Vincitore del Premio Falcolini 2023

The care of the patient with X-linked hypophosphatemic rickets

I. Capotosti[1], G.I. Baroncelli[2], S. Ligori[1], E. Zampollo[1], M.R. Giuca[1], E. Carli[1]

[1]*Department of Surgical, Medical, Molecular and Critical Area Pathology, Unit of Pediatric Dentistry, University of Pisa, Pisa, Italy*

[2] *Pediatric and Adolescent Endocrinology, Division of Pediatrics, Department of Obstetrics, Gynecology and Pediatrics, University Hospital, Pisa, Italy*

Email: isacapo@hotmail.it

DOI 10.23804/ejpd.2024.25.04.02

Abstract

Aim X-linked hypophosphatemic rickets (XLH) is characterised by severe skeletal deformities and dental abnormalities. The aim of this work is to examine the prevalence of abscesses, the features of pulp chambers, and the biochemical and histological signs of the disease.

Methods Pulp chambers size, shape, and morphology were assessed by orthopantomography in XLH patients (n = 24, age 5.8 ± 1.6 years) and in sex and age-matched healthy controls (n = 23, age 6.2 ± 1.4 years). Histological analysis of the dentin of the primary teeth by Hematoxylin-eosin and Massontrichromic Goldner-blue aniline staining was then performed, comparing the results with those obtained in healthy controls.

Results XLH patients showed enlarged pulp and altered morphology with prominent pulp horns into the tooth crown. Deficiency of 1,25-dihydroxyvitamin D induced by Fibroblast Growth Factor 23 resulted in enamel, dentin, and cement defects. Histological analysis demonstrated a poor mineralisation of these structures with significant irregularities. Patients with a history of abscesses were 67; canines and molars are less affected than incisors.

Conclusions Enlarged pulpal chambers with altered shape and morphology affect most XLH patients, setting them up for periapical abscesses with fistulas occurred without any history of trauma or dental decay. Patients with XLH should be considered high-risk patients. It is important to treat and manage them early by a multidisciplinary approach.

KEYWORDS X-linked hypophosphatemia, periapical dental abscesses, PHEX gene, dentin enamel, periodontal disease.

Introduction

X-linked hypophosphatemia (XLH; OMIM 307800) is the most common genetic form of rickets, with a prevalence of 1:20,000 - 1:60,000 [Baroncelli et al., 2006]. XLH is characterised by stunted growth with disproportionate short stature, bowing of the lower limbs associated with wadding gait, [Carpenter et al., 2011; Haffner et al., 2019] . XLH is due to inactivating mutations of the PHEX gene (OMIM: 300550) causing excessive production of Fibroblast Growth Factor 23 (FGF23). The increased concentration of FGF23 represents a main pathogenetic mechanism of XLH, stimulating urinary phosphate wasting and renal 24-hydroxylase activity, and reducing renal 1α-hydroxylase activity with insufficient production of 1,25-dihydroxyvitamin D (1,25$(OH)_2$D) [Nakanishi and Michigami, 2022]. PHEX protein is also expressed in osteoblasts, osteocytes, and odontoblasts [Tagliabracci et al., 2014]. In patients with XLH, FGF23-induced 1,25$(OH)_2$D insufficiency results in poor mineralisation of enamel [Beck-Nielsen et al., 2019]. Regardless of its systemic effects on phosphate homeostasis, odontoblast differentiation and dentin formation, FGF23 overexpression decreased osteoblast differentiation and matrix mineralisation. Without signs of trauma or dental decay, XLH patients experience dentinal and periodontal anomalies that lead to recurrent periapical abscesses with fistulas. The aim of the study was to evaluate the size, shape, and morphology of the pulp chambers as well as the disease's biochemical and histological indicators using orthopantomography (OPT) testing.

Materials and Methods

Nine male and fifteen female Caucasian prepubertal XLH patients, with an average age of 5.8 ± 1.6 years, were selected from the University Hospital's Endocrine Unit of Pediatrics. Twenty-three Caucasian prepubertal children (11 boys and 12 girls), aged 6.2 ± 1.4 years, were enrolled as controls. The OPT examination was used to evaluate the size, shape, and morphology of the pulp chamber in each patient. The Cameriere et al.[2012] approach was used to estimate the size of the pulp chamber. In dental examinations, the prevalence of abscesses or fistulae was assessed by evaluating the aetiology of the lesion and location. Histologic analysis of dentin of primary teeth was performed by Hematoxylin-eosin (EE) and Massontrichromic Goldner-blue aniline staining and scanning electron microscopic examination (SEM-EDS) comparing the results with those obtained in primary teeth of controls. The measurements between patients and controls were compared using Wilcoxon's nonparametric rank-sum test (Mann-Whitney).

