Dental and periodontal features and management in XLH children and adults

Martin Biosse Duplan 1,2,3,4, Elvire Le Norcy 1,3,5, Frédéric Courson 1,3,6, Catherine Chaussain 1,3,5

1 Université de Paris, Faculty of Dental Surgery, Montrouge, France; 2 APHP, Department of Oral Medicine, Bretonneau Hospital, Paris, France; 3 APHP, Reference Center for Rare Disorders of Calcium and Phosphate Metabolism, filière OSCAR, Paris, France; 4 INSERM 1163, Imagine Institute, Paris, France; 5 URP 2496, Faculty of Dental Surgery, University of Paris, Montrouge, France; 6 Division of Research for Innovative Biomaterials and Interfaces, URP4462, University of Paris, Montrouge, France

ABSTRACT
The formation and homeostasis of the mineralized tissues that make up the tooth and its periodontium show many similarities, but also differences, with respect to bone tissue. Accordingly, oral manifestations are often present in skeletal diseases. The manifestations in X-linked hypophosphatemia (XLH) are a good illustration of the potential impact of skeletal diseases on the teeth and periodontium: they can affect all oral mineralized tissues; they differ between children and adults; and they have a strong impact on the quality of life of the affected individual. In addition, the frequency and severity of the oral manifestations depend on the general management of the skeletal disease. The main dental tissues affected by XLH are the dentin and cementum, whose formation and mineralization are impaired. Clinically, poorly mineralized dentin leads to spontaneous endodontic infections, and dental abscesses in seemingly intact teeth are frequent in affected children. Reduced cementum formation results in periodontal attachment loss, and the prevalence and severity of periodontitis are elevated in adults with XLH. Prevention or improvement of these dental manifestations is first achieved by conventional treatment of XLH with active vitamin D analogs and phosphate supplementation. In addition, local treatments preventing bacterial invasion of dentin are beneficial.

KEYWORDS
Tooth, Periodontium, Dentin, Cementum, Periodontitis, Dental Pulp Necrosis.

Introduction
Skeletal diseases frequently have oral manifestations. The impact of X-linked hypophosphatemia (XLH) on the oral cavity has been recognized for decades [1], as has the need for specific dental care [2-5].

Oral manifestations are present because several tissues that compose the tooth and its periodontium, namely, the enamel, dentin, cementum and alveolar bone, are mineralized and hence, like skeletal bone, are affected when mineralization is disturbed [6]. Nonetheless, in contrast to bones, teeth have little potential to remodel and improve their mineralization over time. In addition, the oral cavity is a reservoir of pathogens, and defective mineralization frequently leads to bacterial infections of either the dental pulp or the periodontium, which, if left untreated, affect the prognosis of the tooth involved and can lead to its loss.

These oral manifestations have a strong impact on the quality of life of the affected individual [7]. It is therefore of prime importance to understand the types of defect created by XLH in dental and periodontal tissues, the clinical manifestations of these defects, and how to prevent and manage these manifestations.

Dental and periodontal tissue anomalies in XLH
All mineralized tissues that compose the tooth and the surrounding periodontium may be affected to some extent in XLH.

Enamel
The enamel is the outer layer of the tooth; endowed with strong mechanical properties, it provides a shell protecting deeper dental tissues. Dental enamel is not vascularized or innervated, and it is devoid of cells. No matrix vesicles are released during the mineralization of enamel, unlike what occurs with collagen-based calcified tissues. This could explain why hypophosphatemia does not appear to affect mineralization of enamel as strongly as it does that of bone and dentin.

In most XLH patients, the enamel appears clinically sound. A few cases of enamel hypoplasia, fracture, dyschromic al-
termination or accelerated attrition have been reported [1,8–10]. On
dental radiographs, the enamel can appear thinner with slightly
reduced radiopacity.

The concentrations of calcium and phosphorus and the cal-
cium/phosphorus ratio of the enamel are comparable to those
found in normal teeth in some patients [11], but different in oth-
ers [12]. Importantly, microcracks in the enamel layer and subse-
quent microorganism invasion have been observed on sections
of extracted XLH teeth [13,14].

**Dentin**

Dentin is the tissue making up the bulk of the tooth crown and
root. Its formation resembles that of bone, with a first layer
of non-mineralized matrix, called predentin, being deposited
by odontoblasts. Predentin is then progressively mineralized as
non-collagenous proteins are incorporated at the mineralization
front [15]. In addition to the mineralization process, the com-
position and proportions of the collagenous and non-colla-
genous proteins in the organic matrix are very similar in bone and
dentin matrices [4]. Dentin, however, does not undergo remodel-
ing and the potential to correct defects acquired during its for-
mation is therefore very limited.

