Familial X-Linked Hypophosphatemic Rickets of 3 Generations: A Clinicohistopathological Study

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Abstract

Introduction: X Linked Hypophosphatemic (XLH) rickets is a systemic disorder resulting from the mutation of PHEX gene (Phosphate regulating gene homologous to endopeptidases, X-linked) present on X-chromosome. Mutated PHEX stimulates phosphatonin fibroblast growth factor-23 and also activates other phosphatonins that promote phosphate excretion. This result in excess excretion of phosphate impairing bone mineralization and these patients demonstrate hypophosphatemia and low or normal serum concentration of calcitriol.

Objectives: The study aims to discuss the manifestations, lab findings, treatment and prognosis of familial XLH rickets and document the gross, radiographic and microscopic alterations of the exfoliated tooth obtained from them.

Materials and Methods: A 35 years old male patient reports with mobility of posterior teeth since a year. Detailed history and examination revealed that the patient and his family are suffering from XLH rickets. Oral and systemic findings of the affected three generation patients were noted. Gross surface features of exfoliated deciduous teeth obtained from XLHR affected patient were observed using stereo-microscope. Radiographic and microscopic examination of the tooth was also done.

Results: The affected patients showed classical rachitic features and younger patients of the 3rd generation on early treatment showed improved height outcome, with milder skeletal features, better biochemical results and an improved oral health. Several enamel depressions, decreased radio-density of enamel and dentin, enlarged pulp chamber and disturbed morphology of enamel rod with faulty mineralization of dentin were the dental findings.

Conclusion: Dental manifestations of XLH rickets patients are often neglected. Dental practitioners should give importance to both dental and skeletal manifestations. Treatment must be advocated as early during 6 months of age to avoid serious complications and deformities. Dental intervention in such cases should be properly assessed and appropriate treatment must be given for better prognosis.

Keywords: X-linked Hypophosphatemic Rickets; Hypophosphatemia; XLH Rickets; Dental Findings

Abbreviations

XLHR: X Linked Hypophosphatemic Rickets; PHEX: Phosphate Regulating Gene Homologous to Endopeptidases, X-linked; FGF23: Fibroblast Growth Factor 23

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Introduction

Albright in 1939 first described the X-linked hypophosphatemic (XLH) rickets as a rare genetic, X-linked dominant disorder [1,2]. It represents a group of heritable disorders of phosphate renal regulation with three known forms of inheritance: autosomal dominant (ADHR), autosomal recessive (ARHR) and X-linked dominant (XLH). Among them XLH is the most common form [3]. Hypophosphatemic vitamin D-resistant rickets or XLH manifests marked hypophosphatemia caused by renal loss of phosphate into urine. Serum calcitriol levels are found to be abnormally low in these patients. XLH is caused by mutations in the phosphate regulating gene homologous to endopeptidases (PHEX) gene [4]. Skeletal features including decreased vertical height, craniotabes (soft skull), rachitic rosary, Harrisons groove, genu varum (bowed-legs), genu valgum (knock-knees) are seen in affected patients. Spinal and pelvic deformities and an increased tendency for pathological fractures are common findings [1]. Classic radiographic findings include widening of the distal physis, fraying and widening of the metaphysis and angular deformities of the arm and leg bones [4]. Dental abnormalities are common and may often include spontaneous abscess formation on non-carious teeth, enamel defects, enlarged pulp chambers, grossly defective dentine [1]. The enamel is described either as relatively thin, hypo-calcified or hypoplastic [5]. Dentinal defects like extensive interglobular dentin, tubular defects and wide predentin are also observed in XLH rickets affected tooth [6]. Generally, both primary and permanent teeth have dentinal dysplasia. The teeth usually show taurodontism, poorly defined lamina dura and a hypoplastic alveolar ridge. Spontaneous abscess formation is often the most striking dental feature observed in patients with XLH [7]. We report a clinicohistopathological study of 3 generations affected with familial XLH rickets (Chart 1).

Chart 1: Family tree of the affected family.
Case Report

A 35-year-old male patient was referred to our hospital with a complaint of mobility of the posterior teeth since one year. Skeletal examination showed frontal bossing, widening of the ankle joints, bowing of the limbs. Dental examination revealed grade II mobility in relation to the existing maxillary posterior teeth and the formation of frequent abscesses was also noted. The patient reported 3 - 4 spontaneous dental abscesses a year since childhood. Loss of attachment was seen in relation to the remaining teeth. The mandibular arch was completely edentulous and maxillary arch was partially edentulous. Reported reasons for the early loss of teeth were gingival recession and mobility (Figure 1-3).

