Hypophosphatasia- Dental considerations

Rohini S.[1] and Deepa Gurunathan[2]

[1]Student, [2] Professor, Department of Pedodontics, Saveetha Dental College and Hospitals Saveetha Institute of Medical and Technical Sciences, Chennai – 600077

(Received: April 2019 Revised: July 2019 Accepted: September 2019)

Corresponding author: **Deepa Gurunathan.** Email: drgdeepa@yahoo.co.in

ABSTRACT

Hypophosphatasia is a hereditary condition characterized by decreased level of serum alkaline phosphatase (APase), elevation of phosphoethanolamine (PEA) in urine, premature loss of teeth, and skeletal abnormalities. Hypophosphatasia (HPP) is also a rare inherited metabolic disease in which mutations in the ALPL gene (encoding tissue-nonspecific alkaline phosphatase) results in varying degrees of enzyme deficiency. Hypophosphatasia manifests in a spectrum of symptoms, including early primary tooth loss (root intact) and alveolar bone mineralization defects. Premature loss of primary and permanent teeth is due to disturbed cementum formation and tooth roots in affected patients do not adequately attach to absorbed alveolar bone due to malformed cementum. Dental professionals are in a position to identify and recognize hypophosphatasia features for timely referral and optimal disease management.

Keywords: Alkaline Phosphatase; hypophosphatasia; hereditary; metabolic disease; mineralization; phosphoethanolamine.

INTRODUCTION

Hypophosphatasia is a rare genetic disorder with autosomal dominant and autosomal recessive inheritance. It is characterized by a mineralization defect affecting the bones and teeth, which is associated with deficient and reduced enzymatic activity of tissue-nonspecific alkaline phosphatase (TNSALP; 1) Mutations of the ALPL gene (1p36.1-p34), which encodes TNSALP, are responsible for the reduction in enzymatic activity. Tissue nonspecific alkaline phosphatase enzyme is expressed in the liver, bones, and kidneys, and also found in the enamel, dentine, cementum, and alveolar bone. During reduced enzymatic activity of TNSALP, substrates such as pyridoxal 50 -phosphate, inorganic pyrophosphate, and phosphoethanolamine (PEA) are not broken down, they build up and produce toxic effects (2). Hypophosphatasia is a hereditary condition characterized clinically by

- Decreased level of serum alkaline phosphatase (APase),
- Elevation of PEA in urine,
- Premature loss of teeth, and
- Skeletal abnormalities.

It usually presents as a continuum, from childhood to adulthood, and its clinical expression changes over the course of the patient's lifetime, in particular during certain periods (adolescence, menopause) or in response to specific events (fractures, ingestion of vitamin D). With increasing age, the problems of osteoarthritis, osteoporosis, nephron-calcinosis, muscle weakness, and repeated fractures may exacerbate the clinical situation (3). Six clinical forms of Hypophosphatasia (HPP) have been classified based on the age of onset of the symptoms. The six forms include perinatal (fatal), benign prenatal, infantile, childhood, adult, and odonto-HPP, which is limited to orodental manifestations. The perinatal form is the most severe form and occurs in utero or at birth, with total absence of bone mineralization. The benign prenatal form can be detected through bone-related symptoms in the prenatal period. Its course is more favorable than the severe perinatal form. The infantile form typically develops at around 6 months of age and results in severe bone deformities and rickets. It also presents with respiratory complications, premature craniosynostosis, hypercalcemia, and nephron-calcinosis (4). Additionally, the onset of epileptic seizures secondary to the build-up of pyridoxal phosphate occurs often as a sign of incompatible with survival.

The childhood form of hypophosphatasia appears after 6 months of age and presents in very diverse forms. Bone deformities may be minor, and the disease may result only in the early loss of the primary teeth, however in some cases, it is associated with moderate HPP related rickets, short stature, delayed walking or gait disorders, and pain in the lower limbs. Adult HPP tends to manifest in middle age, but there is usually history of premature loss of primary teeth. It involves early loss of the permanent teeth, which is usually associated with multiple fractures, osteomalacia, chondrocalcinosis, osteoarthropathy, and stress fractures (5).

