X-linked Hypophosphatemic Rickets

Mehmedali Azemi¹, Majlinda Berisha¹, Selim Kolgeci², Vlora Ismaili-Jaha¹, Rina Hoxha³, Teuta Hoxha-Kamberi¹
Pediatric Clinic, University Clinical Center of Kosovo, Prishtina, Kosovo¹
Obstetrics and Gynecology Clinic, Department of Cytogenetics, University Clinical Center of Kosova, Prishtina, Kosovo²
National Institute of Public Health, Department of Statistics, Prishtina, Kosovo³

Aim: The aim of this work was the presentation of one case with X-linked hypophosphatemic rickets. Methods: Diagnosis has been established based on the anamnesis, physical examination, anthropometric measurements, laboratory tests and radiological examination. Results: A male patient (age 3 years) has been hospitalized due to the growth delay, bone deformity, bone pain and walking difficulties. The laboratory tests have revealed that the calcium value was in the reference range, that of phosphates was low (0.45 mmol/L), the alkaline phosphatase value was quite high (1864 IU/L), the value of parathyroid hormone and of 25- hydroxyvitamin D₃ were in the reference ranges, whereas the value of 1,25- dihydroxyvitamin D₃ was low. Radiographic changes were evident and typical in the distal metaphysis of radius and ulna as well as in the bones of the lower limbs. After treatment with synthetic analog of vitamin D₃ – calcitriol and phosphates, the above mentioned laboratory test values and the radiographic changes in bones withdrew. Conclusion: X-linked hypophosphatemic rickets is a rare disease inherited through X chromosome, and its treatment includes a constant use of calcitriol and phosphates with the aim of avoidance of clinical and laboratory manifestations. Key words: X-linked hypophosphatemic, bone deformities, hypophosphatemia, short stature.

Corresponding author: Assoc prof Mehmedali Azemi MD PhD, Pediatric Clinic, University Clinical Center of Kosovo, Mother Teresa street nn, Prishtinë. Tel: +377(44)146-463; E-mail: mehmedaliazemi@hotmail.com

1. INTRODUCTION
Among the genetic disorders causing rickets due to hypophosphatemia, X-linked phosphatemic rickets is the most common, with an approximate prevalence of 1 in 20,000 live births (1, 2). The defective gene is called PHEX because is a Phosphate regulating gene with Homology to Endopeptidases on the X chromosome. The product of this gene appears to have either a direct or an indirect role in inactivating a phosphatonin (as humoral mediator) or phosphatoninins. Fibroblast growth factor-23 (FGF-23) may be the target. In the absence of PHEX, there is decreased degradation of phosphatonin. Because the actions of phosphatonin include inhibition of phosphate reabsorption in the proximal renal tubule, there is increased phosphate excretion. Phosphatonin also inhibits renal 1α-hydroxylase, leading to decreased production of 1,25- dihydroxyvitamin D₃ (1, 2, 3, 5, 8, 9).

2. AIM
The aim of the work was a presentation of one case with X-linked hypophosphatemic rickets treated in the Pediatric Clinic.

3. METHODS
For the disease diagnose the following were used: anamnesis, physical examination, concentration in serum of calcium, phosphorus, and alkaline phosphatase (using a photometric method I Lab-650), parathyroid hormone (using radioimmunometric assay), 25- hydroxyvitamin D₃ and 1,25-dihydroxyvitamin D₃ (using HPLC-High Performance Liquid Chromatography, which tests were done in Tirana Lab - Albania) and radiographic examination of the bones, pedigree and karyotype which was done from the peripheral blood lymphocytes.

4. CASE PRESENTATION
The male patient (E.K) (age 3 years), with the body weight 15 kg (50-75 percentile), height 82 cm (<5 percentile) was hospitalized in the Pediatric Clinic (in 2011) due to the growth delay, bone deformity, bone pain and walking difficulties. He was a fourth child born without any complications, the parents and other children were healthy (Figure 1). Rickets prevention with vitamin D daily dosage 800 IU was done on a regular basis during the first year, whereas...
X-linked hypophosphatemic rickets during the second and third year of life patient was not given vitamin D. As an outpatient and in a regional hospital, child was treated with calciferol twice with attacking doses (600,000 IU) intramuscularly, but without positive results.

Laboratory findings: red blood cell count was 4.3x10^12/L, haemoglobin values 121 g/L, hematocrit level 38%, white blood cell count 8.1 x10^9/L, serum iron 12 μmol/L, peripheral blood smear without changes and karyotype was normal 46 X,Y (Figure 2).

