Annotated Bibliography
***The Causal Link Between Premature Dental Abscess and X-Linked Hypophosphatemia* (February 2012)**

By

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February 20, 2012

This annotated bibliography and a compilation of existing evidence from the XLH Network online community, aggregates the empirical research linking premature dental abscesses and pathogenesis associated with the metabolic disorder X-LINKED HYPOPHOSPHATEMIA (XLH).

Annotated Bibliography
The Causal Link Between Premature Dental Abscess and
X-Linked Hypophosphatemia

This annotated bibliography is a compilation of empirical resources derived from medical Research databases (e.g. PUBMED, MEDLINE). Also, included are three full-length, *Creative Commons* licensed research publications offering insight into the relationship and documented LINK between the metabolic disorder, X-Linked Hypophosphatemia (XLH) and dental abscesses. Related online conversations on the XLH Network between those directly affected with XLH and how they are addressing the associated complications is included. Proprietary information from these conversations has been removed to protect their identity. This aggregation of **35** research studies between years provides strong evidence of a causal link.

The purpose of this paper is to provide substantiated evidence demonstrating that the high frequency of abscess teeth is directly linked to the XLH metabolic disorder. The causation of an abnormally high incidence and early onset of dental abscesses are attributed not to dental care but to an incurable MEDICAL disorder.

Database search parameters included the following keywords: XLH, dental, adolescent, adult, Dentin; Female; Gene Expression; Humans; Hypophosphatemia, Familial; Kidney; Linkage (Genetics); Male; Mutation; Odontometry; Phosphates; Sex Factors; Tooth; X Chromosome

ITEMS IN YELLOW, BOLD UNDERLINE emphasis was added.

This document will be updated periodically based on the publication of related literature.

It is my hope that this document contributes to the understanding of the XLH disorder and treatment of dental irregularities. Bottom line: Medical insurance **must** provide coverage for the dental abscesses and treatment.

G. Andrew Page, PhD
Anchorage, AK
February 8, 2012

SECTION I: Annotated Bibliography

This first of three sections includes XX citations and their abstracts.

The first reference provides a recent update answering the definitive question: What is XLH?"

RESEARCH PUB #1

Raghbir Kaur A Clinician's Guide to X-Linked Hypophosphatemia. Journal of Bone and Mineral Research, Volume 26, No. 7, pp.1-8 DOI: 10.1002/jbmr:340

Abstract

Many messages on this reflector ask, "What should my doctor, who has never heard of XLH, do?" The frequent response is, "Have your physician consult with an expert." Well, I guess the experts at Yale got tired of answering the same questions. In August of 2010, they submitted an article to the **Journal of Bone and Mineral Research, titled, "A Clinician's Guide to X-Linked Hypophosphatemia.**"

RESEARCH PUBLICATION #2

ASDC J Dent Child. 1986 May-Jun;53(3):223-6.

Hereditary hypophosphatemia rickets: an important awareness for dentists.

Herbert FL.

Abstract

Because X-linked hypophosphatemia VDRR is reported to be the most common form of rickets in the United States today, it is important for dentists to be aware of this condition. Characteristic dental findings are often the first clinically noticeable signs of the disease. The confirmation of hypophosphatemia with dental findings will permit early diagnosis and prevent crippling rachitic deformities, otherwise certain to follow. Reports in the literature confirm the validity of conservative, **prophylactic full coverage restorations in patients with VDRR**.

PMID:3011866 [PubMed - indexed for MEDLINE]

RESEARCH PUBLICATION #3

X-linked hypophosphatemia: the mutant gene is expressed in teeth as well as in kidney. **E D Shields, C R Scriver, T Reade, T M Fujiwara, K Morgan, A Ciampi, S Schwartz Am J Hum Genet Mar 1990 (Vol. 46, Issue 3, Pages 434-42).**

MEDLINE

Abstract

Mutation at a locus (HPDR) on the X chromosome (McKusick 30780 [HPDR1]; 30781 [HPDR2]) causes impaired renal phosphate transport, hypophosphatemia, and an associated **impairment in the process of mineralization in bone and teeth** (X-linked hypophosphatemia [XLH]). We measured the dental pulp profile area (PRATIO [= pulp area/tooth area]) and serum phosphorus (Pi) values in uniformly treated XLH patients (six males, 81 teeth, 1,457 Pi values; 11 females, 129 teeth, 1,439 Pi values). Serum Pi values, reflecting the metabolic environment of tooth development, were obtained by repeated measurement between 1 mo and 26 years of age during treatment. PRATIO values calculated from standardized Rinn radiographs were used as outcome measurements of tooth development in XLH patients and in age-matched controls (12 males, 100 teeth; 27 females, 275 teeth). Age-dependent serum Pi values were not different in the treated XLH males and females. In teeth forming primary dentin there was no gene dosage effect on PRATIO values apparent in subjects below 15 years of age. However, in teeth forming secondary dentin a gene dosage was found in the subjects aged 15 to 25 years: XLH male teeth (n = 65) mean +/- SD = 0.163 +/- 0.046; XLH female teeth (n = 75) mean +/- SD =

0.137 +/- 0.039; control teeth (n = 209) mean +/- SD = 0.116 +/- 0.023; (higher PRATIO values mean less development or mineralization of secondary dentin); differences in these PRATIO values (males vs. female and XLH vs. control) were significant by mixed-model analysis of variance.(ABSTRACT TRUNCATED AT 250 WORDS)

RESEARCH PUBLICATION #4

PMCID: PMC31866
Proc Natl Acad Sci U S A. 2001 April 10; 98(8): 4516–4521. Published online 2001 April 3. doi: 10.1073/pnas.081075198
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Cell Biology

Differentiation of embryonic mesenchymal cells to odontoblast-like cells by overexpression of dentin matrix protein 1

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Communicated by Emanuel Margoliash, University of Illinois, Chicago, IL
Received October 20, 2000; Accepted February 14, 2001.
This article has been cited by other articles in PMC.

Cells of the craniofacial skeleton are derived from a common mesenchymal progenitor. The regulatory factors that control their differentiation into various cell lineages are unknown. To investigate the biological function of dentin matrix protein 1 (DMP1), an extracellular matrix gene involved in calcified tissue formation, stable transgenic cell lines and adenovirally infected cells overexpressing DMP1 were generated. The findings in this paper demonstrate that overexpression of DMP1 in pluripotent and mesenchyme-derived cells such as C3H10T1/2, MC3T3-E1, and RPC-C2A can induce these cells to differentiate and form functional odontoblast-like cells. Functional differentiation of odontoblasts requires unique sets of genes being turned on and off in a growth- and differentiation-specific manner. The genes studied include transcription factors like core binding factor 1 (Cbfa1), bone morphogenetic protein 2 (BMP2), and BMP4; early markers for extracellular matrix deposition like alkaline phosphatase (ALP), osteopontin, osteonectin, and osteocalcin; and late markers like DMP2 and dentin sialoprotein (DSP) that are expressed by terminally differentiated odontoblasts and are responsible for the formation of tissue-specific dentin matrix. However, this differentiation pathway was limited to mesenchyme-derived cells only. Other cell lines tested by the adenoviral expression system failed to express odontoblast-phenotypic specific genes. An *in vitro* mineralized nodule formation assay demonstrated that overexpressed cells could differentiate and form a mineralized matrix. Furthermore, we also demonstrate that phosphorylation of Cbfa1 (osteoblast-specific transcription factor) was not required for the expression of odontoblast-specific genes, indicating the involvement of other unidentified odontoblast-specific transcription factors or coactivators. Cell lines that differentiate into odontoblast-like cells are useful tools for studying the mechanism involved in the terminal differentiation process of these postmitotic cells.

RESEARCH PUBLICATION #5

Familial hypophosphatemic vitamin D-resistant rickets--prevention of spontaneous dental abscesses on primary teeth: a case report.

Douyere D, Joseph C, Gaucher C, Chaussain C, Courson F.

Department of Pediatric Dentistry, Dental School, Bretonneau Hospital, AP-AH, Paris Descartes

University, Paris, France.

Abstract
Familial hypophosphatemic vitamin D-resistant rickets is a hereditary disease generally transmitted as an X-linked dominant trait and characterized by distinctive general clinical signs. Dental features **include spontaneous dental abscesses that occur in the absence of a history of trauma or dental decay.** The challenge for the dentist is to prevent and treat these lesions. This report describes the case of a young hypophosphatemic boy with abscesses. In this case, the application of fluid resin composites with a self-etching primer bonding system to all primary teeth prevented abscess formation for more than 1 year and thus avoided endodontic treatment or extraction. This constitutes a new approach to the prevention of **spontaneous abscesses on primary teeth in children with familial hypophosphatemic rickets**. **PMID: 19201216**

RESEARCH PUBLICATION #6

Gaucher C, Boukpessi T, Septier D, Jehan F, Rowe PS, Garabédian M, Goldberg M, Chaussain-Miller C: **Dentin noncollagenous matrix proteins in familial hypophosphatemic rickets.** *Cells Tissues Organs*; 2009;189(1-4):219-23
[Source] The source of this record is MEDLINE®, a database of the U.S. National Library of Medicine.

ABSTRACT
Dentin noncollagenous matrix proteins in familial **hypophosphatemic rickets**.
Familial **hypophosphatemic rickets** is transmitted in most cases as an X-**linked dominant** trait and results from the mutation of the PHEX gene predominantly expressed in osteoblast and odontoblast. Patients with **rickets** have been reported to display important dentin defects.Our purpose was to explore the structure, composition and distribution of noncollagenous proteins (NCPs) of **hypophosphatemic** dentin. We collected teeth from 10 **hypophosphatemic** patients whose mineralization occurred either in a **hypophosphatemic** environment or in a corrected phosphate and vitamin nvironment. In conclusion, dentin mineralization in a corrected phosphate and vitamin D environment compensates the adverse effect of PHEX mutation.
[MeSH-major] Dentin / metabolism. Extracellular Matrix Proteins / metabolism. **Hypophosphatemic Rickets**, X-**Linked Dominant** / metabolism

RESEARCH PUBLICATION #7

Chaussain-Miller C, Sinding C, Wolikow M, Lasfargues JJ, Godeau G, Garabedian M. Dental abnormalities in patients with familial hypophosphatemic vitamin D-resistant rickets: prevention by early treatment with 1-hydroxyvitamin D. J Pediatr. 2003 Mar;142(3):324-31. PMID: 12640383

Abstract
OBJECTIVE:
To evaluate the dental effects of 1-hydroxylated vitamin D3 treatment in patients with familial hypophosphatemic vitamin D-resistant rickets. Study design Forty-eight children and adult patients were included in the study; 16 had received no treatment or phosphate supplements with vitamin D/25-(OH) D3 before puberty. The 32 younger ones had received phosphate supplements with 1alpha-(OH)D3 from infancy. All patients were clinically examined, and panoramic and periapical radiographs were made. Evaluations of decayed, missing, or filled teeth and decayed or filled teeth indexes and of pulp ratios allowed comparison with healthy age-matched control patients.

RESULTS:
Poor dental health and characteristic dental anomalies were found in the 16 older patients. In contrast, the 32 younger patients had a normal dental status as regards reference ranges in healthy age-matched populations, although they still showed prominent pulp horns on deciduous teeth and increased pulp area/tooth area ratios.

CONCLUSIONS:
This investigation shows the beneficial effects of 1alpha-(OH)D3 treatment on the dental status of vitamin D-resistant rickets patients and emphasizes the necessity of early treatment. Remaining defects may result from early exposure of odontoblasts and surrounding osteoblasts to hypophosphatemia, before the commencement of treatment, and/or from intrinsic cell disturbances linked to the genetic alteration(s).

