What is XLH?

XLH is also known as X-Linked Hypophosphatemia (sometimes also spelled as hypophosphataemia), X-Linked Hypophosphatemic Rickets, Familial Hypophosphatemia, Vitamin D-Resistant Rickets (VDRR) Rickets and even Genetic Rickets. Its notable characteristics are bowed legs, short stature, poor teeth formation causing spontaneous dental abscesses, and low blood phosphorus levels.

Quick Facts

- XLH is a genetic metabolic condition also known as X-Linked Hypophosphatemia (sometimes also spelled as hypophosphataemia), X-Linked Hypophosphatemic Rickets, Familial Hypophosphatemia, Vitamin D-Resistant Rickets (VDRR) and even Genetic Rickets.
- **X-Linked Hypophosphatemic Rickets (XLH) primarily affects bone and tooth development. The result is that the bone and teeth are not as well mineralized as they should be. Its notable characteristics are bowed legs, short stature, poor teeth formation causing spontaneous dental abscesses**, elevated alkaline phosphatase (mostly in children) and low blood phosphorus levels due to phosphate wasting (high urine phosphorus). Intact parathyroid hormone (PTH) can also be mildly elevated even before treatment.
- Diagnosis is often made by considering a number of factors such as family history, blood tests and observation of symptoms.
- Since Symptoms vary from patient to patient in their severity, and labs often do not report pediatric reference ranges, diagnosis can sometimes be difficult.
- While each patient's needs may differ and must be determined by his own physician, the standard treatment regimen for X-Linked Hypophosphatemic Rickets (XLH) involves carefully balanced amounts of phosphorus and a specifically-activated form of vitamin D, which together improve the body's ability to process the raw materials necessary for healthy bone formation.
- The physician managing XLH care must be one who understands the counter-intuitive nature of its treatment.

Supplemental Research on XLH and Congenital Bone/Teeth Abnormalities

From the XLH website. http://xlhnetwork.org

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

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.

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

Dental problems associated with hypophosphataemic vitamin D resistant rickets.Goodman JR; Gelbier MJ; Bennett JH; Winter GB Int J Paediatr Dent, 8(1):19-28 1998 Department of Paediatric Dentistry, Eastman Dental Hospital and Institute, London, UK.

OBJECTIVE: To review a series of cases of hypophosphataemic vitamin D resistant rickets. SUBJECTS INCLUDED: Seventeen cases, aged between 2 years 1 month and 15 years 9 months at first referral, and with an established diagnosis of vitamin D resistant rickets from

twelve families were included in the review. Information was drawn from patient records for follow-up periods between 9 months and 20 years 4 months. SETTING: All subjects had been referred to the Eastman Dental Hospital between 1973 and 1997. FINDINGS: Abscessed non-carious primary and/or permanent teeth were a presenting feature in eleven of the seventeen cases. Although attrition and exposure of the abnormally formed dentine accounted for the route of infection in primary teeth, the route for microbial invasion of pulpal tissues in permanent teeth remained unexplained in a number of patients. The possible part played by infractures of the enamel as a portal of entry for infection is discussed. Enamel defects were observed in only six patients, in three of whom these changes were limited to the primary dentition. Taurodontism of permanent molar teeth was confirmed as a feature of the condition in the more severely affected male subjects

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

The basic dental defects in vitamin D-resistant rickets seem to be manifested in dentin. Enamel is usually reported to be normal. This histologic examination showed the penetration of microorganisms through the calcified structures of the enamel layer without visible caries. The microorganisms passed through the dentinoenamel junction and invaded dentin, which was characterized by calcospherites and large amounts of interglobular dentin. Furthermore, microorganisms could be detected in dentinal tubules, which were exposed to the oral cavity when enamel was removed. However, large areas of tertiary dentin extended between such tubules and the pulp. These light microscopic results suggest that clinical manifestations, such as pulp necrosis and periapical lesions (without carious defects) may be caused by the penetration of microorganisms through microclefts of the enamel layer as well as pathologically altered enamel microstructures of affected teeth.