XLH affects dentin formation at several levels, leading to: a
reduced level of phosphate, impaired production of active vita-
m D, and accumulation within the predentin matrix of acidic,
serine- and aspartic acid-rich motif peptides, which are derived
from the abnormal cleavage of non-collagenous proteins and
act as mineralization inhibitors [16]. Normally, these peptides are
selectively cleaved and cleared from the local matrix environ-
ment by the PHEX enzyme.

In XLH, defective dentin mineralization is readily detected.
On histological sections, poorly mineralized dentin is evident
with the presence of non-mineralized interglobular dentin [17]
(Fig. 1A). Undecalcified sections of teeth also show this in-
complete mineralization (Fig. 1A). The collagen matrix ap-
pers normal, but an accumulation of inhibitory peptides is
observed. Clinically, the small amount of dentin formed tends
to lead to enlarged pulp chambers with prominent pulp horns
extending toward the enamel-dentin junction, as seen on dental
radiographs [15] (Fig. 2A, 2B, 3A & 3B). The reduced miner-
alization results in radiolucent dentin, especially the layer of
dentin immediately under the enamel (Figs. 2A, 2B, 3A & 3B).

**Cementum**

The cementum is a thin layer of mineralized matrix that covers
the root dentin. On the coronal half of the root, it anchors the col-
lagen fiber bundles of the periodontal ligament and, as such, is
an essential constituent of the attachment apparatus. This cemen-
tum is slowly and constantly formed by cementoblasts, directly
on the surface of the root dentin, with no layer of non-mineral-
ized matrix involved. Its formation is thought to be extremely
dependent on the local concentration of calcium and phosphate
and under physiological conditions it is not remodeled [18].

In XLH teeth, acellular cementum appears hypoplastic
(Fig. 1C and 1D). Reduced thickness has been observed in adul-
ts and likely interferes with the correct attachment of the
root [19]. Cementum hypoplasia is also evident in the hyp mouse,
which is the most studied model of XLH [20,21].

**Alveolar bone**

The alveolar bone is defined as the part of the jawbone that
surrounds the teeth. It is part of the facial skeleton and both its
formation by membranous ossification and its homeostasis are
similar to these processes in other bones.

XLH likely causes mineralization defects in alveolar bone,
but they have not been studied in humans. Radiographically,
the lamina dura may be absent [22] (Fig.s 2A, 2B, 3A & 3B). In
the alveolar bone of the hyp mouse, hypomineralized matrix
and accumulation of non-collagenous matrix proteins are ev-
ident [23].
Clinical manifestations and management of children with XLH

Endodontic infections

The major clinical dental manifestation of XLH in children is the occurrence of endodontic abscesses in teeth that seem intact, that is, devoid of caries, and with no history of trauma or periodontal disease (Fig. 2C & 2D). The abnormal mineralization of the dentin is thought to induce microcracks in the enamel that allow bacterial leakage; when this happens, bacteria easily reach the pulp chamber and infect the pulp tissue. The acute manifestation of this infection is a dental abscess, whose main symptoms are pain and swelling.

Endodontic infections are not always symptomatic and may go unnoticed for a long time. They are frequently diagnosed on x-rays and the clinical presentation of an intact tooth with an endodontic abscess often results in delayed diagnosis and treatment. The abscess can evolve into maxillofacial cellulitis, which can be life threatening and requires immediate care. Alternatively, drainage of the abscess can occur via oral or extraoral sinus tracts (fistulae), resulting in a chronic dental abscess.

These dental abscesses are very common in children with XLH, with up to 70% affected [9,23], and they occur in both deciduous and permanent teeth. In the primary dentition, the incisors and canines are the teeth most frequently affected, followed by the first and second molars.

Early detection and management of these infections greatly improve the prognosis of the tooth. For this reason, early and regular dental check-ups are required during childhood. Intervals of 6 to 12 months are recommended[24]. Systemic antibiotics are used in the case of an acute abscess, and are followed by endodontic treatment or extraction of the tooth.