RESEARCH PUBLICATION #8

Shroff DV, McWhorter AG, Seale NS. Evaluation of aggressive pulp therapy in a population of vitamin D-resistant rickets patients: a follow-up of 4 cases. Pediatr Dent. 2002 Jul-Aug;24(4):347-9. PMID: 12212880

Abstract
This investigation collected clinical and radiographic data from a retrospective chart review of 4 patients receiving prophylactic formocresol pulpotomies and stainless steel crowns following a dental abscess associated with a medical diagnosis of vitamin-D resistant rickets (VDRR) at Texas Scottish Rite Hospital for Children in Dallas, Tex. Clinical and radiographic data were available for 29 primary teeth in 4 children, with follow-up times ranging from 2 years, 1 month to 5 years, 6 months. Based on available recalls of **29 teeth treated following the prophylactic formocresol pulpotomy, 22 failed clinically**. The earliest failure occurred at 3 months; the longest time to failure was 3 years, 9 months. No trends were discernable between tooth type and failure rate, although the shorter the time between eruption of the tooth and pulpotomy treatment, the greater the chance of success. Presently, **there is not enough evidence to suggest that prophylactic pulpotomy therapy in VDRR patients is beneficial in preserving their primary dentition.**

RESEARCH PUBLICATION #9

Murayama T, Iwatsubo R, Akiyama S, Amano A, Morisaki I.; Oral Surg Oral Med Oral Pathol Familial hypophosphatemic vitamin D-resistant rickets: dental findings and histologic study of teeth. Oral Radiol Endod. 2000 Sep;90(3):310-6.PMID: 10982952

Abstract
A case of familial hypophosphatemic vitamin D-resistant rickets or X-linked hypophosphatemia (XLH) accompanied by specific systemic and dental findings is reported. A 15-year-old boy with XLH visited our facility complaining of a toothache in the left lower canine region. Two other family members of the patient, his younger sister and their mother, also had XLH, whereas the other 2 members, his younger brother and father, are healthy. Those with XLH show systemic signs of the disease, such as growth retardation, limb deformity, and spinal curvature disorders; however, these symptoms **are more severe in the patient than in the others. The patient had multiple periodontal abscesses**, but no evidence of dental caries, trauma, or periodontal disease on the corresponding teeth at the time of his oral examination. A radiographic examination showed root dysplasia and enlarged pulp chambers.A histologic examination of an extracted third molar showed marked globular dentin and an increased predentin width. The abscess was thought to be caused by pulpal infection, which came from bacterial invasion through enamel cracks and dentinal microcleavage of the teeth. The treatments provided in this case are discussed.

RESEARCH PUBLICATION #10

Pex mRNA is localized in developing mouse osteoblasts and odontoblasts.
Ruchon AF, Marcinkiewicz M, Siegfried G, Tenenhouse HS, DesGroseillers L, Crine P, Boileau G.;J Histochem Cytochem. 1998 Apr;46(4):459-68. PMID: 9524191

Abstract
Mutations in PEX, a phosphate-regulating gene with homology to endopeptidase on the X chromosome, were recently identified in patients with X-linked hypophosphatemia (XLH), an inherited disorder of phosphate homeostasis characterized by growth retardation and rachitic and osteomalacic bone disease. To understand the mechanism by which loss of PEX function elicits the mutant phenotype, a study of its mRNA localization and ontogenesis was undertaken. Using the reverse transcriptase-nested polymerase chain reaction (RT-nested PCR) with polyA+ RNA purified from mouse testis, a 337-bp Pex cDNA fragment was generated and cloned in the pCRII plasmid. The cDNA was used to generate sense and anti-sense Pex riboprobes for in situ hybridization (ISH) and Northern analysis. To survey a large number of different tissues, sagittal sections of embryos and newborn mice were examined. ISH showed the presence of Pex mRNA in osteoblasts and odontoblasts. Pex gene expression was detectable on Day 15 of embryonic development, which coincides with the beginning of intercellular matrix deposition in bones. Finally, Northern analysis of total RNA from calvariae and teeth of 3-day-old and adult mice showed that the abundance of the 7-kb Pex transcript is decreased in adult bones and in nongrowing teeth. **The present study demonstrates that Pex mRNA is expressed in bones and teeth** and suggests that this putative endopeptidase plays an important role in the development of these tissues.

RESEARCH PUBLICATION #11

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. PMID: 10321209

Abstract
There continues to be increased expansion of implant services corresponding to the public's increased awareness of implant-borne prostheses as a **regular part of treatment planning**. This rise in public awareness as practitioners expand their skills will lead to the consideration of an implant option for growing groups of patients whose medical histories may have previously contraindicated implantology. This presentation is one such case.

RESEARCH PUBLICATION #12

Am Dent Assoc. 1976 Jan;92(1):120-9.

Origin, diagnosis, and treatment of the dental manifestations of vitamin D-resistant rickets: review of the literature and report of case.

Cohen S, Becker GL.

Abstract
Previous discussions center on early diagnosis, initial treatment, and follow-up therapy for the patient with vitamin D-resistant rickets. Both the medical and dental aspects of treatment for these patients has a long-range effect on the normal developmental patterns. Although treatment is begun at an early age, some rachitic skeletal effects such as minor bowing of the legs and bossing of the skull will invariably be noticed. **In patients with controlled rickets the alveolar processes undergo normal development, with apparent normal dental eruption**. The poor development and calcification of the alveolus seen in the untreated patient leads to loss of the lamina dura and periodontal ligament of the teeth. Patients with resistant rickets possess a functional dentition, although not without inherent defects. Various degrees of fracture and attrition of enamel can be seen, and hypoplasia of dentin is nearly a universal result. Defects extending to the dentinoenamel junction have been shown in repeated cases. Cementum, because of its close relationship with dentin calcification, also appears abnormal. Pulp tissue may undergo abberations of physiology in resistant rickets, although further work in this respect is needed. With respect to the possible dental pathoses seen in this disease, the dental history of the patient with resistant rickets discussed in this report showed that several of the deciduous teeth, possibly the mandibular left second premolar and right first molar, and definitely the maxillary right second premolar and canine and the mandibular left canine had all undergone pulpal degeneration of apparently unknown causation. In the maxillary right second premolar and the mandibular left canine, enamel fractures were clinically and radiographically apparent. However, the maxillary right canine originally had an acute abscess with no defects other than normal, minimal wear facets. No causative factor for its necrosis could be found. Overt enamel fractures in the maxillary right second premolar and the mandibular left canine may have led to microexposures of the pulp with subsequent bacterial pulpal contamination. Suppuration present in several of the pulps when first entered during endodontic treatment, as well as chronic fistulas in several areas, support the conclusion that contamination by some means does indeed occur.

RESEARCH PUBLICATION #13

Orthodontic treatment of a patient with hypophosphatemic vitamin D-resistant rickets. Kawakami M, Takano-Yamamoto T.; ASDC J Dent Child. 1997 Nov-Dec;64(6):395-9.
PMID: 9466008

Abstract
Hypophosphatemic vitamin D-resistant rickets, when developed later in life, is less severe and may not be characterized by rickets or other osseous deformities. A Japanese girl, age nine years and one month, was first seen in the Dental Hospital of Osaka University, complaining of the crowding of the maxillary teeth. At one year of age, the patient was admitted to Osaka University Hospital for her leg deformities. Although the patient has been administered 4 micrograms 1 alpha/-hydroxyvitamin D3 and 1.0 g phosphorous daily, the serum phosphate has been low and never reached normal level. This case was a Class II division 2 malocclusion with severe anterior crowding and retarded mandibular growth. We treated her with a functional appliance (elastic open activator), followed by the extraction of four premolars and the use of an edgewise appliance. No unfavorable root resorption or bone defect occurred. Good occlusion was achieved and the facial features were pleasing.

RESEARCH PUBLICATION #14

Protein cDNA cloning of the murine Pex gene implicated in X-linked hypophosphatemia and evidence for expression in bone.Du L, Desbarats M, Viel J, Glorieux FH, Cawthorn C, Ecarot B.; Genomics. 1996 Aug 15;36(1):22-8. PMID: 8812412

Abstract
The recently identified human PEX gene apparently encodes for a neutral endopeptidase that is mutated in patients with X-linked hypophosphatemia. The 3' and 5' ends of the coding region of PEX have not been cloned, nor has the tissue expression of the gene been identified. Here we report the isolation and characterization of the complete open reading frame of the mouse Pex gene and the demonstration of its expression in bone. Mouse Pex cDNA is predicted to encode a protein of 749 amino acids with 95% identity to the available human PEX

sequence and significant homology to members of the membrane-bound metalloendopeptidase family. Northern blot analysis revealed a 6.6-kb transcript in bone and in cultured osteoblasts from normal mice that was not detectable in samples from the Hyp mouse, the murine homolog of human X-linked hypophosphatemia. Pex transcripts were, however, detectable in Hyp bone by RT-PCR amplification. Of particular interest, a cDNA clone from rat incisor shows 93% sequence identity to the 5' end of Pex cDNA, **suggesting that Pex may be expressed in another calcified tissue, the tooth**. The association of **impaired mineralization of bone and teeth and disturbed renal phosphate reabsorption** with altered expression of Pex suggests that the Pex gene product may play a critical role in these processes.

RESEARCH PUBLICATION #15

Mineral content of different areas of human dentin in hypophosphataemic vitamin D-resistant rickets
Hietala EL Larmas MA; J Biol Buccale (1991 Jun) 19(2):129-34 PMID: 92041779

Abstract

Calcium, phosphorus, fluoride, sodium, magnesium and zinc estimations were carried out on teeth from a patient with hypophosphataemic vitamin D-resistantrickets (HVDRR) and from a patient with acquired rickets with the aim of determining differences in the composition of dentine in these two types of rickets. Normal deciduous teeth served as controls. Mineral analyses were carried out using an electron probe micro-analyser after carefully polishing the hemisected specimens. After the analyses the specimens were coated with gold-palladium for more detailed SEM studies. The Ca, P, F and Zn contents of the calcospherites were normal, while there was more Na and less Mg in the dentine of HVDRR teeth than of controls. The significance of this remains unexplained.
The mineral content of the interglobular spaces was very limited, but there was more Zn in these than in other parts of the HVDRR teeth, in the acquired rickets teeth or in the control teeth. The excess of Zn in the interglobular spaces is thought to have an effect on the mineralisation process in HVDRR teeth. The globular nature of HVDRR teeth is thought to be genetically controlled and the result of a reduction in the number of calcification nuclei. The globular nature of the HVDRR teeth was not due to lack of Ca and P, as the serum levels of these minerals were maintained within normal limits during tooth development by controlled phosphate supplementation. Because in acquired rickets the globules were seen at the developmental stage that the teeth had reached when the nutritional disturbance occurred, the fault in **mineralisation** is thought to be different from that in HVDRR teeth.

RESEARCH PUBLICATION #16

The effect of medical therapy on dentin formation in vitamin D-resistant rickets
Seow WK; Pediatr Dent (1991 Mar-Apr.) 13(2):97-102 PMID: 91351905

Abstract

Vitamin D-resistant rickets (VDRR) is one of the most common forms of rickets in developed countries today. Widely practiced medical treatment regimens usually include replacing phosphorus and calcium lost through urination. In this study, 20 teeth from five patients with varying grades of dental manifestation of VDRR were examined to relate the institution of medical therapy with any observed improvement of dentin calcification. In all the teeth examined, there was no correlation between the time of appearance of dentin changes and the commencement of medical therapy. Furthermore, in several teeth from the patients with Grade III severity, there were no signs of improvement in dentin calcification even after prolonged medical therapy. This study suggests that **current medical treatment of VDRR has no beneficial effect on the dental structures and dentists should not rely on medical treatment to correct dental calcification problems.**

RESEARCH PUBLICATION #17

Oral manifestations of familial hypophosphatemic rickets after phosphate supplement therapy: a review

of the literature and report of case Larmas M, Hietala EL, Simila S, **Pajari U; ASDC J Dent Child 1991 Jul-g;58(4):328-34 PMID: 92042986**

ABSTRACT
The patient was a seven-year-old boy with familial vitamin D-resistant hypophosphatemic rickets. His mother, and her mother, were also affected. Before phosphate treatment was introduced in the patient, an impaired incorporation of calcium, and its exchange with sodium, was thought to be the principal etiological factor in the formation of globules. **Supplementation therapy** then resulted in a less elevated Ca/P ratio in the root area of the affected teeth, as well as a cure for the boy's bone structure. What the therapy **did not cure** was the globular appearance of the dentin and the hypomineralized stripe of pulpal horn extending to the cusp tips, an apparent permanent outcome of the disease.

RESEARCH PUBLICATION #18

Prevalence of dental abscess in a population of children with vitamin D-resistant rickets. McWhorter AG, Seale NS.; Pediatr Dent. 1991 Mar-Apr;13(2):91-6.
PMID: 1652746

Abstract
A population of patients with vitamin D-resistant rickets whose present ages range from 4 to 22 years was examined to determine the **prevalence of dental abscess associated with that condition.** For those patients affected with abscesses in the primary dentition, four associated factors were examined: 1) the age at onset of the first abscess; 2) the tooth/teeth most commonly involved; 3) whether or not other teeth were involved over time; and 4) the order of occurrence of multiple abscesses. Six of 24 patients (25%) were affected with abscesses of the primary dentition; **all had multiple abscesses**. Males were more commonly involved than females. The sequence of involvement generally followed the pattern of tooth eruption; however, dental treatment in susceptible individuals shortened the time between eruption and abscess. Medication dose and measurement of radiographs were not reliable predictors of the occurrence of abscesses in this population; however, the results indicate that **one abscess is a predictor of future abscesses for that patient.**

RESEARCH PUBLICATION #19

Familial hypophosphatemic vitamin D-resistant rickets: review of the literature and report of case. Fadavi S, Rowold E.; ASDC J Dent Child. 1990 May-Jun;57(3):212-5. Review. PMID: 2161025

Familial hypophosphatemia, commonly known as vitamin D-resistant rickets, is inherited in an x-linked dominant manner. This condition is characterized by impairment of renal tubular reabsorption of inorganic phosphate and is inherited as a sex-linked dominant trait. Early clinical signs, usually detected about two years of age, included lateral bowing of the lower extremities, scoliosis, and frontal bossing. **Characteristic dental findings are often the first clinically noticeable signs of the disease**. This case report describes the typical dental findings in a 10-year old Hispanic female.