Figure 1: 35-year-old male patient showing limb deformity.

Figure 2: Intraoral photograph of 35-year-old patient showing partially edentulous maxillary arch.

Family history revealed that his mother and 3 daughters also have similar skeletal and dental problems. He also reports that his deceased grandfather (maternal) was affected with the same condition. The patient’s sister was unaffected. Premature loss of teeth was a prominent feature seen in the patient and his mother. Clinical diagnosis of XLH rickets was made upon physical examination and confirmed with the help of a medical expert by blood investigations and anteroposterior radiographs. All the 5 patients affected with XLH were examined with a detailed case history and the skeletal and dental findings were observed. The patient’s mother, who was 70 years old also reported history of frequent abscess in the oral cavity. She experienced decreased salivation causing burning sensation and difficulty in speech. Classical features of rickets were observed. At present she is partially paralyzed on the right side. Medical history showed that she has chronic gastritis for which she is under medication along with anti-hypertensives and calcium supplements. Even though she is completely edentulous since the age of 18, minimal ridge resorption was noted. Extra oral examination showed slight deviation of face towards right side on opening and closing the mouth with incompetent lips (Figure 4-6).

All his 3 daughters showed the classical rachitic features including frontal bossing and bowing of the limbs. The first daughter, 12 years of age gave medical history showing presence of renal calculi of size 12 mm since 2 months. Dental examination revealed periodontal abscess in relation to 31 and grade II mobility and enamel hypoplasia in relation to 31 and 41 (Figure 7). Dental caries were also observed in most of her teeth. Developing Angle’s class I malocclusion with anterior cross bite were also seen. The second daughter, 8 years of age, showed chronic pulpitis in relation to 53, 55, and 63 and dental caries in relation to 26, 36, and 46. Angle’s class III molar relation with everted lips was observed. Spontaneous abscess was reported on the upper and lower anterior teeth. The youngest 6-year-old daughter complained of frequent abscess in relation to 51 and 61. Mild skeletal features of rickets were observed. Decay was noted on 6 of her teeth.

Methodology

Exfoliated deciduous mandibular teeth obtained from the 8-year-old female patient (second daughter) was examined. Stereo-microscope was used to examine the gross surface defects. In order to study pulp morphology and to compare the radiodensity of enamel and dentin, radiographs was taken. Microscopic structural alterations were studied with the help of ground and decalcified sections. The findings were then compared with unaffected deciduous teeth.

Results and Discussion

Laboratory investigations in all the patients showed low levels of serum phosphate, normal or slightly below serum calcium levels and high alkaline phosphatase levels. Calcitriol levels were found normal (Table 1).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal levels</th>
<th>Patient</th>
<th>Mother</th>
<th>1st Daughter</th>
<th>2nd Daughter</th>
<th>3rd Daughter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphorous</td>
<td>2.5 - 4.5 mg/dL</td>
<td>1.8</td>
<td>1.62</td>
<td>2</td>
<td>2.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.5 - 10.2 mg/dL</td>
<td>9</td>
<td>8.1</td>
<td>9.6</td>
<td>9.4</td>
<td>10</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>44 - 147 IU/L</td>
<td>997</td>
<td>870</td>
<td>1018</td>
<td>1050</td>
<td>1185</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>9.7 - 41.7 mg/ml</td>
<td>15</td>
<td>11.5</td>
<td>25</td>
<td>28</td>
<td>33</td>
</tr>
</tbody>
</table>

*Table 1: Laboratory data of the 3 generations affected with XLHR.*

Stereo-microscopic examination presented a glassy appearance demonstrating altered enamel translucency. Surface irregularities with areas of enamel hypoplasia were also seen on the tooth surface when compared to the unaffected deciduous tooth. Reduced radiodensity of enamel and dentin, enlarged coronal pulp chambers with indistinct border was seen on radiographic comparison with unaffected tooth. Pulpal calcification was observed in the coronal region of one of the affected teeth (Figure 8).
Microscopic examination of ground and decalcified sections showed relatively thin enamel with long cracks, disturbed enamel rod morphology and prominent striae of Retzius when compared to the unaffected tooth. Dentin tubular defects, extensive interglobular dentin and wide zone of pre-dentin was also noted (Figure 9).
Treatment and prognosis

The patient’s mother (first generation) was given only calcium supplements. The patient and his children were supplemented with regular vitamin D3 injection, calcium supplements and sodium phosphate. Inj. Arachitol 1 ampule once a month is given along with Tab Folifer (OD), Tab Osteocalcium (1/2BD) and sodium phosphate (1/2 g/day). Dental treatments including oral prophylaxis, restorations and abscess drainage were done for the patient and his 3 children. Since they are on monthly monitoring and continuous treatment, the severity of the skeletal features has reduced especially in the youngest daughter showing a better prognosis.