Odonto-HPP is limited to dental manifestations alone and can occur at the age of 13 years. Alveolar bone loss is apparent, with no other skeletal abnormalities. The most common oral manifestation presented with Hypophosphatasia includes: Lack of cementum formation, root resorption, enamel hypoplasia and delayed appearance and premature decay of deciduous and permanent dentition and total tooth loss before 20 years of age. There is no male or female predilection and mean age for the first tooth to be lost is 21-22 months (6). Enlarged pulp spaces and reduced cortical bone thickness of the mandibular angle are one of the common characteristics. Roots either fail to develop fully or there is early resorption of the apices.

Etiology and pathogenesis

Alkaline phosphatase (ALP) is essential for skeletal mineralization. Its main role is the liberation of inorganic phosphate (Pi) for hydroxyapatite (HA) crystal propagation. This enzyme is found to be abundant also in non-calcifying tissues such as liver, intestine, and placenta. There are four ALP isoenzymes, encoded by four separate genes: three isoenzymes are tissue specific (intestinal, placental, and germ cell ALP) and the fourth is the tissue nonspecific alkaline phosphatase (TNSALP), present in all cell types (7). The extracellular accumulation of phosphoric compounds, especially inorganic pyrophosphate, leads to the impairment of hydroxyapatite crystal formation and growth, thereby producing rickets and osteomalacia, respectively in children and adults and a wide range of other symptoms (8).

Clinical signs and characteristic symptoms of hypophosphatasia

Dental symptoms – Early exfoliation of teeth

Early loss of primary teeth before the age of 3 years is seen, either affecting all teeth or just those in the incisor– canine region. The primary teeth are shed with their roots intact. The first sign is often tooth mobility, which leads the patient and their family to seek advice; subsequent radiographs reveal severe alveolar bone loss. Early loss of primary teeth exists in all forms of hypophosphatasia and should be part of the medical/dental history questionnaire for patients of all ages. The clinical picture in older children and adults with hypophosphatasia generally includes the early loss of all or some of the permanent teeth. However, there are no associated skeletal deformities, such as in odonto-hypophosphatasia (9). Primary incisors, canines and primary molars exfoliate before the permanent teeth began to erupt. In most of the reported cases of hypophosphatasia there was premature exfoliation of teeth, with hypoplasia or aplasia of the cementum. Since the stability and retention of the teeth depend on the attachment of the periodontal fibers from the cementum to alveolar bone, the irregular deposition or the absence of the cementum accounts for the premature loss of teeth. In the previous studies it was suggested that normal cementogenesis does not take place in these affected patients and abnormality of the cementum matrix formation was directly due to the deficiency of the enzyme alkaline phosphatase (10).

The dysregulation of pyrophosphate causes abnormalities affecting the formation of the cementum covering the tooth root, which is essential for tooth structure and attachment to the alveolar bone, thereby contributing to early tooth exfoliation. Problems with the formation of dentine and amelogenesis also occur. In children with hypophosphatasia, hypercalcemia may result in a poor appetite and eating problems, and severe dental caries. Zones of predentin were unusually wide within the pulps of affected teeth. The odontoblasts were reduced in number. In addition, dentinal tubules were enlarged and less numerous than in normal teeth. The remainder of the pulp tissue appeared to be normal. There were changes indicative of retarded calcification. Interglobular dentin was abundant, the over-all thickness of dentin was reduced, and incremental lines were both more numerous and more prominent than expected. In the roots of some affected teeth, areas of osteodentin formation were observed. This is usually found only in the coronal portion of the pulp and often represents a response to injury. Osteodentin rarely replaces primary dentin in developing teeth (11). Ordinarily, root resorption is not a continuous process. Intervals of resorptive activity alternate with periods of rest and reposition of cementum. This process is responsible for the retention of deciduous teeth until most of the root has been resorbed.