RESEARCH PUBLICATION #20

Structural deformities of deciduous teeth in patients with hypophosphatemic vitamin D-resistant rickets. Abe K, Ooshima T, Lily TS, Yasufuku Y, Sobue S. Related Articles ; Oral Surg Oral Med Oral Pathol. 1988 Feb;65(2):191-8. PMID: 2830573

Abstract
Structural deformities of deciduous teeth from patients with hypophosphatemic vitamin D-resistant rickets (HVDRR) (1 male and 2 female patients) were examined by means of transmitted light microscopy, contact microradiography, and x-ray microanalysis. Freshly extracted teeth were fixed in formalin and subsequently hemisected longitudinally through the midline. One half was prepared for ground sections and the other half for

decalcified sections. Neither gross nor microscopic abnormalities were present in enamel of patients with HVDRR. The concentration of calcium and phosphorus and the calcium/phosphorus ratio of the enamel of patients with HVDRR were nearly equal to those of normal teeth, although the degree of radiopacity was less in HVDRR. On the other hand, **numerous microscopic abnormalities in the dentin of patients with HVDRR were found, such as interglobular dentin, wide predentin zones, and tubular defects.** The concentration of phosphorus in the dentin of a patient with familial HVDRR was extremely low. Furthermore, formation of reparative dentin was observed at the pulp horn of teeth in patients with HVDRR that had been subjected to definite attrition at the corresponding dentin site.

RESEARCH PUBLICATION #21

Oral findings in patients with autosomal dominant hypophosphatemic bone disease and X-linked hypophosphatemia: Further evidence that they are different diseases; Schwartz S, Scriver CR, Reade TM, Shields ED; Oral Surg Oral Med Oral Pathol 66:310-4, 1988 PMID: 2845325

Abstract

Oral examinations were performed on 5 patients with hypophosphatemic bone disease (HBD) (2 males and 3 females), 14 patients with X-linked hypophosphatemia (XLH), and 4 affected XLH relatives (6 males and 12 females). The control subjects were the unaffected siblings and parents of the patients and unrelated healthy, gender- and age-matched subjects. Serum phosphorus values were the same by disease type and gender in patients with HBD and XLH. They shared certain dental abnormalities, in particular pulpal necrosis and large pulp spaces. However, only patients with XLH had Class III malocclusions and mild enamel defects, and males with XLH had more severe occlusal and enamel defects than females with XLH. **Different dental phenotypes are further evidence that XLH and HBD** are different diseases. The dental abnormalities were **not prevented by treatment**, instituted early in life, which raised serum phosphorus to the near normal range.

RESEARCH PUBLICATION #22

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

Osaka University Faculty of Dentistry, Japan.

Abstract

Structural deformities of deciduous teeth from patients with hypophosphatemic vitamin D-resistant rickets (HVDRR) (1 male and 2 female patients) were examined by means of transmitted light microscopy, contact microradiography, and x-ray microanalysis. Freshly extracted teeth were fixed in formalin and subsequently hemisected longitudinally through the midline. One half was prepared for ground sections and the other half for decalcified sections. Neither gross nor microscopic abnormalities were present in enamel of patients with HVDRR. The concentration of calcium and phosphorus and the calcium/phosphorus ratio of the enamel of patients with HVDRR were nearly equal to those of normal teeth, although the degree of radiopacity was less in HVDRR. On the other hand, **numerous microscopic abnormalities in the dentin of patients with HVDRR were found,** such as interglobular dentin, wide predentin zones, and tubular defects. The concentration of phosphorus in the dentin of a patient with familial HVDRR was extremely low. Furthermore, formation of reparative dentin was observed at the pulp horn of teeth in patients with HVDRR that had been subjected to definite attrition at the corresponding dentin site.

PMID:2830573 [PubMed - indexed for MEDLINE]

RESEARCH PUBLICATION #23

Prophylactic dental treatment for a patient with vitamin D-resistant rickets: report of case. Breen GH.;

ASDC J Dent Child. 1986 Jan-Feb;53(1):38-43.

RESEARCH PUBLICATION #24

Management of the primary dentition in vitamin D-resistant rickets
Rakocz M, Keating III J, Johnson R ;Oral Surgery 66(3):166-171, 1982 PMID: 83013944

Abstract
Vitamin D-resistant rickets (familial hypophosphatemia) is a systemic disease secondary to defective renal-tubular reabsorption of phosphate. The major oral manifestations are spontaneous abscesses in a caries-free dentition. Pulpotomies or extractions were frequently described in the dental literature as the therapies of choice. This article presents a new prophylactic approach utilizing zinc oxide--eugenol pulpectomies and full crown coverage in an attempt to retain the primary dentition and prevent abscess formation.

RESEARCH PUBLICATION #25

The Journal of Pediatrics

Volume 116, Issue 3 , Pages 365-371, March 1990 Linear growth in patients with hypophosphatemic vitamin D-resistant rickets: Influence of treatment regimen and parental height Sonia Balsan Martin Tieder

Abstract
The effects of different treatment regimens and the influence of parental height on the statural growth of 40 patients with hereditary vitamin D-resistant hypophosphatemic rickets were investigated. Three treatment regimens, each with oral phosphate, were used: vitamin D (0.5 to 2 mg/day), calcidiol (50 to 200 µg/day), and 1α-hydroxyvitamin D_3 (1 to 3 µg/day). Mean duration of follow-up was 9.5±5.1 years. The results show that (1) there was no acceleration of growth before puberty for the majority of children treated with vitamin D (12/16) or calcidiol (13/15), whereas 1α-hydroxyvitamin D_3 promoted catch-up growth in 10 of 16 patients; (2) height gain during puberty was normal, irrespective of the treatment; (3) most vitamin D-treated male and female subjects and calcidiol-treated male subjects had short adult stature, but the majority (75%) of the 1α-hydroxyvitamin D_3-treated groups had normal stature; (4) parental stature had little influence on the adult height of male subjects, but that of affected girls was positively correlated ($p<0.002$) with mid-parental height. These results demonstrate that 1α-hydroxyvitamin D_3 is superior to vitamin D or calcidiol for improvement of stature of patients with hypophosphatemic vitamin D-resistant rickets, and indicate the importance of parental height in determining the adult height of affected girls.

RESEARCH PUBLICATION #26

Shields ED, Scriver CR, Reade T, Fujiwara TM, Morgan K, Ciampi A, et al. X-Linked hypophosphatemia: the mutant gene is expressed in teeth as well as in kidney. *Am J Hum Genet*. 1990;46:434–442 MEDLINE

Abstract
The Hyp mouse is a murine homolog of human X-linked hypophosphatemic rickets and displays hypo-mineralization in bone and dentin due to a defect of the phosphate-regulating gene with homology to endopeptidase on the X chromosome (Phex) gene. **It has long been considered that the bone and dentin defects in Hyp mice are caused by hypophosphatemia alone,** however, several recent studies have indicated the possibility that intrinsic defects are present in Hyp mice osteoblasts. Further, we previously found a hyper-expression of osteocalcin (OC) mRNA in Hyp mouse odontoblasts and suggested the possibility of the presence of intrinsic defects. In the present study, we evaluated morphological features and OC mRNA expression levels in tooth germs of Nor mice with a normal phex gene and a low concentration of serum phosphate, and compared

them to those in Hyp and wild-type mice. Nor mice exhibited low serum phosphate levels, however, did not show the characteristic features of dentin defects seen in Hyp mice, such as widened predentin and hyper-expression of OC mRNA.

RESEARCH PUBLICATION #27

ADHR Consortium, T. White KE, Evans WE, O'Riordan JLH, Speer MC, Econs MJ, Lorenz-Depiereux B, Grabowski M, Meittinger T, Strom TM. Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. *Nat Genet.* 2000;26:345–8. [PubMed]

Abstract

Proper serum phosphate concentrations are maintained by a complex and poorly understood process. Identification of genes responsible for inherited disorders involving disturbances in phosphate homeostasis may provide insight into the pathways that regulate phosphate balance. Several hereditary disorders of isolated phosphate wasting have been described, including X-linked hypophosphataemic rickets (XLH), hypophosphataemic bone disease (HBD), hereditary hypophosphataemic rickets with hypercalciuria (HHRH) and autosomal dominant hypophosphataemic rickets (ADHR). Inactivating mutations of the gene PHEX, encoding a member of the neutral endopeptidase family of proteins, are responsible for XLH (refs 6,7). ADHR (MIM 193100) is characterized by low serum phosphorus concentrations, rickets, osteomalacia, lower extremity deformities, short stature, bone pain and dental abscesses. Here we describe a positional cloning approach used to identify the ADHR gene which included the annotation of 37 genes within 4 Mb of genomic sequence. We identified missense mutations in a gene encoding a new member of the fibroblast growth factor (FGF) family, FGF23.

RESEARCH PUBLICATION #28

Connect Tissue Res. 2003;44 Suppl 1:33-40.

Six genes expressed in bones and teeth encode the current members of the SIBLING family of proteins.

Fisher LW, Fedarko NS.

Source

Matrix Biochemistry Unit, Craniofacial & Skeletal Diseases Branch, NIDCR, NIH, HHS, Bethesda, Maryland 20892-4320, USA. LFISHER@dir.nidcr.nih.gov

Abstract

Bone sialoprotein (BSP), dentin matrix protein 1 (DMP1), dentin sialophosphoprotein (DSPP), enamelin (ENAM), matrix extracellular phosphoglycoprotein (MEPE), and osteopontin (OPN) are glycophosphoproteins expressed in bones and/or teeth. Direct comparison of their amino acid sequences do not suggest that they belong to a single genetic family, but a detailed analysis of their **chromosomal location and gene structure does**. Analysis of human brain mRNA by RT-PCR has led to the discovery of two additional exons thereby making it more convincing that MEPE is a member of the SIBLING (Small Integrin-Binding LIgand, N-linked Glycoprotein) family. We propose that the members of this SIBLING family are extended, flexible proteins in solution that can facilitate the formation of a number of different complexes. For example, OPN can bridge complement Factor H to either an RGD-dependent integrin or to CD44 forming a membrane-bound complex that actively suppresses the alternate complement pathway. Two possible mechanisms for inhibiting the lytic pathway of alternate complement are presented.

PMID:12952171 [PubMed - indexed for MEDLINE]

RESEARCH PUBLICATION #29

J Endod. 2004 Apr;30(4):241-5.

Dental alterations associated with X-linked hypophosphatemic rickets.

Pereira CM, de Andrade CR, Vargas PA, Coletta RD, de Almeida OP, Lopes MA.

Source

Department of Semiology and Oral Pathology, School of Dentistry of Piracicaba, State University of Campinas, Piracicaba/SP, Brazil.

Abstract
The X-linked hypophosphatemic rickets is a rare metabolic disorder characterized by low serum phosphate levels caused by a decreased renal tubular reabsorption of inorganic phosphates. The initial complaints are a delay in the development of walking caused by deformity of the legs. **Oral findings include poorly mineralized dentin, enlarged pulp chambers and root canals, and periradicular abscesses in caries-free teeth**. We present three patients from the same family with X-linked hypophosphatemic rickets showing bone and dental alterations.

RESEARCH PUBLICATION #30

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;7:61–6. [PubMed]

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.

RESEARCH PUBLICATION #31

J Can Dent Assoc. 2006 Feb;72(1):69-72.

X-linked hypophosphatemia: dental and histologic findings.

Batra P, Tejani Z, Mars M.

Source

Institute of Dental Studies and Technologies, Delhi, India. pbatra87@hotmail.com

Abstract

The recurrent spontaneous formation of abscesses affecting multiple noncarious primary as well as permanent teeth is the principle clinical dental feature in cases of hypophosphatemia, a condition inherited through the X chromosome. **Patients often have high pulp horns, large pulp chambers and dentinal clefts.** We report a case of hypophosphatemic vitamin D-resistant rickets in a patient who reported to our department on multiple occasions with spontaneous abscesses in relation to his primary teeth. The aim of this article is to review the features of this disorder and to discuss the risks and benefits of the treatment options suggested in the literature.