The calcium value was normal i.e. 2.31 mmol/L (reference value 2.20-2.70 mmol/L), those of phosphates were low i.e. 0.45 mmol/L (reference value 1.4-2.1 mmol/L), the alkaline phosphatase value was quite high in the beginning (1864 IU/L), then 1740 IU/L, 884 IU/L and in the end of the treatment it decreased to 150 IU/L, 25- hydroxyvitamin D₃ was in normal value (23.4 µg/L-reference range 7.3-53.3 µg/L) whereas 1,25-dihydroxyvitamin D₃ was in low values (45 µmol/L-reference range 60-108 µmol/L), parathyroid hormone was in normal value (2.1 pmol/L-reference range 0.95-6.8 pmol/L) as shown in the Figure 3. After the treatment with calcitrol and phosphates, the values of alkaline phosphatase, phosphates and 1,25- dihydroxyvitamin D₃ got back to normal values (75 µmol/L).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Before treatment</th>
<th>During treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>2.31 mmol/L</td>
<td>2.31 mmol/L</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>0.45 mmol/L</td>
<td>1.6 mmol/L</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>1864 IU/L</td>
<td>150 IU/L</td>
</tr>
<tr>
<td>25-hydroxyvitamin D₃</td>
<td>23.4 µg/L</td>
<td>29.8 µg/L</td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D₃</td>
<td>45 µmol/L</td>
<td>75 µmol/L</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>2.1 pmol/L</td>
<td>3.12 pmol/L</td>
</tr>
</tbody>
</table>

Figure 2. Karyotype of patient with X-linked hypophosphatemic rickets (47, XY)

Figure 3. Laboratory findings in a case with X-linked hypophosphatemic rickets

Figure 4. Widening of the distal metaphysis of radius and ulna (so-called double joints)

Figure 5. Metaphyseal fraying and cupping of distal end of radius and ulna, also with double contour of diaphysis. Skeletal maturation corresponds with age 2 year.

Figure 6. Hand radiography after six months of treatment shows significant resolution of prior changes, with incomplete fracture of ulna and higher number of ossification centers. Skeletal maturation corresponds with the age of child.

Figure 7. Widening of the distal metaphysis of fibula above fibular malleolus (so-called Marfan’s tubercle)

108 µmol/L), parathyroid hormone was in normal value (2.1 pmol/L-reference range 0.95-6.8 pmol/L) as shown in the Figure 3. After the treatment with calcitrol and phosphates, the values of alkaline phosphatase, phosphates and 1,25- dihydroxyvitamin D₃ got back to normal values (75 µmol/L).

Figure 8. Radiographic changes are evident in distal metaphysis of femur and proximal metaphysis of tibia and fibula, with double contours and with generalized rarefaction
Radiographic changes in bones were typical in our case. The widening of the distal metaphysis of the radius and ulna (so-called double joints) are evident (Figure 4). The specific radiographic changes in the bones of the arms were expressed in the distal metaphysis of the radius and ulna: the metaphysis is widened and deepened (gaining a concave shape), the line between the epiphysis and diaphysis is not clear (it appears in a shape of a brush), as shown in Figure 5. After the treatment these changes withdrew with incomplete spontaneous fracture of ulna, also there is evident a higher number of ossification centers (Figure 6).

As a result of distal metaphysis widening of fibula, two malleoli can be seen, so-called Marfan’s tubercule (Figure 7). Radiographic changes in our case are evident in distal metaphysis of femur and proximal metaphysis of tibia and fibula (Figure 8), also lower limb deformities were evident crura vara rachitica with double contours of bones (Figure 9).

5. DISCUSSION

This is the first case with X-linked hypophosphatemic rickets diagnosed in Kosova as a type of vitamin D resistant rickets, more specifically hypophosphemic rickets. Two decades ago vitamin D deficiency rickets used to be quite frequent (30%) and it was a public issue, whereas nowadays thanks to the constant prevention with vitamin D it decreased considerably to 1%. Different forms of rickets used to exist even before, but it is evident that a priority in preventive pediatrics in our country was vitamin D deficiency rickets. The frequency scale is 1 in 20.000 live births disregarding ethnic or gender differences. The parents noticed the first clinical manifestations of the disease in children during the second year of life, when he started standing on his legs and when he started walking. Genua vara was present and child had difficulties in walking. Clinical manifestations (neurovegetative signs, rickets rosary, Harisson’s groove, hypotonia etc) were not present in our case as those are characteristic for vitamin D deficiency rickets (9, 6).

