine gait on widened support base. The anthropometric parameters were below the third percentile, with a body height of 84 cm, -2 SD. Biochemical data have shown the presence of hypophosphatemia (2.78 mg/dl), hypovitaminosis D (16.2 ng/ml), increased alkaline phosphatase (364 U/L) and normal values of calcium (9.62 mg/dl) and PTH (53.7 pg/ml). IGF-1 values were within the normal range for age and sex, amounting to 69.5 ng/ml (30-40°percentile). 24-hour urine collection was performed for evaluation of tubular reabsorption of phosphorus (TRP), which resulted reduced. It was performed lower limb X-ray confirming the presence of varus knee without evident focal lesions, characterized by procure deformed of the femurs and tibias (Figure 1). On the basis of clinical, laboratory and instrumental picture, hypophosphatemic rickets was suspected and genetic investigation was performed. Molecular analysis of PHEX gene (Xp22.11) finally detected a “loss of function” heterozygous variant c.1303-1G>A in intron 11, with consequent increased expression of FGF23, causing renal phosphate loss and reduced synthesis of the active form of vitamin D. The analysis of PHEX gene made possible the diagnosis of XLHR. Therapy was started with calcitriol and phosphate until May 2019, then Burosumab was performed twice a month at the dosage of 0.8 mg/kg. At the follow-up, values of vitamin D and alkaline phosphatase were normalized (30 ng/ml and 260 U/L respectively) with a satisfactory improvement of Rickets Severity Score (RSS) (from a value of 5 to 3.5 and finally to 2) and linear growth velocity (10°-25°percentile) and a complete resolution of varus knee (Figure 2), although the phosphate values and TRP always remained in the lower limits of the range after the start of the therapy (respectively 3.0 mg/dl and 85.3%). Over the last 4 years of follow-up, no adverse effects of treatment were recorded. At the latest control a dose adjustment of Burosumab was made according to weight, increasing to 1.2/kg twice a month, currently in progress (Table 1 and 2).

Figure 1: X-ray of lower limbs in our patient with XLHR at diagnosis

Figure 2: Clinic follow-up
Table 1: Biochemical data at diagnosis and at 4-year follow-up

<table>
<thead>
<tr>
<th></th>
<th>Diagnosis</th>
<th>4-year follow-up</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcemia</td>
<td>9,62</td>
<td>9,3</td>
<td>8,8-10,8 mg/dl</td>
</tr>
<tr>
<td>Phosphatemia</td>
<td>2,78</td>
<td>3,0</td>
<td>3,6-5,8 mg/dl</td>
</tr>
<tr>
<td>PTH</td>
<td>53,7</td>
<td>23,9</td>
<td>8,70-79,60 pg/ml</td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D</td>
<td>16,2</td>
<td>35,2</td>
<td>30-40 ng/ml</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>364</td>
<td>326</td>
<td>38-126 U/L</td>
</tr>
<tr>
<td>Phosphaturia</td>
<td>2,3</td>
<td>0,3</td>
<td>0,4-1,3 g/24h</td>
</tr>
</tbody>
</table>

Table 2: Normal blood phosphate values by age

<table>
<thead>
<tr>
<th>Age</th>
<th>Blood phosphate mmol/L</th>
<th>Blood phosphate mg/dl</th>
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</thead>
<tbody>
<tr>
<td>0-12 months</td>
<td>1,55-2,39</td>
<td>4,8-7,4</td>
</tr>
<tr>
<td>1-5 years</td>
<td>1,45-2,10</td>
<td>4,5-6,5</td>
</tr>
<tr>
<td>6-12 Years</td>
<td>1,16-1,87</td>
<td>3,6-5,8</td>
</tr>
<tr>
<td>13-20 years</td>
<td>0,74-1,45</td>
<td>2,8-4,5</td>
</tr>
</tbody>
</table>

4. Discussion

XLHR is the commonest form of hereditary hypophosphatemic rickets, inherited in dominant manner with full penetrance, due to PHEX gene inactivating mutations [9]. The gene (Xp22.11 region) encodes for a transmembrane endopeptidase expressed in osteoblasts and osteocytes, which is hypothesized to play a role in regulation of FGF23 [10,11]. FGF23 is a phosphatonin involved in phosphate homeostasis, whose gene is located on chromosome 12p13.3, which causes an increased renal phosphate wasting and a reduced synthesis of the active form of vitamin D [12]. It exerts its effects by blockage of the sodium-phosphorus cotransporter IIa and IIc of proximal tubule with consequent phosphaturic effect and by inhibition of 1-alpha-hydroxylase and up-regulation of 24-hydroxylase activity with reduced calcitriol synthesis and consequent reduction of intestinal phosphorus absorption through the sodium-phosphorus cotransporter IIb [13,14]. Therefore, mutations inactivating PHEX gene lead to an increasing expression of FGF23, resulting in hypophosphatemia and hypovitaminosis D with consequent clinical manifestations of rickets (short stature and skeletal disorders). The PHEX gene consists in 22 exons and 21 introns and currently about 870 pathogenic variants have been documented, which correlate with variable phenotypic pictures depending on the residual enzymatic activity of the PHEX protein [15]. Conventional treatment for XLHR is characterized by combined administration of phosphate and calcitriol in divided doses distributed throughout the day, increasing bone mineralization and improving signs of rickets and linear growth [16-18]. Limitations of conventional therapy includes poor patient compliance since treatment involves multiple daily administrations, increased risk of complications such as nephrocalcinosis due to renal phosphate loss, adverse gastrointestinal effects and hyperparathyroidism related to phosphate administration [19]. In 2018 EMA and FDA approved a new drug, the Burosumab, a human anti-FGF23 monoclonal antibody, for the treatment of XLHR in pediatric and adult age [20]. Burosumab inactivates FGF23, resulting in reduced renal phosphate loss and increased levels of phosphatemia and active vitamin D. It can be used in pediatric patients at a dosage determined by weight and phosphatemia levels ranging from 0.8 to 1.2 mg/kg every two weeks by subcutaneous administration [21]. Several clinical trials have been conducted on the use of Burosumab in the pediatric age which have documented improved clinical outcomes and better RSS, laboratory and instrumental parameters than those observed with conventional therapy [22,23]. Short-term side effects of burosumab included local injection site reactions, fever, and hypersensitivity reactions; however, there are still not enough data to make an assessment of any long-term adverse effects [24]. In our case genetic analysis of PHEX gene found the heterozygous splicing variant of c.1303-1 G>A in intron 11. This is the first clinical description available in literature for this pathogenic variant, associated with the development of lower limb deformity and pain, short stature and gait disorders. During a 4-year of follow-up we obtained a complete resolution of varus knee, gait disorders, lower limb pain and an improvement of RSS and linear growth velocity. Furthermore, we observed good laboratory results regarding values of vitamin D and alkaline phosphatase but not of phosphatemia and TRP, which remained constantly at the lower limits of the normal range. Therefore, we may suppose that discrepancy between clinical results and laboratory data may characterize this genetic variant. The knowledge of mutations, causing XLHR, is important for the genotypic and phenotypic characterization of pathology in order to identify the correct therapeutic approach and the expected results. From the results obtained during a follow-up of about four years, we can conclude that the mutation found in our patient is responsive to therapy with monoclonal antibodies, although the values of phosphorus remain constantly at the lower limits of the normal range.
References


