Dental and periodontal features and management in XLH children and adults

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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-

teration 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 calcium/phosphorus ratio of the enamel are comparable to those found in normal teeth in some patients [11], but different in others [12]. Importantly, microcracks in the enamel layer and subsequent 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 composition and proportions of the collagenous and non-collagenous proteins in the organic matrix are very similar in bone and dentin matrices [4]. Dentin, however, does not undergo remodeling and the potential to correct defects acquired during its formation is therefore very limited.

XLH affects dentin formation at several levels, leading to: a reduced level of phosphate, impaired production of active vitamin 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 environment 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 incomplete mineralization (Fig. 1A). The collagen matrix appears 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 [2] (Fig.s 2A, 2B, 3A & 3B). The reduced mineralization 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 collagen fiber bundles of the periodontal ligament and, as such, is an essential constituent of the attachment apparatus. This cementum is slowly and constantly formed by cementoblasts, directly on the surface of the root dentin, with no layer of non-mineralized 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 adults 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].

Figure 1 A. Non-demineralized histological section of a tooth extracted from an XLH patient and stained with von Kossa. Poorly mineralized dentin is evident, illustrated by the presence of unfused calcospherites (*). p: pulp, pd: predentin, d: dentin. Scale bar = 50μm.
B. Demineralized histological section of a tooth extracted from a patient in good general health and stained with hematoxylin eosin. A thick layer of acellular cementum is present. f: collagen fibers from the periodontal ligament, c: cementum, d: dentin. Scale bar = 100μm.
C. Demineralized histological section of a tooth extracted from a patient with XLH, and stained with hematoxylin eosin. A thin layer of acellular cementum and unfused calcospherites (*) are present. f: collagen fibers from the periodontal ligament, c: cementum, d: dentin. Scale bar = 100 μm.
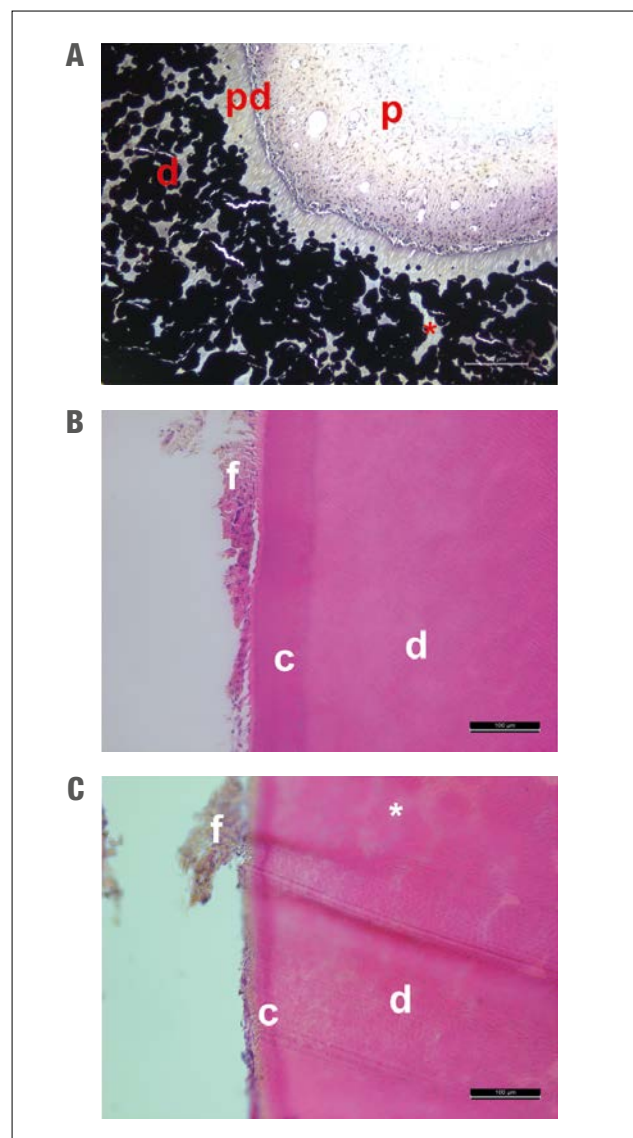

Alveolar bone

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 evident [21].