Short stature is an obligatory clinical feature of X-linked hypophosphatemic rickets. Body height was 82 cm (< 5 percentile). Based on many publications (7, 14, 24), there is no benefit in treating these children with growth hormone.

Full blood count was normal (hematocrit values were on the border of the reference range). If there is no other cause, the mentioned hematological reference values shall not change in cases with X-linked hypophosphatemic rickets. The other authors didn’t registered full blood count changes in those cases (9, 16).

Calcium values in the serum were on the reference range (2.40 mmol/L), because X-linked hypophosphatemic rickets is the hypophosphatemic rickets (non calcipenik) and it is not accompanied by disorder of calcium metabolism. The obligatory laboratory findings in X-linked hypophosphatemic rickets is hypophosphatemia with hyperphosphaturia, increase of values of alkaline phosphatase and decrease of values of 1,25 dihydroxyvitamin D, in serum (as it was in our case). Hypophosphatemia and hyperphosphaturia are caused due to mutation in X chromosome. Mutant gene is called Phosphate regulating gene with Homology to Endopeptidases on the X chromosome (PHEX). The product of this gene appears to have either a direct or indirect role in activating a phosphatonin. Fibroblast growth factor-23 may be the target phosphatonin. In the absence of PHEX, there is decreased degradation of phosphatonin. Phosphatonin inhibits phosphate reabsorption in the proximal renal tubule, which results in increased phosphate excretion. Phosphatonin also inhibits renal 1α-hydroxyxylase, leading to decreased production of 1,25-dihydroxyvitamin D, in serum (23).

Activity of serum alkaline phosphatase has been increased to the very high values (1864 IU/L) due to the increased activity of osteoblasts, as a result of delayed start of treatment of the patient with X linked hypophosphatemic rickets. After a long treatment of rickets with calcitriol and phosphates the values of alkaline phosphatase, phosphates and 1,25 dihydroxyvitamin D, were brought into normal i.e. they reached the above borders of the reference values. Even the other authors (17, 18) registered the similar laboratory findings with X-linked hypophosphatemic rickets, but not with decreased values of phosphates or with the increased alkaline phosphatase values in serum as in our case (as the diagnosis and treatment started with delay).

The major radiographic changes in X-linked hypophosphatemic rickets appeared on the long bones, in the distal parts of radius, ulna and femur and proximal parts of tibia and fibula (10, 19, 21). Due to poor mineralization, the cartilage cells instead of dying proliferate and therefore there are some widened and deepened non calcified cells in the metaphyses of those bones in a form of a cup. Due to the insufficient mineral deposition in the newly formed osteoid tissue, the deposition of the osteoid tissue appears around the trabecula on the outer surface of the long bone diaphysis. Also, the diaphysis of those bones had the double contours. The fractures (of ulna) like in our case were not rare as well. In our case with X-linked hypophosphatemic rickets due to increased long bone metaphysis proliferation, in upper limbs (distal metaphysis of radius and ulna) appear so-called double joints as well as the so called Marfan’s tubercule on lower limbs (distal metaphysis of fibula).

The treatment started with delay, when the patient was three years old
(a child was taken to the hospital with delay). He was treated as an outpatient and in the regional hospital with vitamin D₃ in daily dosage of 800 IU and with calciferol 600.000 IU (intramuscular), however it did not show any improvements. After establishing a diagnosis of the disease, we started the treatment with calcitriol and phosphates. The different authors (7, 11, 12, 13, 15, 25) recommend different daily dosages and different time periods for treatment with calcitriol and phosphates (in our case we administered average doses of them). Calcitriol (that consists of active vitamin D₃ metabolite -1,25-dihydroxyvitamin D₃) is given in daily dosage of 50 ng/kg/day divided into two doses, whereas phosphates in form of basic phosphorus were given in the daily dosage of 150 mg/kg/day divided into four doses.

Treatment of our case is continuous and it is followed with constant control of the values of calcium, phosphorus, alkaline phosphatase, 1,25-dihydroxyvitamin D₃ and parathyroid hormone has to be controlled every 3-4 months, whereas that of the 1,25-dihydroxyvitamin D₃ and parathyroid hormone has to be controlled once a year. The ultrasound of kidneys helps in early detection of nephrocalcinosis as a complication to the therapy.

REFERENCES