Prevalence and pathogenesis of dental and periodontal lesions in children with X-linked hypophosphatemic rickets


ABSTRACT. Aim To assess the prevalence and to investigate the pathogenetic mechanisms of dental and periodontal lesions in children with X-linked hypophosphatemic rickets (XLH) examined at diagnosis or during treatment.

Methods Nine children with XLH (age 7.2 ± 3.3 years) were enrolled in the study (at diagnosis, n = 2; during treatment with oral inorganic phosphate salts combined with 1,25-dihydroxyvitamin D3, n = 7). Oral examination was performed according to the evidence of carious and gingival lesions. Decayed or filled teeth (dft) index for primary teeth, and the decayed, missing, or filled teeth (DMFT) index for permanent teeth was assessed. All patients with a history of spontaneous dental abscesses underwent orthopantomography examination.

Results d/D ranged from 0 to 9 and f/F from 0 to 3. DMFT/dft index was 0 in the three youngest patients. One patient had enamel hypoplasia and two had enamel dyschromic alterations. Six out of nine patients (67%) had a history of spontaneous fistulae as a consequence of periapical abscesses occurring in the absence of dental decay or history of injury. In these patients, orthopantomographies showed enlarged pulp chambers associated with prominent pulp horns extending up to the dentino-enamel junction in both primary and permanent dentition.

Conclusion XLH patients show some peculiar dentinal abnormalities. Treatment prevents only in part dental and periodontal lesions. Genetic mechanisms have a main role in causing defective dentin mineralisation.

KEYWORDS: Globular dentin, Large pulp chambers, Spontaneous abscesses, Spontaneous fistulae, X-linked hypophosphatemic rickets.

Introduction

X-linked hypophosphatemic rickets (XLH, OMIM 307800) is the most common heritable form of vitamin D-resistant rickets, and it is transmitted as an X-linked dominant disorder [Rasmussen and Tenenhouse, 1995]. The main clinical features of XLH patients are growth failure with disproportionate short stature, rickets, and lower limb deformities [DiMeglio and Econs, 2001; Rasmussen and Tenenhouse, 1995]. XLH is determined by defective renal tubular reabsorption of phosphate and reduced or inappropriately normal serum 1,25-dihydroxyvitamin D [1,25(OH)2D] levels related to the degree of hypophosphatemia [DiMeglio and Econs, 2001; Rasmussen and Tenenhouse, 1995]. In addition, XLH patients have a primary abnormality in osteoblast function leading to hypomineralised periosteocytic lesions [Marie and Glorieux, 1983].

Furthermore, XLH patients showed dental and periodontal lesions, such as spontaneous periapical abscesses and fistulae occurring without any history of trauma or dental decay. Histologic analysis showed marked globular dentin and increased predentin width [Abe et al., 1988; Larmas et al., 1991; McWorther and Seale, 1991; Hillmann and Geurtsen, 1996; Murayama et al., 2000].

Recent studies demonstrated that XLH is caused by mutations in the PHEX (phosphate regulating gene with homology to endopeptidases) gene, which is located on Xp22.1. PHEX is expressed in osteoblasts, osteocytes, odontoblasts, and parathyroid glands.
[Beck et al., 1997; Ruchon et al., 1998]. Inactivating mutations in PHEX activity could determine an inadequate degradation of a substance, namely fibroblast growth factor-23 (FGF-23), that accumulates in circulation causing an impaired phosphate metabolism and 1,25(OH)\(_2\)D synthesis, and a primary defect of osteoblasts and odontoblasts function [Baroncelli et al., 2004]. However, the mechanisms of action of PHEX and FGF-23 are not clearly defined. Indeed, in addition to FGF-23, other phosphaturic substances, namely "phosphatonin", could be also involved in the pathogenesis of skeletal and dental lesions in XLH patients [Baroncelli et al., 2004].

Few data on the prevalence of dental and periodontal abnormalities, and on the effects of treatment of XLH patients on the oral findings are available. The aim of the study was to assess the prevalence and to investigate the pathogenetic mechanisms of dental and periodontal lesions in XLH children examined at diagnosis or during the conventional treatment.

**Patients and methods**

We examined nine children with XLH as outpatients at the Department of Pediatrics of our University, ranging in age from 2.0 to 13.3 years (7.2 ± 3.3 years; females n = 6, males, n = 3). Two patients were observed at diagnosis and the remaining during the conventional treatment with oral inorganic phosphate salts (Reducto-Spezial, Temmler Pharma, 50-70 mg/kg/d) associated with 1,25(OH)\(_2\)D\(_3\) (Rocaltrol Roche, 30-40 ng/kg/d). The compliance with the treatment was good in all the treated patients.