Figure 2 A. Retro-coronal radiograph of 10-year-old boy in good general health.
B. Retro-coronal radiograph of 10-year-old boy with XLH. Note the enlarged pulp chambers (*), decreased radiopacity of the dentin and enamel, and the absence of alveolar bone lamina dura.
C. Clinical view of a 4-year-old child with XLH presenting with spontaneous endodontic infection of both primary central maxillary incisors (#51 & #61). In the case of tooth #51, the endodontic infection resulted in an acute dental abscess.
D. Retro-alveolar radiograph of the corresponding sector in the same patient. Periapical bone loss is evident in teeth #51 and #61.
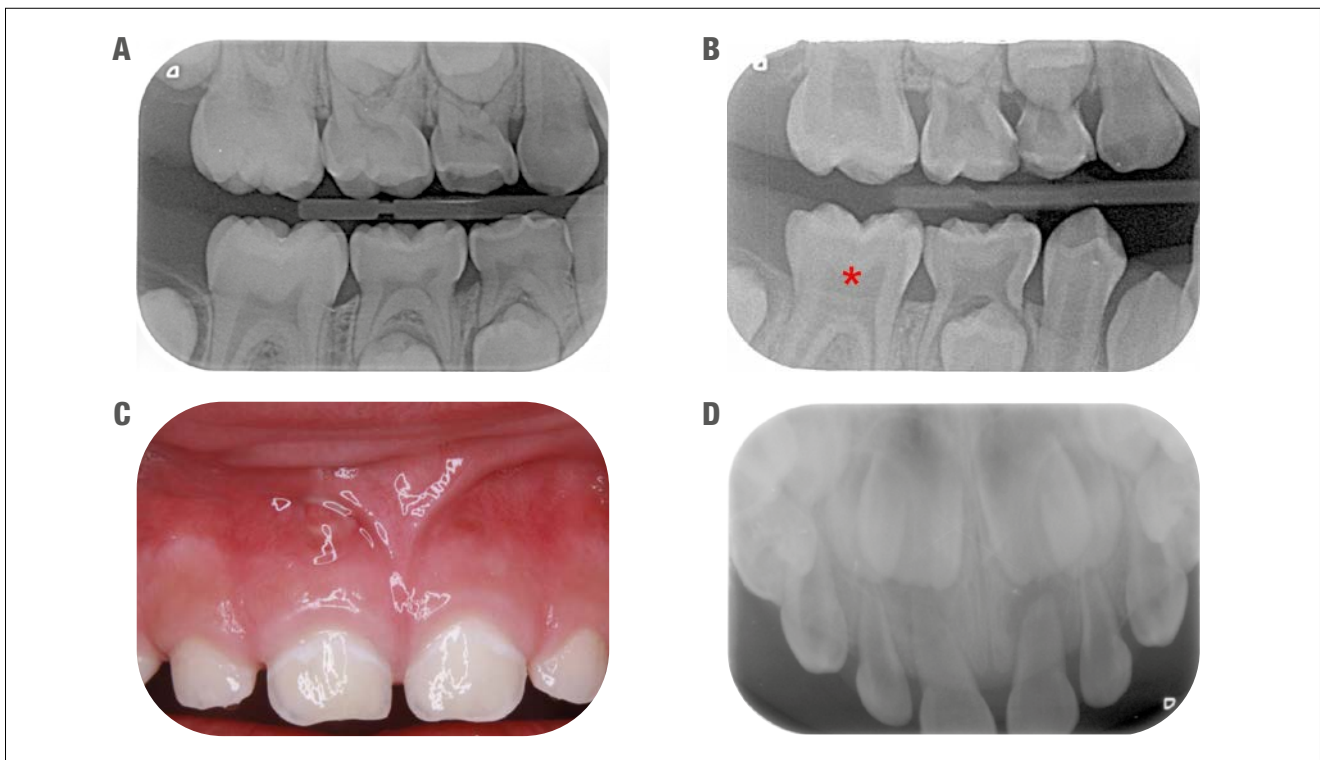
Clinical manifestations and management of children with XLH

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 extra oral 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 [3]. 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 [2,9,23].