SECTION II:XLH NETWORK Communication

NOTE: *The qualitative information in this section is email correspondence from the online XLH Network. To be accepted as a member of this network, an individual must have been diagnosed with XLH, be a validated parent of guardian of a child with XLH, or a physician or researcher interested in the study of XLH. For privacy reasons, any and all identifying information has been redacted.*

MISSION: THE XLH Network (http://xlhnetwork.org)

A worldwide patient support organization for people living and dealing with X-Linked Hypophosphatemia (XLH)

YC XLH

Rickets Research

X-linked Hypophosphatemic Rickets International Registry (HIC# 0907005408)

WHO:

- Exclusively for Patients with a Clinical Diagnosis of XLH

PURPOSE:

- To compile clinical data on XLH (age of diagnosis, symptoms, treatment history, etc.)
- To gain a greater understanding of the complex and varied profiles of patients with XLH
- To improve the global understanding of this disease
- To determine an accurate assessment of the incidence of XLH in the population worldwide

FUTURE GOALS:

- Resource for patients and families with XLH
- Connection between clinicians, researchers, and patients

FOR MORE INFORMATION & TO JOIN THE REGISTRY

CONTACT:

Yale Center for X-linked Hypophosphatemic Rickets

ycxlhinfo@yale.edu

APPROVED BY THE OCT 1 7 2010 Yale University Human Investigation Committee

Message:1
Date: Tue, 25 Oct 2011 15:48:41 +0100
From: **NAME REDACTED**
To: XLH List <f-hypdrr@xlhnetwork.org>
Subject: [F-HYPDRR] Dental implants

Hello everybody.
I have had a terrible time with my teeth over the last few years but I've found a really good dentist now and with good treatment I've not had an abscess for nearly a year. I was having them on a monthly basis last year so this is progress!

However, he was attempting to restore a badly broken down tooth today and it snapped. He and his colleague aren't optimistic about saving it and it's a front tooth. Bridging would be difficult, there's not enough structure left to do a post crown and implants aren't available on the NHS in the UK.
I'm thinking that I would find the money to have it/them (may need the other front tooth done as well) but that will cost four thousand pounds and I don't know how successful implants in XLHers may be.
Does anybody have any advice or experience on this?

Many thanks

Message:2
Date: Tue, 25 Oct 2011 08:25:03 -0700 (PDT)
From: **NAME REDACTED**
To: XLH List <f-hypdrr@xlhnetwork.org>
Subject: Re: [F-HYPDRR] Dental implants

I have several implants, and have not had any major problems with but they are all on molars.? What my dentist did was scrape the bone fragments off the teeth that were pulled, then added a bit of dental bone graft material and filled the socket, then let it sit and heal for several weeks before going back to do the implant.? The front of my jaw bone is a bit thin so they were unsure if it would hold implants there or not, but that was several years ago and technology and methods may have changed enough to allow it now.

The very first implant the dentist did, he used a type where the tooth has a screw in the top where it can be easily removed later.? I don't know if the implant was in crooked or if the tooth was improperly made, but that tooth kept loosening up.? He attempted to tighten it with what he called his "barbie ratchet" and ended up stripping the implant post out of the jaw bone while I was not under anesthetic. Extremely painful.? He replaced it with another type of implant where the tooth is attached to the post with adhesive and I had no further issues.? All in all now I think I have about 6 implants at the cost of around $2000 US dollars each.? One of them has loosened up in the last few weeks, but I'm sure the adhesive has just loosened up from the post and the tooth needs to be glued back down.
Hope this helps,
NAME REDACTED

Message:3
Date: Tue, 25 Oct 2011 10:42:31 -0500
From: **NAME REDACTED**
<F-HYPDRR@xlhnetwork.org>
Subject: Re: [F-HYPDRR] Dental implants

Id get an awesome set of dentures if I had to do it again. I must be up to 50 grand now with everything and my

10 g bridge cracked. Also have a twice failed root surgery thing up front and on a posted rooted crowned tooth..5 g on that one tooth..I hate having a constant infection up there...its not healthy.but I'm wih you..what do I do? Throw everything I've done away? Its a never ending sickening battle that is ultimately not healthy for our whole body and a dentiment of our finances
NAME REDACTED

Message:4
Date: Tue, 25 Oct 2011 16:29:40 +0000
From: **NAME REDACTED**
To: <f-hypdrr@xlhnetwork.org>
Subject: Re: [F-HYPDRR] Dental implants

I am currently going through serious dental work, i call it serious cause they have had to remove all my teeth and fit new implants, this is being done with the NHS because of the XLH condition although mine is on the serious side but it is good for your GP to be aware cause my GP refered me to the Eastman Dental Hospital hope this helps.
NAME REDACTED

Message: 5
Date: Tue, 25 Oct 2011 12:44:27 -0400
From: **NAME REDACTED**
To: XLH List"'<f-hypdrr@xlhnetwork.org>
Subject: Re: [F-HYPDRR] Dental implants

I to have implants in my front lower four teeth. Had bone grafting and sat for 6 weeks with a "flipper" for 6 weeks a real joy that was. MY implants are fine now 4+ years later. Hope to have them 40+ more years. I guess that is extreme wishful thinking huh. We sure pay our dues with this disease.

Message: 6
Date: Sat, 19 Mar 2011 19:05:59 -0700
From: **NAME REDACTED**
To: f-hypdrr@xlhnetwork.org
Subject: Re: [F-HYPDRR] pth and calcium levels

As always, I am not a doctor, so this is just my lay understanding about the relationship between PTH and vitamin D and phosphorus and calcium.

The parathyroid hormone is involved with regulation of the phosphorus and calcium in the bloodstream. The two should be sort of balanced, so in a normal person, when the phosphorus is low, the calcium should also be low. Except, of course, for those of us with XLH, the body dumps most of the phosphorus but keeps the calcium, so the classic blood test result is "low phosphorus coupled with unexpectedly normal calcium levels."

We take phosphorus in an attempt to raise the blood levels of phosphorus and also to get more phosphorus to our bones and teeth. But the increased phosphorus apparently triggers the parathyroid hormone to increase its production. Vitamin D (in the form of calcitriol,
since we don't fully metabolize regular vitamin D) can calm down the parathryoids, sort of sending them a message to chill, it's okay for the blood phosphorus levels to be higher than our natural levels.

Now, PTH can be "high" or it can be "dangerously high." Sort of like a "normal temperature of 98.6 is really just an average, and some of us have a "normal" temperature that's higher than that and others have a "normal" temperature that's lower than that. The lab tests will flag

anything that's above/below the "normal" (think of it as an average for non-XLH) people for phosphorus blood levels, but it takes XLH experience to know whether that level is worrisome.

Many of us have slightly high PTH levels in the absence of phosphorus treatment (I did), which may be "normal" for us. But then adding the phosphorus supplements can send the PTH higher. The real issue is the line between "high" and "dangerously high." This is just MY PERSONAL EXPERIENCE, but my doctor (endocrinologist with XLH experience) wasn't worried when my PTH was just a little bit above normal, but simply monitored me to make sure I didn't go even higher, until it got to a range that worried her, and it still wasn't really in the dangerous range, although we did some things to lower it a bit.

The thing is, that line between "high" (as compared to non-XLH patients) and "something to worry about" is not likely to be clear to anyone except a doctor with XLH experience. Mine was technically high but stable and non-problematic for at least twenty years.

There are a few things that are frequently done when the PTH levels are high enough to require treatment. The first is simply stopping the phosphorus supplements or increasing the calcitriol. (You don't want to take this step without a doctor's advice, though, especially during pregnancy.) We always say "no unopposed phosphorus," but there's no rule against unopposed calcitriol (vitamin D), in moderation. That's in a non-pregnant patient, though; vitamin D is one of the few vitamins that can be toxic in large doses, so there may be risks to the child if he/she does not have XLH, so again, it's important to get an expert opinion, rather than self-treating.

Sometimes, either stopping the phosphorus (which triggers the increased production) or increasing the calcitriol (which soothes the parathyroids) can bring down the PTH levels. If that doesn't work, sometimes sensipar is added, and can bring down PTH levels. It worked for me and some others on the list, not so much for yet other patients. (I have no idea if that's safe for use during pregnancy, though.) Sometimes the parathyroid glands are so used to over-producing, that they'll keep going, even after the phosphorus supplements are stopped, the calcitriol is increased and sensipar is added. In those cases, removal of some of the parathyroid glands can be necessary, if the PTH is really in the dangerous ranges.

Finally, it worries me whenever I hear that a doctor is advising that an XLH patient take calcium and regular vitamin D. There may well be perfectly good reasons for that -- most of us, women in particular, get too little of both in our diet. But they're not, by any stretch of the imagination, treatment for any XLH symptoms like high PTH. XLHers have no more need for calcium, and no more trouble metabolising it, than anyone else. And we can't really use regular vitamin D particularly well, so it won't work to bring down the PTH.

This may just be a hot button for me, because I'm of an age when the doctors believed that calcium and potentially-toxic doses of vitamin D were the appropriate treatment for XLH, so that's what I took as a kid in the 1950s/60s. I've had doctors as recently as the mid-1980s (when the experts knew the disorder involved phosphorus, not calcium) advise me to take calcium and regular vitamin D. They were perfectly good doctors, at top-notch institutions, but they had **no XLH experience**. Which is why seeing that combination recommended tends to make me see red.

So, bottom line: we start out with a tendency toward elevated PTH, then the phosphorus supplements can raise the PTH, especially if not balanced sufficiently with calcitriol (which, remember, is vitamin D, not calcium) to bring it back down. As far as I know, there's no direct relationship between calcium supplements and/or regular vitamin D (taken by a person with XLH) and the PTH levels. The metabolized version of vitamin D (calcitriol) may reduce PTH levels and increase the vitamin D in the bloodstream. But it's also important to find out

whether anything at all needs to be done, or if the "high" pth is just normal for that patient and not causing any real problems.

Again, I'm not a doctor, so this is just my lay understanding. For anyXLH patient who's having problems (i.e., high PTH), it's important to get an opinion from a doctor with XLH experience, since it really is a complicated balancing act. That's even more true during pregnancy, when the treatment also affects the fetus.

Most doctors do not focus on the VitD. I was always told that the main markers they monitor are Phosphorous, Calcium, PTH, and urine Calcium to creatinine in a 24 hour period. And renal ultrasounds.

They key balance is between the calcium and the phosphorous. Our calcium tend to be normal to high, high calcium is not good. High dosage of phosphorous to increase it, may trigger high PTH. Which could be controlled with addition of Rocaltrol, but Rocaltrol is not recommended if there is high calcium.

High PTH+High Calcium = no good

So the goal is to increase the phosphorous without triggering the high PTH and to increase the Rocaltrol until/unless the calcium is high. And never give phosphorous without Rocaltrol.

Not a doctor, but a level of 3.6 is a nice number; many of us rarely reach that value. I personally don't think I've ever been more than 2.5. My kids have been in the 3's but not high 3's.

Sincere thanks for the prompt replies from everyone of the list in relation to this current issue I am experiencing. I have a root canal on this tooth earlier in the year, followed by a post and crown in May, the pain is not intense but I just mentioned it to the dentist yesterday when I was there to replace a filling. I am to return tomorrow for the diagnostic testing to see if it is that. I notice on the general web that it isn't easy to diagnose and I will be proceeding with caution (as sometimes I feel the $$$$ in their sights outway what is truly best for the patient). I have no discomfort when I brush my teeth and on a pain scale 1 - 10, it would be a 1. It just feels like a stone bruise does on your foot, or that the placement of the crown has stirred things up. Either way I shouldn't be feeling much because the tooth is dead anyway. However when I touch it I know something is going on.

Sincere thanks again to everyone, I'll keep you informed

Cheers **NAME REDACTED**

Message: 7

On Tue, Jul 26, 2011 at 3:17 AM, **NAME REDACTED** wrote:
I had problems with my teeth breaking after root canals and even crumbling.
I also had some teeth re-abscess.. I finally got Dentures and just use a bit of Fixodent in them. they take some getting used to but my teeth look better now than they ever have in my life....Dentures do take some getting used to though.

When I got mine I did the Top first then 6 months later did the bottom at the time i probably only had about 9 teeth left on top and 5 or 6 onbottom....(I had been wearing a partial denture on the bottom for 3-4 years already.
Or get a copy of the latest Dr. Carpenter article (I don't have the link any longer; I thought it was at the Network's website, but couldn't find it, but maybe someone else kept it), on "**A Clinician's Guide to X-Linked Hypophosphatemia**," where it says, in a section entitled "surgical and DENTAL CARE," for goodness sake:

Some children are prone to dental abscesses; one abscess predicts future abscesses. Defective dentin and microdefects in the enamal diminish the barrier between the oral environment and the pulp chamber, allowing

increased microorganism access to the pulp chamber and abscess formation.
Some dentists have suggested sealant application. The incidence/severity of commonly encountered dental abscesses is not clearly affected by medical therapy."