A dramatic reduction in the occurrence of endodontic infections can be achieved through conventional treatment of XLH, consisting of supplementation of oral phosphate, with multiple daily intakes, and of active vitamin D analogs (alfacalcidol or calcitriol). The oral health of supplemented children may be similar to that of age-matched controls [2]. Supplementation greatly improves dentin mineralization and formation, reducing the size of the dental pulp canal and chamber[14]. Both deciduous and permanent teeth can potentially benefit from supplementation, depending on when the treatment is started. As for the skeletal features of XLH, adherence to the treatment and its continuation over time are crucial to improve mineralization [5]. The effect of anti-FGF-23 antibody (burosumab) on dentin mineralization and endodontic infections is currently unknown.

Local prophylactic treatments can also contribute to the prevention of endodontic infections. They consist of sealing the pits and fissures of the occlusal surface of the tooth where bacteria accumulate. This is done using flowable resin-based dental composites that fill microcracks in the enamel and prevent bacterial invasion [13]. This sealing is most important for molars and premolars and is performed on both deciduous and permanent teeth.
Caries
It is unclear whether XLH increases the prevalence and/or severity of dental caries. Reduced enamel thickness and poorly mineralized dentin could certainly contribute to dental caries, but studies in the largest cohorts of XLH children failed to show an increased risk.

Malocclusion
Delayed dental development and an abnormal eruption pattern do not seem to be more common in XLH than in the general population. In contrast, specific malocclusions could be overrepresented in these patients, such as maxillary retrognathism and impacted or dystopic maxillary canines. Defective maxillary growth or defective cranial-base growth could contribute to these malocclusions.

Orthodontic treatment is routinely conducted in XLH children, adolescents, and adults. It is likely, however, that bone remodeling during tooth movement is influenced by XLH, as it is in the hyp mouse, and therefore effective and continued general treatment of XLH with conventional supplementation is usually considered mandatory during any orthodontic treatment.

Clinical manifestations and management of adults with XLH

Endodontic infections
Dental abscesses in seemingly intact teeth are common in adults with XLH, although the incidence of these infections decreases with age. In contrast with the general population, in which it is estimated that 5% of adults have had at least one abscess, it has been reported that more than 60% of adults with XLH have experienced five or more dental abscesses.

In the permanent dentition, the mandibular incisors seem to be the most frequently affected teeth. Maxillofacial cellulitis is rare in XLH adults.

Endodontic treatment of the tooth is indicated following an endodontic infection and is therefore far more common in adults with XLH than in the general population (Fig. 3C & 3D). Conventional XLH treatment during childhood is associated with fewer endodontically treated teeth in adulthood. Importantly, continued supplementation during adulthood may reduce the incidence of dental abscesses and the number of endodontically treated teeth.

Periodontitis
A major cause of tooth loss in adults with XLH is periodontitis, whose prevalence and severity are increased by the disease (Fig. 3C & 3D). We observed that nearly 80% of XLH adults have moderate or severe periodontitis. Radiographically, adults show varying degrees of horizontal alveolar bone loss with frequent infrabony defects.

The increased risk of periodontitis could be related to the cementum hypoplasia observed on teeth extracted in XLH adults. Importantly, conventional supplementation also improves periodontal health; adults treated during childhood only or during childhood and adulthood show fewer deep periodontal pockets and less severe alveolar bone loss than those not treated.
Despite similar plaque control\(^{19}\), treatment of periodontitis in XLH adults is similar to that in healthy adults, with emphasis on supportive periodontal therapy.

**Implant failure**

Because of the increased tooth loss in adults with XLH, there is a strong need for dental implant therapy in this population. The presence of large pulp chambers and in many cases the reduced periodontium contraindicate the use of fixed or removable partial dentures to replace the missing teeth.

It is not known whether successful implant therapy can consistently be achieved in XLH patients. Two reports provided encouraging results concerning implant success, with confirmed osseointegration up to 4 years after implant placement\(^{12,33}\), another report presented less encouraging outcomes\(^{134}\). In our experience, however, implant failure is far more common than in the general population, especially in patients not supplemented with the conventional XLH treatment. Bone healing around the implant could benefit from restarting supplementation before implant placement and continuing it during implant healing, as is recommended in orthopedic surgery. Allowing an extended healing time could also favor implant success.

**Conclusion**

There is a great need for specific and regular dental care in children and adults with XLH. The general treatment of XLH (e.g., supplementation with phosphate and vitamin D analogs), especially during childhood, greatly reduces the severity of the abnormalities in dental tissues and their resulting clinical oral manifestations\(^{12,19}\). As new therapeutic strategies emerge, notably with burosumab, their impact on dental tissues must be evaluated. Overall, dentists following patients with XLH and, more broadly, patients with skeletal genetic disorders should work closely with the pediatricians, endocrinologists and rheumatologists in charge of their care.

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