Colin Steeksma has spent considerable time searching the literature for useful information on teeth problems in Hypophosphatemia. Following are some notes he's contributed to the F-HYPDRR mailing list:

Colin has contributed a file of abstracts, of which I've managed to mount the first half. The second half on quick browsing looks just like the first!? Maybe they are just duplicate files -- I'll check this out over the next few days, in which time I'll also seek to hyperlink titles with abstracts, as I've done with the other pieces.

Briefly, Colin recommends the following references as a useful contribution to our understanding of the problems of teeth in Hypophosphatemia:

For clinical info- consult the following journal articles and authors:

- Any article by K Abe or T Ooshima in Japan.
- Any article by WK Seow in Australia.

(One Specific title to follow for each). Numbers at end are medline ref numbers.

- Abe K, Ooshima T, Lily TS, Yasufuku Y, Sobue S

Structural deformities of deciduous teeth in patients with hypophosphatemic vitamin D-resistant rickets. Oral Surg Oral Med Oral Pathol 1988 Feb;65(2):191-8 ***88143604***

- Archard HO

The dental defects of vitamin D-resistant rickets. In: Birth Defects (1971 Jun) 7(7):196-9 ***75109614***

- Breen GH

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- Fadavi S, Rowold E

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- Herbert FL

Hereditary hypophosphatemia rickets: an important awareness for dentists. In: ASDC J Dent Child (1986 May-Jun) 53(3):223-6 ***86224833***

- Larmas M, Hietala EL, Simila S, Pajari U

Oral manifestations of familial hypophosphatemic rickets after phosphate supplement therapy: a review of the literature and report of case. ASDC J Dent Child 1991 Jul-Aug;58(4):328-34 ***92042986***

- Rakocz M Keating J 3d Johnson R

Management of the primary dentition in vitamin D-resistant rickets. In: Oral Surg Oral Med Oral Pathol (1982 Aug) 54(2):166-71 ***83013944***

- Seow WK

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

- Seow WK et al

Effect of familial hypophosphatemic rickets on dental development: a controlled, longitudinal study. In: Pediatr Dent 1995 17(5):346-50

CASE STUDY

Introduction to Family with an XLH Spontaneous Child

Personal Case History from British Columbia

Our son born in 1987, is under treatment for Hypophosphatemic Vitamin D-Resistant Rickets (HVDRR) now more commonly known as X-Linked Hypophosphatemia (XLH), diagnosed when he was two and a half years old.

This is a metabolic gene disorder first identified in the 1930's, and although comparatively rare, is now recognized as the most common form of rickets in the developed world. It is not nutrition related. The genetic defect, which is passed down via the X-Chromosome, is known to cause renal tubular phosphate wasting, and is theorized to also affect Vitamin D metabolism. It affects the bones, teeth, kidneys, parathyroid gland, and upsets the balance of calcium/phosphate levels. Naturally growth is stunted. Untreated it appears to lower the immune system, (not noted scientifically) which allows the infant sufferer to catch every cold, flu and ear infection that comes around.

At present, the best treatment requires daily doses consisting of 1-alpha-hydroxycholicalciferol (a Vitamin D3 supplement) and Neutra-phos (a sodium phosphate). Treatment has evolved over the years from straight Vitamin D or phosphate supplementation only, to combinations of both, using different variations of Vitamin D to compare re-absorption levels for calcium and phosphate. Since there have been few studies possible under consistent treatment regimens, and given the widely varying degrees of severity from one patient to the next, there is little known of long-term effects of the treatment itself. Currently, there is growing evidence to indicate that nephrocalcinosis (a deposition of calcium phosphate in renal tubules) of the kidneys is a probable outcome of the treatment. Nephrocalcinosis blocks the tubules and decreases the ability to function properly-causes kidney stones and possible renal failure.

My son showed early bowing of legs, tibial torsion, frontal bossing, and enlarged wrist and ankle joints. His head appears abnormally large, as well. His height growth pattern before treatment was not even near the chart standard percentiles. Since treatment, he has remained below the 5th percentile or between the 5th and 10th.