Results

The pulp chamber appeared significantly larger, with pulpal horns close to the occlusal plane, in the primary teeth and first permanent molars of XLH patients compared with healthy controls. There was a decrease in fusion of calciospheres and an excess of interglobular dentin that did not mineralise. The rate of spontaneous abscesses was 67% in patients with XLH; incisors were more affected than canines and molars. Histological analysis showed inhomogeneous dentin with significant structural irregularities and extensive areas of loss of substance especially at the amelo-dentinal junction. Figure 1 showed the main clinical, radiographic, and histologic features in patients compared with controls.

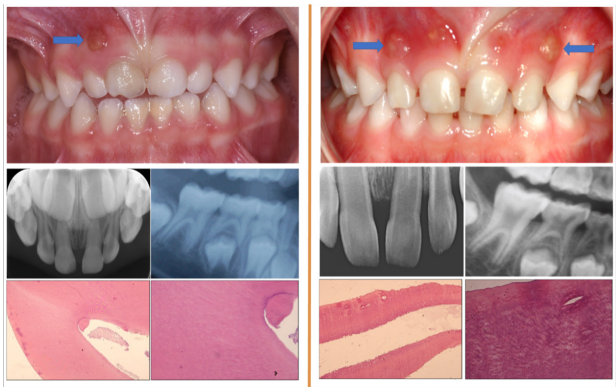

FIG. 1 Clinical, radiographic, and histologic features between controls (left) and XLH patients (right).

Discussion

The study showed that the periapical abscesses with fistulae occurred without any history of trauma or dental decay in patients with XLH, and it was mainly due to aberrant dentin mineralisation. FGF23 overexpression likely suppress osteoblast differentiation and matrix mineralisation independently of its systemic effects on phosphate homeostasis [Duggal et al., 2002] as well as odontoblasts differentiation and dentin formation [Burgueño Torres et al., 2015]. Even in the absence of carious lesions, deep fissures from the pulp horns to the dentin-enamel junction are risk factors for bacterial penetration and the development [Duggal et al., 2002] of periapical abscesses that more commonly afflicted the incisors. The incisors' higher vulnerability may be partially explained by the age range of the individuals under examination and the differences in eruption timing between canines, molars, and incisors [Burgueño Torres et al., 2015]. In contrast to primary molars, primary incisors and canines may be more susceptible to enamel cracks due to thinner enamel in front teeth than in posterior primary teeth [Elfrink et al., 2016; Tosco et al., 2023; Corica and Caprioglio, 2014]. The OPT analysis revealed several variations in the morphology, size, and shape of pulp chambers between controls and XLH patients. XLH patients showed enlarged pulp chambers because of a bigger surface of the pulp chamber with respect to the tooth surface, abnormal shape due to a greater height than the width and altered morphology with prominent pulp horns into the tooth crown. In addition, a lack of pyrophosphate hydrolysis and reduced hydroxyapatite formation and mineralisation lead to an increased risk of developing periodontal disease. The extensive areas of interglobular dentin found on histological analysis, with abundant amounts of spheroidal formations ("calcareous spherules"), were an expression of abnormal mineralisation process of dentin tissue.

Conclusions

The paediatric dentist should always suspect an impairment of phospho-calcium metabolism in children showing uncaused periodontal abscesses and require bone specialist and genetic investigations. Periodontal abscesses are peculiar lesions of patients with XLH. They should be considered high-risk patients [Franciosi et al., 2024], so it is important to treat and manage them early with a multidisciplinary approach [Cenzato et al., 2024; Giuca, 2024], including appropriate medical treatment. It is important to set up individualised recalls, with professional oral hygiene, professional fluoroprophylaxis [Zampetti and Scribante, 2020], and fissure sealing [Colombo and Ferrazzano, 2018] and motivate the parents for proper home oral hygiene and diet.

Acknowledgement

This work is generated within the European Reference Networks for Rare Bone Diseases (BONDERN). G. Baroncelli is a representative of the BOND-ERN.