Malocclusion

Delayed dental development and an abnormal eruption pattern do not seem to be more common in XLH than in the general population [25]. In contrast, specific malocclusions could be overrepresented in these patients, such as maxillary retrognathism and impacted or dystopic maxillary canines [26]. Defective maxillary growth or defective cranial-base growth could contribute to these malocclusions [26].

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 [21], 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 [27], it has been reported that more than 60% of adults with XLH have experienced five or more dental abscesses [28]. 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 [29,30] (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 [19,28].

Periodontitis

A major cause of tooth loss in adults with XLH is periodontitis, whose prevalence and severity are increased by the disease [19,31] (Fig. 3C & 3D). We observed that nearly 80% of XLH adults have moderate or severe periodontitis [19]. 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,

Figure 3 A. Retro-coronal radiograph of 39-year-old woman in good general health.
B. Retro-coronal radiograph of a 34-year-old woman with XLH. Note the enlarged pulp chambers (*), decreased radiopacity of the dentin and enamel, and vertical bone loss around tooth #46.
C. Clinical view of a 45-year-old woman with XLH. Teeth #32 and #46 have been lost following endodontic infection, and teeth #21 and #31 present with discoloration following endodontic treatment. Gingival inflammation and periodontal recessions are present.
D. Panoramic radiograph of the same patient. Generalized horizontal moderate bone loss is evident.
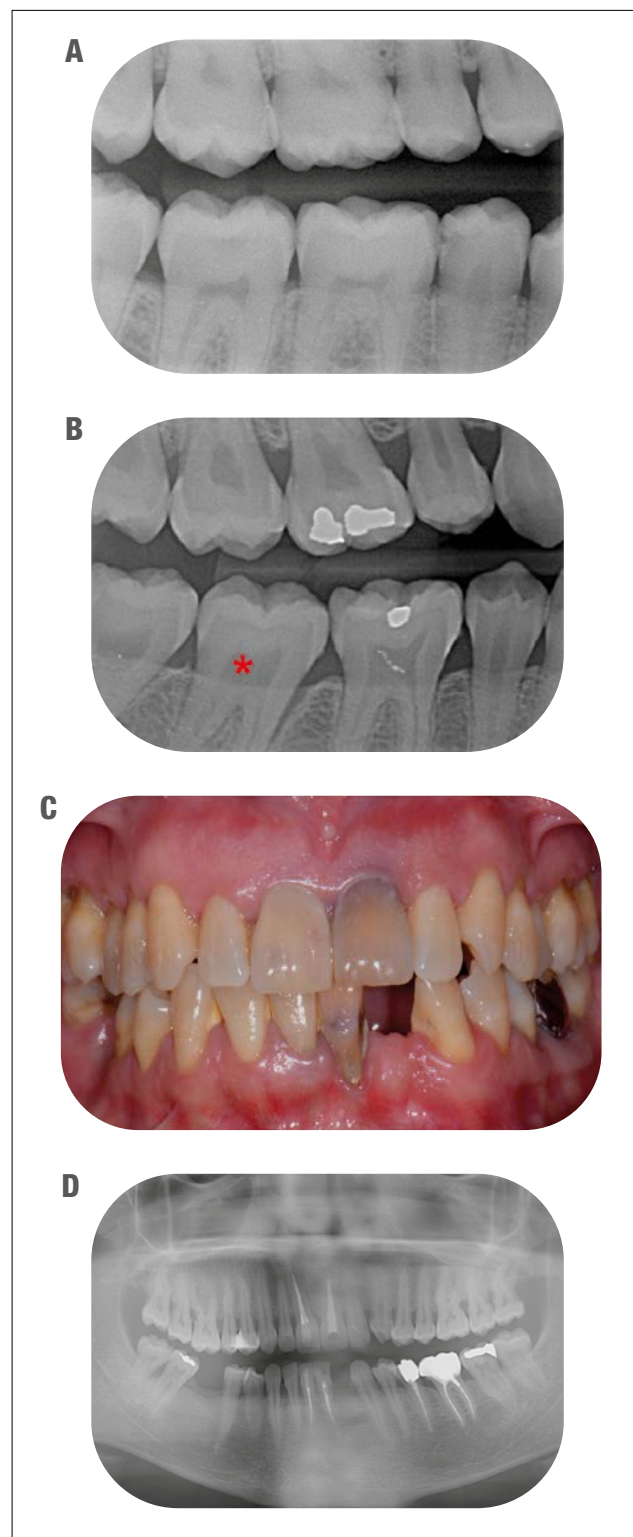
despite similar plaque control [19].Treatment of periodontitis in XLH adults is similar to that in healthy adults, with emphasis on supportive periodontal therapy.