Clinical and biochemical data at entry into the study are summarised in Table 1; all patients had hypophosphatemia, reduced maximum rate of renal tubular reabsorption of phosphate normalized to the glomerular filtration rate (TmP/GFR), and increased serum alkaline phosphatase levels. Figures 1 and 2 show the typical clinical and radiological features of XLH patients, respectively.

All the treated patients showed an improvement of the biochemical findings, linear growth, and radiological signs of rickets. Familial X-linked dominant inheritance was documented in five out of nine patients. None of the patients were relatives.

Oral examination was performed according to the evidence of carious and gingival lesions. For each patient the decayed or filled teeth (dft) index for primary teeth, and the decayed, missing, or filled teeth (DMFT) index for permanent teeth was assessed. In all patients, macroscopic examination of the enamel was performed to assess the presence of hypoplasia or dyschromic alterations. Furthermore, in order to examine the volume of the pulp chamber and to detect periodontal, dental, and periapical lesions an orthopantomography was performed in all patients who had a history of spontaneous dental abscesses. Informed consent to perform the study was obtained from the parents of each patient. The study was approved by our ethics committee for human investigation.

![Table 1](image)

**Table 1 - Clinical and biochemical data of patients at entry into the study.**
Statistical analysis. The results are expressed as mean ± SD.
Comparison of biochemical parameters between patients and normal values was assessed by the nonparametric Mann-Whitney rank-sum test. A P < 0.05 was considered significant for all statistical analyses. All statistical analyses were carried out using the SPSS (Statistical Package of Social Sciences, Chicago, IL, USA) for Windows software program, version 9.0.

Results
Data on dental and periodontal lesions in the examined patients are reported in Table 2. The results of dft/DMFT index showed that d/D ranged from 0 to 9, and f/F from 0 to 3. In the three youngest patients (cases 1, 2, and 3) dft/DMFT index was 0. Only one patient had enamel hypoplasia (Fig. 3), whereas two patients showed enamel dyschromic alterations (Fig. 3 and 4).
Six out of nine patients (67%) had a history of spontaneous fistulae as a consequence of periapical abscesses (Fig. 5); in all these patients spontaneous fistulae occurred in the absence of dental decay or history of injury. History was negative for spontaneous abscesses or fistulae in the three youngest patients.

In the six patients having a history of spontaneous fistulae, orthopantomography examination showed enlarged pulp chambers associated with prominent pulp horns extending up to dentino-enamel junction in many teeth of both primary and permanent dentition (Fig. 6).
Only one patient (case 9) underwent endodontic treatments.

Discussion
The majority of our XLH patients showed dental and periodontal alterations. The main clinical feature we observed was the occurrence of spontaneous abscesses and fistulae without any history of trauma or dental decay, according to other studies [Batra et al., 2006; Chaussain-Miller et al., 2003; Goodman et al., 1998; Hillmann and Geurtsen, 1996; McWorther and Seale, 1991; Murayama et al., 2000; Seow, 1991]. Orthopantomography examination demonstrated
FIG. 3 - Case 7: enamel hypoplasia of the teeth 11 and 21, and enamel dyschromia of the tooth 63.

FIG. 4 - Case 5: enamel dyschromia of the tooth 74.

FIG. 5 - Case 4: spontaneous fistula corresponding to tooth 54.

FIG. 6 - Case 8: orthopantomography showing enlarged pulp chambers associated with prominent pulp horns extending up to dentino-enamel junction in many teeth of both primary and permanent dentition.

### TABLE 2 - Dental and periodontal lesions in the examined patients.

<table>
<thead>
<tr>
<th>Case</th>
<th>d/D</th>
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<th>f/F</th>
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<th>Enamel dyschromic alterations</th>
<th>Spontaneous fistulae</th>
<th>Endodontic treatments</th>
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<td>mean ± SD</td>
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<td>0.7 ± 1.2</td>
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*Examined at diagnosis.
some peculiar signs, such as wideness of pulp chambers with horns extending to the dentino-enamel junction, that were evident in all patients with a history of spontaneous fistulae. These data suggest that the occurrence of spontaneous fistulae is probably related to the morphological abnormalities of the tooth.