We suspected something was wrong due to the above symptoms, but accepted the opinion of our G.P, pediatric and orthopedic specialists; all of whom had varying diagnoses from: "his diapers are to large", to: "he needs a brace to straighten his legs out", to: "it's just him - his father's family is short with big heads, too"!

Luckily, (sort of) he contracted pneumonia, and was seen again by the same pediatric specialist. It was then he noticed his skeletal abnormalities such as barreled chest, bowed legs, toed-in feet, short stature and large head. He had trouble even toddling. The doctor then referred him to BC Children's Hospital for metabolic and genetic testing.

There he was diagnosed with HVDRR (XLH); a spontaneous, or sporadic case, having no family history.

In 1995 at age nine, he was having many challenges with his dental health. Most, or at least, many dentists have little knowledge of this disease, and its effect on teeth. Paradoxically, dentists could sometimes be the first health professionals to diagnose a patient, especially in those patients (usually females) who do not present bone malformation as severely. His teeth, upon visual examination, look beautiful, hard and well-formed. There is no enamel hypoplasia, as some might expect. It is in the formation of the unseen dentin and pulp that there are problems. This even fooled a pediatric dental specialist, who saw him when he was five years old, and who could have prevented most of his future tooth loss.

He has had, to date, all of his upper, and four lower primaries removed due to abscessing. His remaining primaries were sealed with chrome crowns for the less noticeable teeth, and a coating for the visible canines. Periapical x-rays taken during the crowning procedure showed a shadow in the erupting upper front left secondary tooth, possibly indicating it was already compromised.

Medically speaking, his rickets appear, under radiology, to have healed. We are concerned about the possibility of tertiary hyperparathyroidism (usually requiring a parathyroidectomy), nephrocalcinosis brought on by the drug therapy (which could result in renal failure) and of course, osteomalacia in his adulthood.

By way of update, in 2000, five years after his dental operations, he has suffered no more abscesses, and is almost completed successful orthodontic work to have his teeth straightened as they came in. The primaries that were capped and since fallen out also gave him no more trouble. A definite personal indication that at present that treatment (chrome crowns on primaries) is the best chance for a nice smile and healthy teeth.

Any parents reading this will already be concerned that doctors and other health professionals, with their busy schedule, volumes of information they must try and remember, and their own personal challenges, cannot be expected to know everything, or to always make the right decisions. As parents, if we suspect a problem, we must follow it up thoroughly and to our satisfaction. Once diagnosed, if the problem is rare, or new to your doctors, nurses, and dentists, we must educate ourselves enough so that we may increase their knowledge to better deal with our child who happens to be their patient.

If your doctor or dentist is unwilling to believe you, or admit they don't know the answer, or even listen to your questions, move on to someone else who will.

Our purpose in writing this article is to raise awareness of this disorder which, although rare, will by nature of its genetic transmittal become more prevalent. Undeveloped countries usually present nutritional rickets problems; genetic cases are prevalent in developed nations. We therefore suspect there may be links between either the mother's work environment, or heavy metal toxicity, or pesticides and pollution, and the spontaneous generation of HVDRR. If so, this disorder will no doubt multiply. In any case, our focus should

not be on the ultimate causes of a spontaneous case, but to find a cure, and support those with XLH until one is found.

One of our main goals is to create a support group or a society of some sort, to initiate and continue research into the disorder.

In the research area, we are interested specifically in the pursuit of the following:

1. anything that will assist or cause dentin to repair and/or build in teeth
2. substances that will coat the teeth (other than chrome crowns) to prevent wear and tear through the thin enamel HVDRR patients display, which allows bacteria to infect the pulp, causing necrosis.
3. replacement for the current medical treatment; one which will not show side-effects as mentioned above.
4. Parathyroid hormone regulators that will also not compromise the renal phosphate absorption.
5. Any dietary information that may assist the current therapy, medically or dentally.
6. now that the location of the HYP gene (PHEX) has been discovered, we are eager to help identify and study the crucial substrate of the endopeptidase PHEX gene that is affected in XLH..