Anyway, it's the Journal of Bone and Mineral Research, Volume 26, No. 7,
July 2001, pages 1-8.

Message:8

Date: Sun, 26 Jun 2011 16:41:18 -0500
From: **NAME REDACTED** >
To: <f-hypdrr@xlhnetwork.org>
Subject: [F-HYPDRR] Abscess teeth

Hello all,
My 3-year old son has had 5 teeth pulled due to abscess, and I think he may have a 6th now. Just wondering, if anyone has any good advice on how to prevent further abscess teeth. We've had sealants put on all the back teeth, and we use the MI paste every evening. So, far he has only lost the front teeth, but I am worried that he could possibly lose his molars and not be able to chew his food. Does anyone have any experience with this?
Thanks for any advice,

SECTION III. FULL RESEARCH ARTICLES

RESEARCH PUBLICATION #32

Familial hypophosphatemic Rickets

A Sattur, VG Naikmasur, R Shrivastava, M Babshet
Department of Oral Medicine and Radiology, SDM College of Dental Sciences and Hospital, Dharwar, Karnataka, India January 2011 **DOI**: 10.4103/0970-4388.76163 **PMID:** 21273721

Abstract

Rickets is the **failure of mineralization** of osteoid and newly formed bones in a child skeleton. It is commonly associated with vitamin D deficiency; however, it can be because of a decrease in the serum phosphate levels leading to inadequate mineralization of cartilage and bone, consequent skeletal deformities, and growth retardation. The hypophosphatemic conditions that interfere in bone mineralization comprise many hereditary or acquired diseases. One of the hereditary types of hypophosphatemic rickets is the familial hypophosphatemic rickets. This rare variety was diagnosed in a 9-year-old patient who had come with a chief complaint of a missing tooth. In the present case, radiographic aspects of **oral and systemic manifestations of familial hypophosphatemic rickets are highlighted**.

Keywords: Cemental dysgenesis, familial rickets, hypophosphatemia

Introduction

The vitamin D-resistant rickets was first documented by Albright *et al*., as early as in the 19th century itself. The pathophysiologic mechanism shared by them is the reduction in the phosphate reabsorption by renal tubuli which leads to hyperphosphaturia and hypophosphatemia, causing rickets. X-linked hypophosphatemic rickets (XLHR) is a familial syndrome characterized by the **inadequate mineralization of cartilage and bone,** consequent skeletal deformities, and growth retardation. The present case report shows the clinical, radiological, and pathological evaluation of familial hypophosphatemic rickets in a 9-year-old boy who came with the chief complaint of pain and missing tooth.

Case Report

A 9-year-old boy visited our hospital with the chief complaint of pain in the lower front region since 3 years and a missing tooth in the upper front region of the jaw since 1 year. The pain was mild and intermittent with occasional pus discharge. There was no eruption of the permanent tooth after the shedding of the deciduous tooth in the second quadrant of the jaw since 1 year. As per the parents' observations, the child had difficulty in walking since he was 3 years old and also bowing was observed in the extremities since 1 year. We could observe that the mother also had a limping gait and short stature. On further investigation, the mother revealed that she had undergone surgery for bow-leg deformity and multiple root canal treatments. The child has two elder sisters who are apparently normal and there was no contributing paternal history.

General physical examination revealed that the height and weight were 114 cm and 18 kg, respectively, which are less as compared to the average height and weight of an age-matched Indian boy. The patient had a dolicocephalic face, frontal bossing, and incompetent lips [[Figure 1]a]. There was bowing of the arms and legs with enlargement at the wrist and the ankle joints [[Figure 1]b and c]. The presence of rachitic rosary, Harrison's groove, and lumbar lordosis was also noted. On intraoral examination, mixed dentition was present with the missing maxillary permanent left central incisor, grade II mobile mandibular deciduous left first molar, and

mandibular deciduous right lateral incisor and decayed maxillary permanent right first molar and maxillary permanent left first molar, with fair oral hygiene [Figure 2]. Considering the familial history and the clinical features favoring rickets, the provisional diagnosis of familial rickets was made.

Figure 1 :(a) Dolicocephalic face, frontal bossing, and incompetent lips. (b and c) Bowing of the arms and legs marked with bold arrows and with the enlargement at the wrist and the ankle joints marked with broken arrows

Click here to view

Figure 2 :The figure shows missing 21

Click here to view

The OPG showed decreased a cortical bone density in both the maxilla and mandible with thinning of the inferior cortical border of the mandible. Both primary and permanent teeth showed taurodontism with a generalized diminished lamina dura [Figure 3]. IOPA radiographs showed generalized taurodontism, reduced density of the enamel and dentine [Figure 4]. Frontal and lateral skull radiographs showed the presence of diffuse copper beaten appearance with premature closure of sutures [Figure 5]and [Figure 6]. The hand and wrist AP radiograph showed diffuse osteopenia in the form of coarse medullary trabeculae and endosteal resorption. The distal end of the radius and ulna showed metaphyseal splaying with widening of growth plates [[Figure 7]a]. A similar finding was observed bilaterally on the distal end of the femori proximal and distal metaphysis of the tibia and fibula [[Figure 7]b]. The femur showed the coxavara type of deformity [[Figure 7]c]. The chest radiograph revealed mild splaying of cartilaginous ends of ribs [[Figure 7]d]. All long bones showed bowing deformity. Sonography of kidneys was advised to rule out nephrocalcinosis, which came negative.

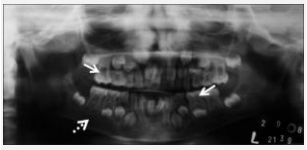

Figure 3 :Orthopantomograph shows a decreased cortical bone density with thinning of the inferior cortical border of the mandible (broken arrow). Both primary and permanent teeth show taurodontism with a generalized diminished lamina dura (bold arrow)

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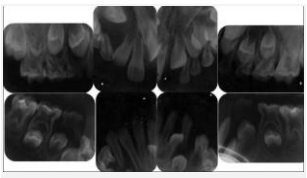

Figure 4 :Full mouth radiographic survey reveals enlarged pulp chambers of all teeth with a reduced density of the enamel and dentine

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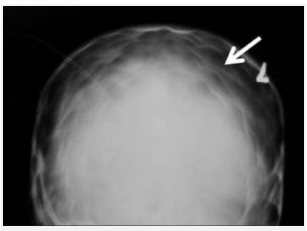

Figure 5 :Posterior-anterior skull radiograph shows a diffuse copper beaten appearance with premature closure of sutures

Click here to view

Figure 6 :Lateral skull radiograph shows a diffuse copper-beaten appearance with premature closure of sutures

Click here to view

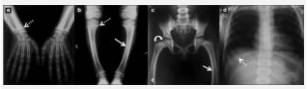

Figure 7 :Diffuse osteopenia of long bones. The broken arrows (a, b, and d) show metaphyseal splaying. The bold arrows (b and c) show bowing deformity of the tibia and femur, respectively. The curved arrow (c) shows the coxavara deformity of the femur

Click here to view

One of the deciduous teeth was subjected to ground sectioning which revealed a large pulp chamber and numerous areas of interglobular dentine throughout the thickness of the dentine. The cementum was absent in the apical third, while only a thin layer was present in the cervical and middle third portion of the root. Observing these dental and skeletal findings, blood investigations were advised. The blood report revealed decreased serum phosphate, 2.6 mg/dL (normal range = 3.7-5.6 mg/dL), and elevated serum alkaline phosphatase, 514 IU/L (normal range = 150-380 IU/L); however, serum calcium was within the normal range, 8.5 mg/dL (normal range = 9-11 mg/dL). The decreased levels of serum phosphate show decreased absorption or increased renal wasting of phosphate, while the elevated serum alkaline phosphatase levels suggest an increased bone turnover. From the above history, clinical examination, and the investigations, we arrived at a final diagnosis of familial hypophosphatemic rickets.

Initially, the dental management was done with oral prophylaxis, the restoration of decayed and the extraction of the mobile teeth. A neutral phosphate syrup, 15 ml, was prescribed with three divided doses daily for hypophosphatemia; also, vitamin D 0.25 ˝g was supplemented in once daily dose. The patient was subjected to physical therapy like cycling and exercise. On 6-month follow-up, the patient showed improvement in gait and physical activity.

Discussion

top

Rickets is the failure of mineralization of osteoid and newly formed bones in a child. The term is derived from an old English word "wrickken," which means "to twist" and a Greek word "rachitis," which means inflammation of the spine. When the demineralized osteoid accumulates at the sites of bone formation, bones gradually soften leading to deformities in association with weight-bearing sites. This clinical entity in England was termed as English disease in the 17 th century by Francis Glisson. Later in the mid-17 th century it was termed as rickets by Park and Hunter. [1] By the end of the 19th century, the near endemic nature of rickets among children under the blackened skies of industrial cities in Europe was widely recognized. [1] It was in the 20th century when vitamin D was discovered and used for therapeutic purpose.[1]

Initially, environmentally caused rickets was very common; however, when it was treated and prevented by public health measures, the vitamin-D-resistant rickets came into picture. Albright *et al*. highlighted that some of the patients with rickets did not respond to physiological doses of vitamin D and named the condition as vitamin-D-resistant rickets. Later studies showed that treatment of rickets was possible by vitamin D in doses higher than its physiological doses and eventually termed it as vitamin D refractory rickets. Fraser and Salter studied 13 cases of hereditary vitamin D refractory rickets. The hereditary forms were further divided into familial hypophosphatemia rickets and vitamin D dependency. The latter is caused by the deficiency of an enzyme 25-hydroxyvitamin D-1a-hydroxylase which is responsible for the synthesis of 1,25 dihydroxycholecalciferol. This substance specifically acts on the intestine to stimulate calcium transport. Therefore, the biosynthesis impairment

of the vitamin D hormone causes calcium deficiency manifesting with signs of hypocalcemia and in later stages with hyperparathyroidism. Vitamin D dependency shows an autosomal recessive pattern.

The familial hypophosphatemic rickets is caused by a renal tubular phosphate-wasting disorder. It shows an X-linked dominant pattern affecting males uniformly and females variably. It has an incidence of 1:20,000. [2] The renal tubular rejection of phosphate in XLHR causes decreased serum phosphate levels. XLHR resulting from inactivating mutations in an endopeptidase termed PHEX (phosphate-regulating gene with homologies to endopeptidase on the X- chromosome). [3] A substrate for PHEX has not yet been identified and hence its role in pathophysiology in hypophosphatemia is not clear. Certain studies have shown that PHEX is highly expressed in bone and in teeth. [3] Since the substrate of PHEX is not yet known, it is not possible to say how the loss of function of PHEX causes these bone and teeth defects and renal phosphate leak. [3]

Clinical features include decreased vertical height, craniotobes, rachitic rosary, bowing leg deformity (genu varum) or knock knee (genu valgum), double malleoli sign of ankles, metaphyseal hyperplasia of wrist, and Harrison's groove on the chest.

In a conventional radiograph, rickets usually presents with widening of the physis with cupped and splayed metaphysis. The skull shows frontal bossing, premature fusion of the sagital suture leading to copper beaten appearance, and postural molding:

1. Axial skeleton shows the following:

    a. Costochondral junction shows cupping and splaying of rib ends.

    b. Spine shows scoliosis or lordosis and biconcave vertebral bodies.

    c. Pelvis shows triradiate appearance due to the inward migration of the sacrum and acetabula.

2. Appendicular skeleton shows the following:

    a. Ossification centers of the epiphyses show an indistinct outline.

Diaphysis shows osteopenia, subperiosteal lucent lines tunneling, and bowing. Bowing deformity is common in the femur and tibia. The femur shows the coxavara type of deformity, wherein the neck makes an angle of less than 120° with the shaft of the femur.