References

› 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 Jun;7(2):61-6. PMID: 16842025.
› Beck-Nielsen SS, Mughal Z, Haffner D, Nilsson O, Levtchenko E, Ariceta G, de Lucas Collantes C, Schnabel D, Jandhyala R, Mäkitie O. FGF23 and its role in X-linked hypophosphatemia-related morbidity. Orphanet J Rare Dis. 2019 Feb 26;14(1):58. doi: 10.1186/s13023-019-1014-8. PMID: 30808384; PMCID: PMC6390548.
› Burgueño Torres L, Mourelle Martínez MR, and De Nova García JM, " A study on the chronology and sequence of eruption of primary teeth in Spanish children. 2015 Dec; PMID: 26637254," Eur J Paediatr Dent., vol. 16, no. 4, pp. 301–4., 2015.
› Cameriere R, De Luca S, Alemán I, Ferrante L, Cingolani M. Age estimation by pulp/tooth ratio in lower premolars by orthopantomography. Forensic Sci Int. 2012 Jan 10;214(1-3):105-12. doi: 10.1016/j.forsciint.2011.07.028. Epub 2011 Aug 6. PMID: 21821373.
› Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. J Bone Miner Res. 2011 Jul;26(7):1381-8. doi: 10.1002/jbmr.340. Epub 2011 May 2. Erratum in: J Bone Miner Res. 2015 Feb;30(2):394. PMID: 21538511; PMCID: PMC3157040.
› Cenzato N, Crispino R, Galbiati G, Giannini L, Bolognesi L, Lanteri V, Maspero C. Premature loss of primary molars in children: space recovery through molar distalisation. A literature review. Eur J Paediatr Dent. 2024 Mar 1;25(1):72-76. doi: 10.23804/ejpd.2024.2110. Epub 2024 Feb 1. PMID: 38353522.
› Colombo S, Ferrazzano GF. Dental Sealants. Part 2: Who should get dental sealants and when. Eur J Paediatr Dent. 2018 Jun;19(2):165-166. doi: 10.23804/ejpd.2018.19.02.13. PMID: 29790783.
› Corica A, Caprioglio A. Meta-analysis of the prevalence of tooth wear in primary dentition. Eur J Paediatr Dent. 2014 Dec;15(4):385-8. PMID: 25517585.
› Duggal MS, Nooh A, High A. Response of the primary pulp to inflammation: a review of the Leeds studies and challenges for the future. Eur J Paediatr Dent. 2002 Sep;3(3):111-4. PMID: 12870998.
› Elfrink ME, Kalin K, van Ruijven LJ, ten Cate JM, Veerkamp JS. MicroCT study on the enamel mineral density of primary molars. Eur J Paediatr Dent. 2016 Mar;17(1):60-4. PMID: 26949242.
› Franciosi G, Fornich S, Di Matteo C, Malvicini G, Marruganti C, Grandini S, Gaeta C. Environmental risk factors analysis in paediatric oral health: a cross-sectional study. Eur J Paediatr Dent. 2024 Apr 1:1. doi: 10.23804/ejpd.2024.1987. Epub ahead of print. PMID: 38655744.
› Giuca MR. Rare diseases: a challenge in paediatric dentistry. Eur J Paediatr Dent. 2024 Sep 3;25(3):171-171. doi: 10.23804/ejpd.2024.25.03.01. Epub 2024 Sep 1. PMID: 39212455.
› Haffner D, Emma F, Eastwood DM, Duplan MB, Bacchetta J, Schnabel D, Wicart P, Bockenhauer D, Santos F, Levtchenko E, Harvengt P, Kirchhoff M, Di Rocco F, Chaussain C, Brandi ML, Savendahl L, Briot K, Kamenicky P, Rejnmark L, Linglart A. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. Nat Rev Nephrol. 2019 Jul;15(7):435-455. doi: 10.1038/s41581-019-0152-5. PMID: 31068690; PMCID: PMC7136170.
› Nakanishi T, Michigami T. Pathogenesis of FGF23-Related Hypophosphatemic Diseases Including X-linked Hypophosphatemia. Endocrines. 2022; 3(2):303-316. https://doi.org/10.3390/endocrines3020025
› Tagliabracci VS, Engel JL, Wiley SE, Xiao J, Gonzalez DJ, Nidumanda Appaiah H, Koller A, Nizet V, White KE, Dixon JE. Dynamic regulation of FGF23 by Fam20C phosphorylation, GalNAc-T3 glycosylation, and furin proteolysis. Proc Natl Acad Sci U S A. 2014 Apr 15;111(15):5520-5. doi: 10.1073/pnas.1402218111. Epub 2014 Mar 26. PMID: 24706917; PMCID: PMC3992636.
› Tosco V, Delfina Valloreo R, Petricca MT, Furlani M, Tripodi D. Relationship between external and internal structures in deciduous teeth: a multidisciplinary study. Eur J Paediatr Dent. 2023 Dec 1;24(4):282-286. doi: 10.23804/ejpd.2023.1882. PMID: 38015111.
› Zampetti P, Scribante A. Historical and bibliometric notes on the use of fluoride in caries prevention. Eur J Paediatr Dent. 2020 Jun;21(2):148-152. doi: 10.23804/ejpd.2020.21.02.10. PMID: 32567947.