None of the three youngest patients (two observed at diagnosis and one after 2.5 years of treatment) (Table 1) had dental lesions or a history of spontaneous abscesses and fistulae. We do not know whether they had the typical alterations of the pulp chambers, as occurred in the other patients, because orthopantomography examination was not performed in these patients. The lack of occurrence of spontaneous abscesses and fistulae in the younger patients may be due to the short time of disease, suggesting that its duration was a main cause in predisposing to oral complications independently of the treatment. Although our results seem to indicate that the treatment usually employed in XLH patients was not able to prevent oral complications, we cannot exclude that it may have beneficial effects on dental and periodontal tissues. Indeed, it has been reported [Chaussain-Miller et al., 2003] that 1α-hydroxyvitamin D₃, another vitamin D metabolite usually used for the treatment of XLH patients, had beneficial effects on dental status, even though the morphological abnormalities of the tooth did not show any change during that treatment. On the other hand, poorly treated adult XLH patients usually showed severe dental and periodontal lesions with premature loss of dentition (unpublished data). These data suggest that the disease progressively affects dental and periodontal status, but early conventional treatment may be effective, at least in part, in improving dental and periodontal alterations.

Some histologic studies demonstrated that spontaneous abscesses occurring in XLH patients are likely due to deficiencies of dentin mineralization which appeared globular and thin with large calcospherites. As a consequence, dentin lesions could cause the alteration of the pulp chambers with increased risk of penetration of microorganisms through dentinal clefts [Abe et al., 1988; Hillmann and Geurtsen, 1996; Lyles et al., 1985; Murayama et al., 2000; Seow, 1991]. Therefore, the altered dentinal structure with prominent horns extending up to dentino-enamel junction, associated with enamel cracks could represent the way leading to a pulp infection and necrosis with recurrent abscesses and spontaneous fistulae.

The mechanisms leading to the dentinal abnormalities are not clearly defined. Phosphate is a compound included in the hydroxyapatite crystals, so that reduced circulating phosphate levels could affect the mineralization process of both dentin and growth plates. However, the low serum phosphate levels may explain only in part the pathogenesis of the dentin lesions, as the increased serum phosphate levels during the treatment showed only partial effects on dental and periodontal lesions. The inappropriate serum 1,25(OH)₂D levels, another peculiar biochemical marker of XLH patients [DiMeglio and Econs, 2001; Rasmussen and Tenenhouse, 1995], could be another candidate in causing the altered dentin mineralization, but it has been demonstrated that this hormone is not directly involved in the process of growth plate mineralization [Underwood and DeLuca, 1984], suggesting that probably it does not have a main role in dentin mineralization.

The recent evidence of the role of PHEX system in regulating the phosphate metabolism [Baroncelli et al., 2004], as well as the localization of a PHEX mRNA expression in osteoblasts and odontoblasts [Ruchon et al., 1998], could suggest that the dentin lesions observed in XLH patients are due to an altered process of dentinogenesis for a impaired activity of the odontoblasts, as occur for osteoblasts [Marie and Glorieux, 1983]. However, it has been reported that XLH odontoblasts had a normal activity as they were able to produce a normal secondary and tertiary dentin [Abe et al., 1988]. These contrasting data require further studies in order to assess whether and how the PHEX system may affect odontoblasts activity.

Enamel lesions, such as hypoplasia or dyschromic alterations, are not common findings in XLH patients [Abe et al., 1988; Berndt et al., 1996; Seow et al., 1984], according to the evidence that the histologic appearance of enamel is usually reported to be normal in the majority of XLH patients [Goodman et al., 1998; Seow, 1984]. Indeed, we found enamel lesions only in two out of nine patients. There are no data indicating a primary abnormal enamel maturation in XLH patients as a consequence of impaired ameloblasts activity. A partial explanation of the enamel alterations may be that they are secondary to the lack of appropriate support from the altered dentin.

Since dentin and enamel formation occur between four months in utero and eleven months of age [Garn and Burdi, 1971], the defects in the primary dentition cannot be prevented. The development of permanent dentition may be improved, at least in part, by early treatment, even though recurrent spontaneous abscesses and fistulae may occur independently of the
therapy, as we found in more than half of our patients. Anyway, regular dental care with periodic examinations by specialists, topical applications and systemic fluoride administration, pit and fissure sealants, and maintenance of good oral hygiene are strongly indicated in order to reduce the risk of spontaneous abscesses and fistulae caused by the penetration of microorganisms through dentinal clefts [Alexander et al., 2001; Batra et al., 2006].

In conclusion, our data show that XLH patients have a high prevalence of dental and periodontal lesions and that it is influenced only in part by the conventional treatment. The peculiar dentinal lesions associated with enlarged pulp chambers with prominent horns extending to the dentino-enamel junction probably represent the main predisposing causes to the occurrence of periapical abscesses and fistulae in patients with this disorder. XLH patients should be accurately followed not only by pediatricians but also by odontologists knowing the oral complications of the disease.

References