The oral finding of XLHR is the presence of multiple dental abscesses in both the dentitions, [4] in the absence of obvious cause such as caries or trauma involving pulp.[5] Radiographs reveal enlarged pulp chambers with pulp horns that extend to enamelodentinal junctions. [5] The occurrence of the periapical lesions or gingival abscesses without any obvious cause is explained in general by the penetration of microorganisms through dentinal clefts, tubular defects, or voids in the calcified metrics of the dentine. [5] The concentration of calcium and phosphorous along with the calcium to phosphate ratio of the enamel in hypophosphatemic rickets are nearly equal to those of normal teeth, although the degree f radiodensity is less in hypophosphatemic rickets. [6] **The concentration of phosphate in the dentine is extremely low**. [6] The microradiograph of teeth in hypophosphatemic rickets showed extensive areas of the circumpulpal dentine consisting of radiopaque calcospherites separated by multiple irregular radiolucent zones of the interglobular dentine. [6] **The early exfoliation of deciduous teeth in rickets** can be attributed to poorly defined lamina dura, dysplastic roots, and hypoplastic alveolar ridge. [4]

The treatment of hypophosphatemic rickets is done by the oral administration of phosphorus, 1-4 g daily in five divided doses. The objective of the treatment is to raise the serum phosphate to about 4 mg/dL. Treatment of hypophosphatemic rickets with orthophosphate in doses sufficient to restore the serum phosphate to normal

results in radiographically evident healing of rickets and promotes "catch-up" linear growth in childhood. [7] Phosphate loading decreases the level of ionized calcium in serum and causes the serum concentration of iPTH to increase. Vitamin D is used as an adjuvant to phosphate therapy to avoid this complication. The dose of vitamin D ranges from 0.1 to 1.2 mg per day depending on the amount of phosphate administered and the patients' particular need for vitamin D. [1]

Conclusion

Being dentists we hardly come across this rare variety of rickets in our clinics. However, with thorough case history, systematic clinical examination, and appropriate investigations, it is possible to diagnose even rare diseases. In this case, though the patient presented with pain and missing tooth, we were able to diagnose familial hypophosphatemic rickets and treat the patient at its earliest.

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RESEARCH PUBLICATION #33

PMCID: PMC2818230
NIHMSID: NIHMS149620
Bone. Author manuscript; available in PMC 2011 ebruaryPublished in final edited form as:Bone. 2010 February; 46(2): 402.Published online 2009 September 29. doi: 10.1016/j.bone.2009.09.016

Identification of a Novel Dentin Matrix Protein-1 (DMP-1) Mutation and Dental Anomalies in a Kindred with Autosomal Recessive Hypophosphatemia

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An autosomal recessive form of **hypophosphatemia** (ARHP) was recently shown to be caused by homozygous mutations in *DMP1*, the gene encoding dentin matrix protein-1 (DMP-1), a non-collagenous bone matrix protein with an important role in the development and mineralization of bone and teeth. Here, we report a previously not reported consanguineous ARHP kindred in which the three affected individuals carry a novel homozygous *DMP-1* mutation. The index case presented at the age of 3 years with bowing of his legs, and showed hypophosphatemia due to **insufficient renal phosphate retention**. Serum alkaline phosphatase activity was elevated, with initially normal PTH. FGF23 was inappropriately normal at an older age while being treated with oral phosphate and 1,25$(OH)_2$D. Similar clinical and biochemical findings, except for elevated FGF23 levels, were present in his 16 month-old brother and his 12.5 year-old female cousin; the parents of the three affected children are first-degree cousins. Nucleotide sequence analysis was performed on PCR-amplified exons encoding DMP-1 and flanking intronic regions. A novel homozygous frame-shift mutation (c.485Tdel; p.Glu163ArgfsX53) in exon 6 resulting in a premature stop codon was identified in all effected individuals. The parents and available unaffected siblings were heterozygous for c.485Tdel. Tooth growth and shape were normal for the index case, his affected brother and cousin, but their permanent and deciduous teeth displayed **enlarged pulp chambers.** The identified genetic mutation underscores the importance of *DMP-1* mutations in the pathogenesis of ARHP. Furthermore, *DMP-1* mutations appear to contribute, through yet unknown mechanisms, to tooth development.

Keywords: dentin matrix protein-1, fibroblast growth factor-23 (FGF-23), hypophosphatemia, rickets, tooth

Dentin matrix protein-1 (DMP-1), an acidic non-collagenous phosphoprotein, is a member of the SIBLING (small integrin binding ligand N-linked glycoprotein) family, which includes osteopontin (OPN), bone sialoprotein, dentin sialophosphoprotein (DSPP), enamelin, and matrix extracellular phosphoglycoprotein (MEPE), which are thought to play an important role in tissue mineralization (10-12, 27). DMP-1, which is produced by osteoblasts and osteocytes, regulates cell attachment (16) and cell differentiation (14, 22), activates matrix metalloproteinase-9 (7), and affects biomineralization (35). Mice that are null for *Dmp-1* develop a bone phenotype characterized by hypomineralization, short and wide vertebrae, long bones with delayed and malformed secondary ossification centers, and abnormal osteocyte morphology associated with loss of dendritic extensions (36). *Dmp-1*-null mice furthermore show increased osteocytic FGF23 expression and elevated FGF23 levels, leading to hypophosphatemia and reduced 1,25$(OH)_2$D levels, leading to mild hypocalcemia and

secondary hyperparathyroidism (9, 17).
Homozygous *DMP-1* mutations were recently identified in the affected members of several unrelated families with an autosomal recessive form of hypophosphatemia (ARHP) (9, 19). The clinical, biochemical, and bone histomorphometric parameters of these individuals are indistinguishable from those observed in patients with X-linked hypophosphatemia (XLH) (9, 19). Similar to the findings in *Dmp-1*-null mice, ARHP patients have furthermore normal or low-normal serum calcium levels with high to normal PTH levels, and slightly elevated or inappropriately normal FGF23 levels resulting in diminished 1,25$(OH)_2$D levels (9, 19). Tooth abnormalities have thus far not been described in humans with homozygous *DMP-1* mutations, yet*Dmp-1* null mice show increased width of predentin with reduced dentin wall thickness and dentin hypomineralization resembling human disease dentinogenesis imperfecta type II and III (35). Here, we report clinical, laboratory, and dental findings of the affected members of an ARHP kindred, in whom we identified a novel homozygous *DMP-1* mutation.
Serum and urine concentrations of calcium, phosphorus, creatinine, and serum alkaline phosphatase activity were measured at the Marmara University Hospital using standard methods. Serum intact PTH concentrations were determined by a solid phase, two-site chemiluminescent enzyme-labeled immunometric assay (Immulite® 2000). Plasma FGF23 levels were measured with an ELISA that detects intact as well as C-terminal FGF23 (Immutopics) (13). TmP/GFR was calculated according to the Walton and Bijvoet nomogram (33) using a fasting 2 hour urine sample and a serum sample that was obtained 1 hour after starting the urine collection.
The blood samples for DNA extractions were collected after informed consent was obtained; the study was approved by Massachusetts General Hospital Institutional Review Board. Nucleotide sequence analysis of the PCR-amplified exons encoding DMP-1 and the flanking intronic regions were performed at the Harvard-Partners Center for Genetics and Genomics (HPCGG). To confirm the presence of the identified mutation, *DMP-1* exon 6 was amplified by using 5′-CGGTTCCTGGAATACTGACC-3′ as forward primer and 5′-TCTTTGGCTGTGTTCTGGTG-′3 as reverse primer to obtain a 1619 bp PCR product, which was then incubated with the endonuclease *Eco*NI.

The index case (#5) (Figure 1, panel A; arrow) was 3 years old when he presented with bowing of both legs that had become apparent during late infancy after he started walking; his height was 91.1 cm (−0.9 SDS) and his weight was 18.0 kg (+1.8 SDS). Besides genua varum, he had rachitic rosaries on physical examination. Laboratory investigations revealed hypophosphatemia (2.8 mg/dl), low tubular phosphate reabsorption (TMP/GFR: 3.0), elevated serum alkaline phosphate activity (964 U/L), and a normal serum PTH level (48 pg/ml) with normal serum calcium (9.6 mg/dl) (Figure 1, panel B). Treatment with oral phosphate (40 mg/kg/day) and 1,25$(OH)_2$D (0.25 µg/day) was initiated, which led to an improvement of his serum chemistries. After a period of five years without follow-up and treatment, the patient presented again with hypophosphatemia (2.2 mg/dl), hypocalcemia (8.5 mg/dl), and secondary hyperparathyroidism (PTH: 74 pg/ml); his height was 119.3 cm (−2.3 SDS) at that time (Table 1). Treatment with phosphate and 1,25$(OH)_2$D was re-initiated, and while under treatment, his plasma FGF23 level was at the upper end of the normal range (see Figure 1, panel B).

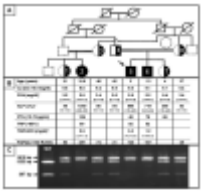

Figure 1
Panel A: Pedigree of the kindred with autosomal recessive hypophosphatemia (ARHP). The index case is indicated by the arrow; solid black symbols depict affected individuals; half-filled symbols represent unaffected, obligate carriers, and healthy siblings(more ...)

Table 1

Laboratory and growth parameters expressed as standard deviation scores (SDS) according to Turkish growth charts (23, 32) at first presentation (1st) and second presentation (2nd) for patients #2, #5, and #6, and at the most recent follow-up visits for patients #5 and #6 during their second year of treatment.

	[redacted]							
	1st	2nd	1st	2nd	Follow-up	1st	2nd	Follow-up
Age (years)	12.5	20.0	3.0	9.2	11.4	1.3	7.5	9.8
Ca (mg/dl)	9.6	9.4	9.6	8.5	*8.6-9.3	9.1	9.1	*8.9-10.1
PO4 (mg/dl)	2.5 (2.9-5.4)	2.2 (2.7-4.7)	2.8 (3.8-6.5)	2.2 (3.7-5.6)	*2.1-2.8 (3.7-5.6)	2.2 (3.8-6.5)	2.4 (3.7-5.6)	*2.1-3.0 (3.7-5.6)
ALP (U/L)	1340 (200-495)	514 (50-130)	964 (145-420)	890 (145-420)	*790-850 (145-420)	719 (145-420)	950 (145-420)	*805-850 (145-420)

Table 1
Laboratory and growth parameters expressed as standard deviation scores (SDS) according to Turkish growth charts (23, 32) at first presentation (1st) and second presentation (2nd) for patients #2, #5, and #6, and at the most recent follow-up visits for (more ...)

Similar clinical and biochemical findings were observed for his brother (#6) at the age of 16 months and for his female cousin (#2) at the age of 12.5 years. Their laboratory data at first presentation are shown in Figure 1, panel B; note that the brother #6 had at the age of 9 years, during treatment with oral phosphate and 1,25$(OH)_2$D, an elevated serum FGF23 level of 167 RU/ml; the cousin #2 had not received any treatment and at the age of 20 years, her FGF23 level was elevated to 257 RU/ml. All other family members were healthy and had normal blood chemistries and normal FGF23 levels. The parents of the three affected children are first-degree cousins (see Figure 1, panel A).

The autosomal recessive mode of inheritance made it unlikely that the hypophosphatemic disorder in this family is caused by mutations in either ***PHEX***(mutated in patients with XLH) (5) or FGF23 (mutated in patients with autosomal dominant hypophosphatemic rickets, ADHR) (1), and we therefore analyzed *DMP-1*. Nucleotide sequence analysis of the PCR-amplified exons encoding DMP-1 and the flanking intronic regions led in the index case #5 to the identification of a novel homozygous mutation in exon 6 (c.485Tdel) that resulted in a frame-shift replacing the 335 conserved amino acids within the carboxyl-terminal region with 53 unrelated amino acids (p.Glu163ArgfsX53) (Figure 2); the same homozygous mutation was also identified in the affected brother of the index case (#6) and the affected cousin (#2). The parents of #5 and #6 (i.e. #4 and #8; see Fig. 1, panel A), the mother of #2 (i.e. #3) and the two available unaffected siblings (#1 and #7) were heterozygous for c.485Tdel; results of nucleotide sequence analyses were confirmed by digesting PCR-amplified DNA with the restriction endonuclease *Eco*NI (Figure 1, panel C); using this method, none of the 148 alleles from healthy controls, which included 36 alleles from healthy Turkish individuals, carried the c.485Tdel mutation.

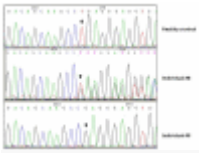

Figure 2
Nucleotide sequence analysis of DNA from a healthy control (upper), from the unaffected family member #8 carrying a heterozygous *DMP-1* mutation in exon 6 (c.485Tdel), and from the affected family member #5 carrying a homozygous mutation.

Upon treatment with oral phosphate and 1,25$(OH)_2$D, serum phosphorous levels of index case (#5) and his effected brother (#6) increased to 2.8 mg/dl and 3 mg/dl, respectively, calcium and PTH levels normalized. Despite improved serum phosphorous levels, the index case #5 and his affected brother #6 showed no catch-up growth over a two-year observation period as their height standard deviation score (SDS) remained at −2.4 to −2.5 and −4.2 to −3.9, respectively. Both of the patients were prepubertal during this period. Their effected female cousin (#2) was diagnosed at the age of 12.5 years during early pubertal development (breast Tanner stage II) and her height improved slightly from an SDS of −4.5 at the age of 12.5 years to −4.05 after 1 year of treatment. She then discontinued treatment, but her SDS improved to −2.86, which could be related to a constitutional delay of pubertal development and thus late fusion of the growth plates (menarche at age 15.5 years). Nevertheless, her final height was only 143.1 cm, which remains 5 cm below the midparenteral height (Table 1).