If anyone reading this article happens to be, or knows of, a researcher, doctor, dentist, or biochemist, interested in this field, or a sufferer of this disorder, please provide us with their contact information, if they are agreeable.

Contact us through via email: Colin Steeksma

Dental Infections in Children with VDRR

Formation of the dentine portion of the teeth is very dependent upon calcium/phosphate metabolism. The cells responsible for making dentine are in the pulp. The pulp is that part of the tooth that has the cells, blood vessels, and nerves. If there is a calcium/phosphate metabolism problem while the tooth is forming, the dentine may be improperly formed. This could lead to a situation where there is a direct connection(s) between the mouth and the pulp, which is(are) undetectable visually as well as on radiographic examination. As you know there are millions of bacteria growing in the mouth. These bacteria are small enough to pass through this(these) connection(s) into the pulp. The pulp behaves just like any other tissue of the body in this situation. That is, an immune response is started to fight off the invasion of the bacteria. The pulp is different from other body tissues only in that it is surrounded by the tooth. Other tissues of the body have access to collateral circulation, usually from all around.

Apparently,because the pulp has its circulation restricted to coming through the apex of the root, the defense is a losing one. In the case of the tooth, another consideration is that there is a constant supply of bacteria in a very confined space unreachable by the blood supply. That

is, the bacterial attack is relentless. The result is that the inflammation/infection in the pulp is progressive, so that in the end the whole of the pulp is infected. The blood supply is either compromised or completely destroyed in the pulp, a circumstance which allows the bacteria to occupy the space previously occupied by the pulp. Antibiotics are only effective when the circulation can bring them into contact with the bacteria they are intended to kill. In the case of the pulp that has been destroyed by infection there is a constant repository of bacteria, with antibiotics only able to contact those bacteria that emerge from the root end. So, antibiotics are of limited value in the treatment of infected pulps.

In summary:

1. Vitamin D resistant rickets can have an effect on the formation of dentine.

2. Bacteria can penetrate these dentine defects, thereby infecting the pulp.

3. If there is no intervention, the pulp infection is progressive.

4. Antibiotics have limited usefulness. The antibiotic of choice is one that would kill bacteria usually found in the mouth. An example is penicillin V.

5. Long term there are two therapies that can be applied by dentists. They are extraction or root canal treatment.

Dr. Marc K. Drezner, M.D., Professor of Medicine and Chief, Division of Endocrinology, Metabolism and Nutrition, and Director, Sarah W. Stedman Nutrition Center wrote to Colin Steeksma in a private email that:

". . .the dental abnormality in affected patients is actually better understood than you may think; the propensity for abscesses is not a defect in the enamel or the dentin per se but rather the inability of the calcospheres in dentin to coalesce leaving soft tissue areas within the teeth into which bacteria can move (Lyles, Burkes, McNamara, Harrelson, Pickett, Drezner; J Clin Endocrinol Metab 60:565-573, 1985); unfortunately the abnormal events happen in utero (for the most part) and correcting the defect after birth appears a formidable poorly understood task . . ."

Hillmann G; Geurtsen W

Pathohistology of undecalcified primary teeth in vitamin D-resistant rickets: review and report of two cases.

In: Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 1996 Aug, 82:2, 218-24

Abstract

The basic dental defects in vitamin D-resistant rickets seem to be manifested in dentin. Enamel is usually reported to be normal. This histologic examination showed the penetration of microorganisms through the calcified structures of the enamel layer without visible caries. The microorganisms passed through the dentinoenamel junction and invaded dentin, which was characterized by calcospherites and large amounts of interglobular dentin. Furthermore, microorganisms could be detected in dentinal tubules, which were exposed to the oral cavity when enamel was removed. However, large areas of tertiary dentin extended between such tubules and the pulp. These light microscopic results suggest that clinical manifestations, such as, pulp necrosis and periapical lesions (without carious defects) may be caused by the penetration of microorganisms through microclefts of the enamel layer as well as pathologically altered enamel microstructures of affected teeth.

Address

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University Hannover, Dental School, FRG.