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 [32,33]; another report presented less encouraging outcomes [34]. 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 [2,19]. 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.

References

1. Cohen S, Becker GL. Origin, diagnosis, and treatment of the dental manifestations of vitamin D-resistant rickets: review of the literature and report of case. J Am Dent Assoc. 1976;92(1):120-9.

2. Chaussain-Miller C, Sinding C, Wolikow M, Lasfargues J-J, Godeau G, Garabédian M. Dental abnormalities in patients with familial hypophosphatemic vitamin D-resistant rickets: prevention by early treatment with 1-hydroxyvitamin D. J Pediatr. 2003;142(3):324-31.

3. Douyere D, Joseph C, Gaucher C, Chaussain C, Courson F. Familial hypophosphatemic vitamin D-resistant rickets--prevention of spontaneous dental abscesses on primary teeth: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;107(4):525-30.

4. Opsahl Vital S, Gaucher C, Bardet C, et al. Tooth dentin defects reflect genetic disorders affecting bone mineralization. Bone. 2012; 50(4):989-97.

5. Linglart A, Biosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. Endocr Connect. 2014;3(1):R13-30.

6. McKee MD, Hoac B, Addison WN, Barros NMT, Millán JL, Chaussain C. Extracellular matrix mineralization in periodontal tissues: noncollagenous matrix proteins, enzymes, and relationship to hypophosphatasia and X-linked hypophosphatemia. Periodontol 2000. 2013;63(1):102-22.

7. Hanisch M, Bohner L, Sabandal MMI, Kleinheinz J, Jung S. Oral symptoms and oral health-related quality of life of individuals with x-linked hypophosphatemia. Head Face Med. 2019;15(1):8.

8. Schwartz S, Scriver CR, Reade TM, Shields ED. Oral findings in patients with autosomal dominant hypophosphatemic bone disease and X-linked hypophosphatemia: further evidence that they are different diseases. Oral Surg Oral Med Oral Pathol. 1988;66(3):310-4.

9. Goodman JR, Gelbier MJ, Bennett JH, Winter GB. Dental problems associated with hypophosphataemic vitamin D resistant rickets. Int J Paediatr Dent. 1998;8(1):19-28.

10. Gjørup H, Beck-Nielsen SS, Haubek D. Craniofacial and dental characteristics of patients with vitamin-D-dependent rickets type 1A compared to controls and patients with X-linked hypophosphatemia. Clin Oral Investig. 2018;22(2):745-55.

11. Abe K, Ooshima T, Lily TS, Yasufuku Y, Sobue S. Structural deformities of deciduous teeth in patients with hypophosphatemic vitamin D-resistant rickets. Oral Surg Oral Med Oral Pathol. 1988;65(2):191-8.

12. Daley TD, Jarvis A, Wysocki GP, Kogon SL. X-ray microanalysis of teeth from healthy patients and patients with familial hypophosphatemia. Calcif Tissue Int. 1990;47(6):350-5.

13. Hillmann G, Geurtsen W. Pathohistology of undecalcified primary teeth in vitamin D-resistant rickets: review and report of two cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1996;82(2):218-24.

14. Chaussain-Miller C, Sinding C, Septier D, Wolikow M, Goldberg M, Garabédian M. Dentin structure in familial hypophosphatemic rickets: benefits of vitamin D and phosphate treatment. Oral Dis. 2007;13(5):482-9.