Upper-to-lower segment ratio (US/LS) of the two younger affected individuals (#5 and #6) was more than +2 SD above the mean of the Turkish reference range (32). There was a further increase in US/LS ratio over a two-year observation period while on therapy with oral phosphate and 1,25$(OH)_2$D, as indicated by the further loss in lower segment SDS to −0.8 and −0.9 SDS, respectively, and a further gain in the upper segment to +0.3 and +0.8 SDS, respectively; a similar growth pattern was also observed in their untreated cousin #2 (Table 1). These findings indicate that our ARHP patients increased their height, regardless of treatment, mainly because of an increase in upper body segment, i.e. the vertebral column. Arm span height difference was within the reference

range for #5 and #6 (albeit slightly higher than +2 SDS for #5) when the diagnosis was established and did not change during treatment. In addition, the younger brother (#6) had limited arm extension at elbow and mild cubitus valgus deformity. The intercondylar distance had decreased from 15.5 cm to 8 cm in older brother (#5) and from 10 cm to 5 cm in more severely affected brother (#6) during the 2 years treatment period; the final intercondylar distance of the cousin (#2) was 5 cm.

Radiographs the lower extremities of patient #6 revealed cupping, metaphyseal fraying and **bowing of the femurs**, which improved after treatment (Figure 3). The medial aspect of the femurs and showed evidence for osteosclerotic changes; similar findings were made for patients #2 and #5 (data not shown). The hand radiographs of patients #5 and #6 revealed bone ages that were consistent with their chronological ages. However, the metacarpals and proximal phalangial bones were short and broad (>2 SD below the mean of healthy controls (26); and additional broading and shortening of the distal phalangial bones, most prominent for the 1st, 3rd and 4th finger of the more severely effected brother (#6), became apparent during the 2 years of treatment (Figure 4). An increase in bone mineral density was detected in patient #2 at the age of 20 years (T-score for L1-L4: +9.4; at the femoral neck: +5.1).

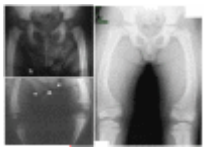

Figure 3
Radiograph of the lower extremities of patient #6 at the age of 16 months before treatment (lower and upper left panel), which showed metaphyseal fraying, cupping and bowing. At the age of 9.5 years, after 2 years of treatment with oral phosphate and (more ...)

Figure 4
Radiographs of the left hand of patient #6 at the age of 16 months (Panel A) and at the age of 9.5 years (Panel B). The metatarsals and phalangial bones were short and broad, the distal phalanges were dysplastic, and ulna and fibula were broad (Panel (more ...)

Review of the dental history of the index case (#5) revealed that the loss of deciduous central incisors had occurred at the age of 4.5 years after moderate trauma to the chin. The growth of his permanent teeth was normal. However, after another minor trauma, his lower central incisor fractured, leading to recurrent dental abscesses. **Dental examination at the age of 10.5 years revealed transverse fissures on upper central incisors, giving the impression of traumatic tooth injury**. Furthermore, a sinus tract on the buccal gingiva of the left mandibular central incisor was noted. The affected younger brother (#6) and the affected cousin (#2) had, at the age of 9 and 20 years, respectively, unremarkable dental histories, although each showed decay of at least one tooth. The panoramic radiographs of affected individuals #2, #5, and #6 revealed wider pulp chambers, thinner dentin, and thinner enamel in erupted teeth in comparison to healthy controls, whereas the shape and the size of each tooth and its root were normal (Figure 5). While enamel thicknesses of unerupted teeth were normal in affected individuals, the enamel of erupted teeth was thinner, indicating rapid post-eruption attrition. Retroalveolar graphs of patient #6 showed, in comparison to healthy controls and to her 21 year old healthy sister (heterozygous carrier #1) wider pulp chambers, thinner dentin, and **thinner enamel and a possible mineralization defect** (Figure 6). Additionally, a panoramic radiograph revealed the absence of the lower third molar in patient #2; individual #1 had one remaining deciduous tooth due to the absence of the root of the permanent tooth.

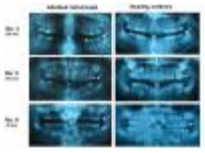

Figure 5
Panoramic radiographs of the three affected individuals (left panel), which show in comparison to the findings in an age-matched healthy controls (right panel), **enlarged pulps, decreased dentin and enamel layers** (*), as well as the absence of the lower (more ...)

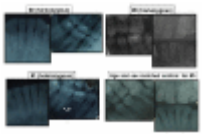

Figure 6
Retroalveolar radiographs of the two affected individuals #2 and #5 at the ages of 20 and 11 years, respectively (upper left and right panel). The films showed, in comparison to the findings in a healthy heterozygous carrier of the mutation (#1; lower (more ...)

Human DMP-1 is encoded by an mRNA with an open reading frame of 1539 nucleotides, and the translated pre-protein of 513 amino acids undergoes extensive post-translational modifications. The resulting 94-kDa mature DMP-1 rapidly undergoes cleavage by subtilisin-like proprotein convertases to generate a 57 kDa and a 37 kDa fragment (20). Homozygous *DMP-1* mutations are the cause of ARHP (9, 19), a rare autosomal recessive disorder with laboratory and skeletal changes similar to those observed in XLH (5), and are furthermore consistent with the findings in *Dmp-1*-ablated mice (9, 17).

The three affected individuals of a previously not reported consanguineous ARHP kindred carry a novel homozygous *DMP-1* mutation (c.485Tdel) that results in a frame-shift replacing most of the conserved carboxyl-terminal portion of DMP-1 with 53 unrelated amino acid residues (Figure 7). The mutation thus eliminates the entire 57 kDa DMP-1 fragment as well as the carboxyl-terminal portion of the 37 kDa fragment. Like the c.485Tdel mutation identified in our kindred, two previously identified nucleotide changes, c.362delC and c.del1484-1490, are also frame-shift mutations (9, 19). While the c.362delC mutation eliminates even more of the protein than does c.485Tdel, the c.del1484-1490 mutation results only in the loss of the most carboxyl-terminal 18 amino acid residues. However, affected individuals carrying either of the previously described deletions presented at similar ages as our patients, and they showed a similar degree of hypophosphatemia and inappropriately elevated renal phosphate excretion.

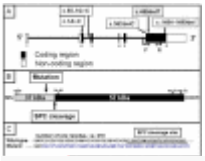

Figure 7
Panel A: Schematic presentation of the gene encoding *DMP-1*showing the approximate locations of the *DMP-1* mutation identified in this report (c.485delT) and of previously defined mutations (9, 19). Coding exons are shown as black boxes and non-coding (more ...)

The fourth DMP-1 mutation leading to ARHP is a homozygous c.1A>G change that results in substitution of the initiator methionine with valine (M1V) (9, 19). Patients carrying this mutation show clinical and laboratory abnormalities that are similar to those observed for patients with mutations affecting the carboxyl-terminal portion of DMP-1. However, one of the patients with the M1V mutation presented at 8 years of age and with a milder phenotype than observed in the other children affected by ARHP, and he showed an excellent response to treatment, reaching a normal adult height (3 cm above to target height) (9). Two other patients carrying the same mutation presented at adult ages and both had a subnormal final height, which is probably related to their long-standing untreated disease (19). These findings could imply a genotype-phenotype correlation, namely that patients carrying the M1V mutation might respond more favorably to early and continuous treatment than patients with any of the three other mutations. However, one of the 3 patients with c.del 1484-1490 mutations reached her genetic target height, and final heights of the affected individuals in the kindred presented herein showed considerable variations, making it likely that other factors affect growth.

Bone radiographs of our patients demonstrated findings typical for rickets, i.e. metaphyseal fraying, cupping and bowing of long bones. However, shortened and widened long bones, metacarpal and phalangial bones, as well as dysplastic distal phalanges were detected in our more severely effected cases, and these latter findings are reminiscent of the chondrodysplastic bone changes observed in *Dmp-1*-null mice (36). The bone histomorphological changes of *Dmp-1*-null mice develop postnatally and are similar to those observed in *Hyp* and VDR-ablated mice (28, 36). Hypophosphatemia is thus likely to contribute significantly to the bone changes in*Dmp-1*-null mice, but may not be the only etiologic factor for bone findings in ARHP. In fact, normalization of serum phosphate levels in *Dmp-1*-null mice maintained on a high phosphate diet corrected the growth plate defects and thus prevents the appearance of rickets, but did not completely normalize osteoid mineralization (9). This is similar to the findings in phosphate-treated *Hyp* mice and in patients with XLH, who show persistent bone abnormalities even when treated aggressively with oral phosphate (6, 18, 21, 30). *Dmp-1* null newborn mice showed no apparent early tooth phenotype, even though this protein is expressed in odontoblasts and is involved in dentin formation (8). **Postnatally these animals develop a profound tooth phenotype characterized by enlarged pulp chambers, increased width of predentin zone with reduced dentin and enamel thickness, and hypomineralization (35). This tooth phenotype is strikingly similar to that observed in *Dspp*-null mice (29) and shares some features of dentinogenesis imperfecta type II and III, a human disease characterized by discoloration, opalescent tooth, rapid attrition, ranging from pulpal**

obliteration to normal or enlarge pulp chambers, but without obvious bone changes (15). These dental findings that are similar to those observed in *Hyp* mice and are reminiscent, but appear to be less severe than those encountered patients with XLH (2-4, 24, 25, 31, 34).
In conclusion, the identified genetic mutation underscores the importance of DMP-1 in the pathogenesis of ARHP, as this protein appears to negatively regulate FGF23 expression under normal physiological conditions, thus playing an important role in the regulation of phosphate homeostasis. It remains to be clarified whether the described bone changes and growth characteristics of ARHP patients are related to the hypophosphatemia, to direct actions of FGF23 on bone, or to other abnormalities involving bone matrix proteins. Likewise, it remains to be determined whether the observed teeth findings, which appear to be similar, yet milder than those in patients with *PHEX* mutations, are caused by the hypophosphatemia and/or by increased FGF23 levels, or whether DMP-1 has a direct role in dental development and the formation of dental abscesses.

This work was support by the National Institutes of Health (R21 DK075856-01 to H.J.). Serap Turan is recipient of a fellowship from the Scientific and Technical Research Council of Turkey (Tubitak), Scientific Human Resources Development (BAYG) within the framework of Postdoctoral Research Fellowship program. Cumhur Aydin is a recipient of a fellowship from the Gülhane Military Medical Academy.

RESEARCH PUBLICATION #34

Dental abnormalities and oral health in patients with Hypophosphatemic rickets

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Received May 25, 2010; Revised June 13, 2010; Accepted July 29**, 2010.**
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INTRODUCTION:
Hypophosphatemic rickets represents a group of heritable renal disorders of phosphate characterized by hypophosphatemia, normal or low serum 1,25 (OH)2 vitamin D and calcium levels. Hypophosphatemia is associated to interglobular dentine and an enlarged pulp chambers.
AIM:
Our goal was to verify the dental abnormalities and the **oral health condition** in these patients.
MATERIAL AND METHODS:
Prospective study of oral conditions in patients with Hypophosphatemic rickets. This report employed a simple method to be easily reproducible: oral clinical exam and radiographic evaluation.
RESULTS:
Fourteen patients were studied, 5 males, median age of 11years (4 to 26). Occlusion defects (85,7%) and enamel hypoplasia (57,1%) were significant more frequently than dental abscesses (one patient). We observed enlarged pulp chambers in 43% of the patients and hypoplasia and dentin abnormalities in 14,3%. We could not detect a significant correlation between dental abnormalities and delayed treatment (p>0,05). DMFT index for 6 to 12 years patients (n = 12) showed that the oral health is unsatisfactory (mean DMFT = 5).