Discussion

XLH first reported by Albright., et al [2] is a syndrome showing marked hypophosphatemia, short stature and rickets. The main abnormality is considered to be a congenital impairment of phosphate transport and hypophosphatemia, resulting from reduced phosphate reabsorption in the brush border membrane on the luminal side of the proximal renal tubule and impaired phosphate absorption in the intestine [8]. Recently XLH has been associated with mutations in the PHEX gene present on the X-chromosome that is positioned at Xp22.14, which is predominantly expressed in osteoblast and odontoblasts [9]. In a study by Kawahara., et al [10] showed that patients with hypophosphatemic rickets exhibited increased serum fibroblast growth factor 23 (FGF23) and explained the PHEX mutation. In most patients, XLH appears in a familial line of X-linked, dominant inheritance with the same prevalence in both sexes; however, it may also occur sporadically. In general, more severe symptoms are noted in males. Hypophosphatemic rickets will usually manifest in 50% of the male children of a woman who is a carrier. It is inherited by a female when the disease manifests in the father and the mother is the carrier of the trait [8,11]. But in the present study, the mother had one son and one daughter, where the son was found to be affected while the daughter was unaffected with the disease. Short stature, frontal bossing, widening of the ankle joints and bowing of the limbs were also seen in our cases which is considered as the classical features of XLH rickets. In the present study, the oral findings such as enamel hypoplasia, frequent dental abscess, mobility and malocclusion are like the findings reported by Souza., et al [3] and are the classical dental manifestations of hypophosphatemic rickets. In our study, enamel defects were noted like those reported by Goodman JR., et al [12], Pereira., et al [13] and Godina., et al [14].

Studies have shown that in the dentition of these patients are highly susceptible to dental caries and bacteria can easily invade from the oral cavity to dental pulp by means of structural defects in enamel and dentin, resulting in pulpitis [6,8,15]. Our patients were also highly susceptible for the development of dental caries. Frequent and spontaneous dental abscess formation is another dental complication often observed in patients with XLH, even without dental caries or traumatic injury. These are treated by incision and drainage. Extraction of the teeth that present peri-radicular abscesses and subsequent restoration with implants is also a possible treatment modality to be considered in these patients. Pit and fissure sealants are to be used when the teeth are erupting as they prevent ingress of bacteria into the enamel micro-fractures as well as initiation of dental caries. Premature loss of deciduous teeth was noted which led to early edentulousness in 2 of our cases. Generalized periodontal disease and growth deficiencies in maxilla were also noted which was also reported by Zambrano., et al [16]. This condition is diagnosed usually by the age of 8 - 10 months [17] and by this time the deciduous dentition would be formed and hence the defects usually cannot be prevented. Therefore, once this condition is diagnosed, supplementation is highly beneficial to reduce the dental defects of permanent dentition. Investigators stress that the treatment should be started early in life as it lessens the disease burden. In these conditions, the treatment with phosphate and calcitriol should be started at a very early age of 6 months, before one year to achieve better results and reduce the deformities [18].

Conclusion

Patients with hypophosphatemic rickets frequently present with dental alterations and these cannot be completely reversed even with the treatment. However, comparing all our five patients, it has been shown quite conclusively that early treatment resulted in improved height outcome at all stages of growth, with milder skeletal features, better biochemical results and an improved oral health in the younger patients (3rd generation). To ensure early treatment, infants of affected parents must be periodically screened for hypophosphatemia and increased levels of serum alkaline phosphatase. Dental care of these patients should consist of periodic oral examination.
and aggressive preventive measures such as topical fluoride application, pit and fissure sealant application and maintenance of good oral hygiene with proper mechanical and chemical plaque control measures. Dental practitioners should be aware of the manifestations of this disorder so that early intervention can be carried out to prevent subsequent serious and more invasive dental procedures.

Bibliography


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