Review of the Literature: (Source abstract is hyperlinked, titles are below this review)

According to the available literature dating from 1965 to 1996, HVDRR always manifests itself, in some form, in the dentition of the patient, with seemingly a prevalence of abscesses reported among the HVDRR population (1, 2, 3, 4, 5, 6, 7, and 8) .

In fact, dentists are sometimes the first to see the complications arising from the disease, and can be the source of end diagnosis (9, 10, 11 and 12) .

However, families themselves are sometimes not even aware of the disease in their midst (13) .

This makes it even more imperative, in our opinion, that dentists be aware and alert to its symptoms, and possible appearance.

There have occasionally been giant cell lesions associated with HVDRR, and one even reported in the sinus (14) .

Unfortunately, the current ongoing medical treatment for the hyposphatemia and rickets does not correct the dental manifestations in any way (15, 16) .

Although there was a suggestion in one report that if the mother was already having phosphate supplementation, the primary dentition may be less affected (17) , we believe more recent historical and anecdotal data indicate supplementation by an affected mother makes little difference in dentition of her affected children.

In fact there is some disagreement as to the actual cause of the abnormalities in the formation of the teeth of HVDRR patients. Some research points to the usual inconsistent balances in Ca and P levels, others indicate an involvement with Zinc and Magnesium, and yet another indicates that the concentrations of PTH (parathyroid hormone) levels can effect the pre-dentin and dentin formation (18, 19)

In any case, this medical disorder appears to affect the deciduous (primary) teeth directly, sometimes causing frequent abscessing, which subsequently can require extraction of the affected primaries, and the sealing of the remaining primaries and existing permanent teeth (7, and 20) .

The outward appearance of the teeth can be close to perfect, since the enamel formation is shown to be unaffected in some of these cases (1, 7, and 8) .

Titles of Source Articles

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

2) Abe K Ooshima T Sobue S Moriwaki Y The crystallinity of human deciduous teeth in hypophosphataemic vitamin D-resistant rickets. In: Arch Oral Biol. (1989) 34(5):365-72

3) Abe K, Ooshima T, Masatomi Y, Sobue S, Moriwaki Y Microscopic and crystallographic examinations of the teeth of the X-linked hypophosphatemic mouse. In: J Dent Res 1989 Nov;68(11):1519-24

4) Abe K Masatomi Y Nakajima Y Shintani S Moriwaki Y Sobue S Ooshima T The occurrence of interglobular dentin in incisors of hypophosphatemic mice fed a high-calcium and high-phosphate diet. In: J Dent Res (1992 Mar) 71(3):478-83

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6) Archard HO The dental defects of vitamin D-resistant rickets. In: Birth Defects (1971 Jun) 7(7):196-9

7) Breen GH Prophylactic dental treatment for a patient with vitamin D-resistant rickets: report of case. In: ASDC J Dent Child (1986 Jan-Feb.) 53(1):38-43

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

9) Diner H Chou MD Dental diagnostic problems of potential genetic significance: the dental practitioner as geneticist in the developmental disabilities clinic. In: Birth Defects (1980) 16(5):151-70

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

11) Herbert FL Hereditary hypophosphatemia rickets: an important awareness for dentists. In: ASDC J Dent Child (1986 May-Jun) 53(3):223-6

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

16) Larmas M, Hietala EL, Simila S, Pajari U Oral manifestations of familial hypophosphatemic rickets after phosphate supplement therapy: a review of the literature and report of case. In: ASDC J Dent Child 1991 Jul-g;58(4):328-34

17) Seow WK Romaniuk K Sclavos S Micromorphologic features of dentin in vitamin D-resistant rickets: correlation with clinical grading of severity. In: Pediatr Dent (1989 Sep) 11(3):203-8,

18) Sakakura Y Effects of parathyroid hormone on odontogenesis of the mouse embryonic molar tooth in vitro. In: Calcif Tissue Int 1987 Jan;40(1):49-54

19) Shellis RP Structural organization of calcospherites in normal and rachitic human dentine. In: Arch Oral Biol (1983) 28(1):85-95

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