15. Nanci A, Cate ART. Ten Cate's Oral Histology: Development, Structure, and Function. Elsevier Health Sciences; 2008.

16. Boukpessi T, Septier D, Bagga S, Garabédian M, Goldberg M, Chaussain-Miller C. Dentin alteration of deciduous teeth in human hypophosphatemic rickets. Calcif Tissue Int. 2006;79(5):294-300.

17. Seeto E, Seow WK. Scanning electron microscopic analysis of dentin in vitamin D-resistant rickets--assessment of mineralization and correlation with clinical findings. Pediatr Dent. 1991;13(1):43-48.

18. Foster BL, Nagatomo KJ, Nociti FH, et al. Central role of pyrophosphate in acellular cementum formation. PloS One. 2012;7(6):e38393.

19. Biosse Duplan M, Coyac BR, Bardet C, et al. Phosphate and vitamin D prevent periodontitis in X-linked hypophosphatemia. J Dent Res. 2017;96(4):388-95.

20. Fong H, Chu EY, Tompkins KA, et al. Aberrant cementum phenotype associated with the hypophosphatemic Hyp mouse. J Periodontol. 2009;80(8):1348-54.

21. Coyac BR, Falgayrac G, Baroukh B, et al. Tissue-specific mineralization defects in the periodontium of the Hyp mouse model of X-linked hypophosphatemia. Bone. 2017;103:334-46.

22. Beltes C, Zachou E. Endodontic management in a patient with vitamin D–resistant Rickets. J Endod. 2012;38(2):255-8.

23. Baroncelli GI, Angiolini M, Ninni E, Galli V, Saggese R, Giuca MR. Prevalence and pathogenesis of dental and periodontal lesions in children with X-linked hypophosphatemic rickets. Eur J Paediatr Dent. 2006;7(2):61-6.

24. Haffner D, Emma F, Eastwood DM, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. Nat Rev Nephrol. 2019;15(7):435-55.

25. Seow WK, Needleman HL, Holm IA. Effect of familial hypophosphatemic rickets on dental development: a controlled, longitudinal study. Pediatr Dent. 1995;17(5):346-50.

26. Al-Jundi SH, Dabous IM, Al-Jamal GA. Craniofacial morphology in patients with hypophosphataemic vitamin-D-resistant rickets: a cephalometric study. J Oral Rehabil. 2009;36(7):483-90.

27. Lewis MA, Meechan C, MacFarlane TW, Lamey PJ, Kay E. Pres-

entation and antimicrobial treatment of acute orofacial infections in general dental practice. Br Dent J. 1989;166(2):41-5.

28. Connor J, Olear EA, Insogna KL, et al. Conventional therapy in adults with X-Linked hypophosphatemia: effects on enthesopathy and dental disease. J Clin Endocrinol Metab. 2015;100(10):3625-32.

29. Lupi-Pegurier L, Bertrand M-F, Muller-Bolla M, Rocca JP, Bolla M. Periapical status, prevalence and quality of endodontic treatment in an adult French population. Int Endod J. 2002;35(8):690-7.

30. Beck-Nielsen SS, Brusgaard K, Rasmussen LM, et al. Phenotype presentation of hypophosphatemic rickets in adults. Calcif Tissue Int. 2010;87(2):108-19.

31. Ye L, Liu R, White N, Alon US, Cobb CM. Periodontal status of patients with hypophosphatemic rickets: a case series. J Periodontol. 2011;82(11):1530-5.

32. Resnick D. Implant placement and guided tissue regeneration in a patient with congenital vitamin D-resistant rickets. J Oral Implantol. 1998;24(4):214-8.

33. Friberg B. Brånemark system implants and rare disorders: a report of six cases. Int J Periodontics Restorative Dent. 2013;33(2):139-48.

34. Lee BN, Jung HY, Chang HS, Hwang YC, Oh WM. Dental management of patients with X-linked hypophosphatemia. Restor Dent Endod. 2017;42(2):146-51.