CONCLUSIONS:
Patients with Hypophosphatemic Rickets frequently present dental alterations and these are not completely recovered with the treatment, unless dental abscess and they need a periodical oral examination.
Keywords: Hypophosphatemic rickets, Children, Dental abscess, Malocclusion, Dentin alterations

Hypophosphatemic rickets represents a group of heritable disorders of phosphate renal regulation with very similar features and with three known forms of inheritance: autosomal dominant (ADHR), autosomal recessive (ARHR) and X-linked dominant (XLH), with the latter being the most common form. In all three types of hypophosphatemic rickets, an increased FGF23 activity has been demonstrated. FGF-23 inhibits renal phosphate resorption in the proximal tubule of the kidney by decreasing of the number of sodium-phosphate cotransporters (NPT2a). It also inhibits 1-alpha hydroxylase[1,2] and, consequently, diminishes the production of 1,25-$(OH)_2$ vitamin D, thus reducing the intestinal absorption of phosphate and calcium. Patients can present osteomalacia or rickets,[3] and the bone abnormalities are frequently restricted to the lower limbs and manifest clinically as pain while walking and skeletal deformities, with frequent *genu varum*. Inorganic phosphate (Pi) is required for cellular functions and skeletal mineralization, and hypophosphatemia is associated with dysplastic, poorly mineralized dentin with areas of interglobular dentin (hypomineralization), and enlarged pulp chambers.[4] Therefore, although the functional properties of odontoblasts are normal, dental and oral abnormalities can occur in these patients and have been observed more frequently in the primary dentition. Recurrent spontaneous abscess formation that affects multiple noncarious primary teeth is the principle clinical

finding described in literature.[5]

Our goal was to verify the dental abnormalities and oral health condition in patients with hypophosphatemic rickets.

We studied 20 patients (aged 0-18 years at diagnosis) with hypophosphatemic rickets who were followed at the Pediatric Nephrology Unit of Instituto da Criança – Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP). The patients presented normal renal function (clearance of creatinine ≥90 ml/minute/1.73 m^2). Only patients with good compliance were included in the study, and this assessment was based on the results of laboratory exams and adherence to the scheduled visits and exams. Patients with other renal or systemic diseases were excluded from the study.

Clinical evaluations of the patients periodically, every 3 or 4 months, in which the patients were submitted to the following exams: serum phosphate and calcium measurements and intact parathyroid hormone (PTH), alkaline phosphatase and urinary calcium. Renal ultrasonography control was performed annually to check for nephrocalcinosis. Other exams were conducted when necessary. The patients received the conventional treatment based on phosphate and 1,25-$(OH)_2$ vitamin D supplementation.

Stature was evaluated each attendance, and the mean deviation score (z-score) for height calculated according to a standard method.[6]
In this study, we employed a stature z-score ≤ - 1,9 as a marker of delayed treatment or poor compliance based on previous reports from others and our group demonstrating the correlation between a higher stature z-score and early and adequate treatment.[7,8,9,10]

Oral Examination

Oral examinations were performed at the Dentistry Division of HC-FMUSP. For each patient, we performed an anamnesis and an interview consisting of identification data, age, medical history including main complaints, presence of other diseases, familial history and treatment administered, dental history and oral hygiene. The same dentist carried out the oral examinations in all patients to assess the teeth, gingival tissue, mucosa, tongue, and hard and smooth palate.
We adopted the following parameters of the World Health Organization Oral Health Survey Basic Methods to evaluate oral health status:[11]

- **d**ecayed, **m**issing and **f**illed **t**ooth (**dmft**) index for primary (0–5 years) and early mixed dentition (6–19 years), and
- **D**ecayed, **M**issing and **F**illed **T**ooth (**DMFT**) index for late mixed dentition (11–15 years).

The results were compared with the findings obtained for the Brazilian general population.[12]
The patients were also submitted to a radiological exam (panoramic X-ray or orthopantomographic X-ray) that was interpreted by the same radiologist, who evaluated the pulp chamber, root canals, dental abscesses, dental agenesis, dental morphology, dental caries and areas of infection.

Statistical Analysis

Data are presented as the mean ± standard deviation for normally distributed data and as the median and range for non-normally distributed data. The chi-square test was used to analyze categorical data, and the correlations were tested using Pearson's correlation coefficients. A p value <0.05 was considered significant.
The Local Ethics Committee approved the protocol.

RESULTS

Fourteen of 20 patients were included in this study: five males and 9 females, aged 4 to 26 years, with a median age of 11 years. Six patients were excluded from the study because they did not fulfill the inclusion criteria for adherence. The diagnosis was established prior to 4 years of age in seven patients (50%). All of the patients were taking phosphate supplementation (20 to 90 mg/kg/day) and calcitriol (0,03 ± 0,01 µg/kg/day), and some of the patients with a tendency to develop hypercalciuria were receiving potassium citrate to prevent nephrocalcinosis

or to avoid its progression, with urinary pH control.

Oral examination

At the time of the study, six patients presented with permanent dentition, 6 patients with mixed dentition and 2 patients with deciduous teeth.

The observed tooth abnormalities are shown in Table 1. As can be observed, occlusion defects and enamel hypoplasia were significantly more frequent than dental abscesses.

Table 1
Clinical findings in 14 patients with hypophosphatemic rickets.

Clinical findings	Number of patients	%
Enamel hypoplasia	8	57.1
Occlusion defects	12	85.7
Dental abscess	1	7.1

Table 1
Clinical findings in 14 patients with hypophosphatemic rickets.

The occlusion defects included an open bite in four patients, an end-to-end rim or occlusion in 2 patients, a cross-bite in 1 patient, an ogival palate in 1 patient and 4 patients were under orthodontic treatment.

Figure 1 shows the dental clinical of a patient with hypophosphatemic rickets.

Figure 1
Clinical aspect of patient with Hypophosphatemic Rickets.

Radiological findings

Table 2 shows the radiological findings in patients with hypophosphatemic rickets. Enlarged pulp chambers were found in 43% of the patients; however, hypoplasia and dentin abnormalities were also observed.

Table 2
Radiological findings in patients with hypophosphatemic rickets.

Radiographic findings	Number of patients	%
Enlarged pulp chambers	6	42.8
Hypoplasia	2	14.3
Dentin alterations (hypomineralization)	2	14.3

Table 2
Radiological findings in patients with hypophosphatemic rickets.

Figure 2 shows the radiological findings of one patient, emphasizing the enlarged pulp chamber.

Figure 2
Radiological aspect - patient with Hypophosphatemic Rickets.

We were unable to detect a significant correlation between the presence of dental abnormalities (radiographic abnormalities, hypoplasia and malocclusion) and delayed treatment or poor compliance (stature z-score $\leq$ -1,9) ($p > 0,05$).

Oral health status

The oral health status of the patients with primary dentition was insufficient for evaluation, because in the present series, this group comprised only two patients, both of whom presented a **dmft** index = 0.

The **DMFT** index of the 6 to 12-year-old patients (12 patients) showed that oral health in this group was unsatisfactory (mean**DMFT** = 5) compared to the Brazilian general population (mean **DMFT** = 1,57).

Inorganic phosphate plays a major role in many biological systems, including cell membrane functions, energy metabolism, cell signaling, and oxygen transport. In hypophosphatemic rickets, renal proximal tubular resorption is compromised, and the patient presents with hypophosphatemia along with a relative 1,25-$(OH)_2$ vitamin D deficiency. Patients with hypophosphatemic rickets often exhibit high pulp horns, large pulp chambers, and dentinal clefts.

Malocclusion associated with hypophosphatemic rickets has not been frequently reported. However, impressive results were obtained herein (12/14 cases). An open bite was the most frequent abnormality detected and can be explained by the delay in maxillary growth in relation to the growth of the mandible (Angle class II).[19] Although taurodontism has been reported in the literature, no cases presented with an abnormality in dental morphology in

the present study.[20,21]
The management of these cases remains controversial. Some authors advocate extraction of the teeth that present periradicular abscesses and eventual restoration with implants. However, endodontic and restorative treatments may not be capable of maintaining asepsis.[22,23] **Dental abscesses are the most frequently reported complication in the literature.[13] Histologically, the teeth exhibit enlarged pulp chambers, wide predentin zone,** marked globular dentin and tubular dentin defects that extend from the pulp to the enamel. Enamel hypoplasia may or may not be present.[14] Most of the analyzed primary incisors displayed fissures that linked the enamel subsurface to the pulp horn. Abe et al (1988) have suggested that the globular dentin caused by hypophosphatemia impairs calcification.[15] The incompletely mineralized dentin exists in the form of calcospherites, which trap microorganisms and impair mechanical endodontic cleaning. These elements may explain the presence of bacteria and dental abscesses. Because enamel and dentin formation occur between 4 months *in utero* and 11 months of age, defects in the primary dentition usually cannot be prevented. According to Hillmann and Geurtsen,[16] the permanent teeth might also be affected by this mechanism, and histopathological examination of the permanent dentition is necessary.
Chaussain-Miller et al (2007) studied seven patients aged 3 to 16 years and observed that untreated or inadequately treated patients had necrotic teeth with impaired dentin mineralization.[17] They concluded that adequate treatment ensures healthy dentin development and mineralization and prevents dental necrosis. This proposition could explain our low rate of dental abscesses, because the patients included is the present study were relatively well treated (50% of the patients started treatment before 4 years of age and appeared to adhere to the treatment).
Typically, the younger the patient when the first abscess appears, the more severe is the dental manifestation.[18] However, permanent teeth form after birth, and their development could potentially be improved by the initiation of medication soon after birth.[16]
The occurrence of spontaneous abscesses following a shallow cavity preparation requires aggressive preventive dental procedures.[24] In this sense, professional dental care consisting of periodic examinations, topical fluoride applications and maintenance of good oral hygiene is imperative.[25]
Pit and fissure sealants are useful when the teeth are erupting, as they prevent the ingress of bacteria into enamel microfractures and the initiation of caries in deep pits and fissures.Few studies have evaluated oral health in patients with hypophosphatemic rickets. Baroncelli et al studied nine children and observed that**d/D** ranged from 0 to 9 and **f/F f**rom 0 to 3. The **dfmt** index was 0 in the three youngest patients.[26] Their findings are similar to ours and demonstrate that oral health in older patients is unsatisfactory compared to that in younger patients and in the healthy population.
In the present study, we evaluated the oral status of patients with hypophosphatemic rickets using a simple, reproducible method: a clinical and radiographic exam. Exams that are more detailed would be useful, but in most situations, such tests are not available. **We conclude that patients with hypophosphatemic rickets can frequently present dental abnormalities that are incompletely reversed with treatment. However, early treatment could probably avoid dental abscess formation. Moreover, dentists and pediatricians should be aware of the features of this disorder, because early intervention could prevent subsequent serious and more invasive dental procedures. Patients with hypophosphatemic rickets require periodic oral examinations; the dental care of these patients should consist of topical fluoride applications, pit and fissure sealants and maintenance of good oral hygiene.**

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RESEARCH PUBLICATION #35

Al-Jundi SH, Hammad MM, Dabous I: Case report: hypophosphatemic rickets and aggressive periodontitis: a review of the role of dentine matrix protein 1 in the pathogenesis. ***Eur Arch Paediatr Dent*; 2011 Feb;12(1):46-50**

Boukpessi T, Septier D, Bagga S, Garabedian M, Goldberg M, Chaussain-Miller C: **Dentin alteration of deciduous teeth in human hypophosphatemic rickets.** *Calcif Tissue Int*; 2006 Nov;79(5):294-300
[Source] The source of this record is MEDLINE®, a database of the U.S. National Library of Medicine.

Abstract
Familial **hypophosphatemic rickets** is in most cases transmitted as an X-**linked dominant** trait and results from mutation of the PHEX gene, predominantly expressed in osteoblast and odontoblast.
Patients have been reported to display important dentin defects, and therefore, we explored the dentin structure, composition, and distribution of extracellular matrix (ECM) molecules in **hypophosphatemic** human deciduous teeth.
Compared to age-matched controls, **the dentin from hypophosphatemic patients exhibited major differences: presence of large interglobular spaces resulting from the lack of fusion of calcospherites in the circumpulpal dentin;** defective mineralization in the interglobular spaces contrasting with normal Ca-P levels in the calcospherites on X-ray microanalysis; abnormal presence of low-molecular weight protein complexes recognized on Western blots by antibodies against matrix extracellular phosphoglycoprotein (MEPE), dentin sialoprotein, osteopontin, and reduced osteocalcin (OC) level; and accumulation in the interglobular spaces of immunolabeling with antibodies against DSP, **dentin matrix protein,** bone sialoprotein, MEPE and OC, while chondroitin/dermatan sulfate glycosaminoglycans were exclusively located inside calcospherites.
Alterations of the post-translational processing or partial degradation of some ECM appear as key factors in the formation of the defective **hypophosphatemic** dentin.

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SUPPLEMENTAL LINKS

1) NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION
   http://www.ncbi.nlm.nih.gov/sites/ga?disorder=XLH
2) National Institute of Health (XLH Search Results)
   http://ghr.nlm.nih.gov/condition/hereditary-hypophosphatemic-rickets
   "Other signs and symptoms of hereditary hypophosphatemic rickets can include premature fusion of the skull bones (craniosynostosis) and dental abnormalities. The disorder may also cause abnormal bone growth where ligaments and tendons attach to joints (enthesopathy). In adults, hypophosphatemia is characterized by a softening of the bones known as osteomalacia."
3)