Symptoms of bone

Bone fragility and deformities may also be present in utero or at birth. Growth in stature and weight gain is poor in forms of hypophosphatasia that manifest at an early age. In childhood forms of HPP, the patient often finds it difficult or even impossible to walk (resulting in a limp and the use of crutches or a wheelchair). Pain, being late to sit up or walk, growth retardation, and muscle weakness are all warning signs for hypophosphatasia. Associated symptoms are premature craniosynostosis with intracranial hypertension, plagiocephaly, or quite the opposite, the presence of a wide fontanelle that is slow to close, metaphyseal abnormalities, diaphyseal incurvation, and highly fragile bones (12).

Clinical oral examination

The clinical examination of patients with hypophosphatasia will always focus on assessing loss of primary/permanent teeth in relation to the patient's age. The mobility of teeth should be assessed together with the health of the periodontium.

Radiographs may include a panoramic image and also includes intraoral periapical radiographs of the areas affected, or even assessment by cone beam computed tomography (CBCT; 13).

Laboratory diagnosis

The pathognomonic symptom is subnormal bodily fluid activity of basic enzyme. In general, the clinical severity of hypophosphatasia reflects the degree of enzyme deficiency. The most sensitive substrate marker for hypophosphatasia is an increased pyridoxal 5'-phosphate (PLP) plasma level, which often correlates with the disease severity. And, though it remains solely a hunt technique, quantitation of urinary inorganic pyrophosphate (PPi) levels, which are elevated in most hypophosphatasia patients, has been reported to accurately detect carriers. In addition, increased urinary levels of PEA are observed in most patients. Differential diagnosis for this disease includes osteogenesis imperfecta, rickets and achondrogenesis (14). Due to the mild nature of hypophosphatasia, the detection of it is not easy. Many such cases have been overlooked and never been diagnosed. Thus, it is important to test the quantity of PEA in the urine and the level of serum alkaline phosphatase when hypophosphatasia is suspected. If PEA is elevated in the urine, the family members should also be tested for hypophosphatasia, or preferably, they should be referred to the genetic clinic for further investigation. The elevation of PEA in the urine alone, however, is not a clear indication of the disease because patients with a variety of metabolic bone diseases and different endocrine disorders also excrete a considerable amount of PEA in the urine (15). For odonto-hypophosphatasia or non-severe forms of HPP (childhood or adult HPP), the level of alkaline phosphatase is closer to the lower limit of normal than in the severe perinatal and infantile forms of hypophosphatasia. Residual enzymatic activity may in fact, continues to minimize the clinical manifestations. In principle, urine PEA tests are carried out only if there is any doubt regarding the diagnosis; levels are elevated in patients with Hypophosphatasia. Serum pyridoxine 50 -phosphate is also elevated and is a sensitive marker for hypophosphatasia. This assessment in children is always completed by an analysis of the following parameters: calcium, phosphate, parathyroid hormone, and vitamin D (16).

Enzyme-replacement therapy for hypophosphatasia

Asfotase Alfa is the first agent approved for the treatment of perinatal, infantile, and childhood-onset forms of hypophosphatasia. A recombinant form of tissue nonspecific alkaline phosphatase, asfotase alfa is intended to enhance deficient alkaline phosphatase enzyme activity in patients with these forms of hypophosphatasia. Safety and efficacy of asfotase alfa were established in patients with perinatal, infantile, childhood-onset hypophosphatasia who received treatment for up to 6.5 years. Results showed that patients with perinatal- and infantile-onset hypophosphatasia treated with asfotase alfa had improved overall survival rate and showed improvements in growth and bone health (17). Asfotase alfa is run as an injection (3 to six injections per week) in weight-based dosing regimens. Warnings and precautions embrace hypersensitivity reactions, lipodystrophy at injection sites (i.e. abnormal thickening or dilution of the skin), and ectopic calcifications in the eye and kidneys. The most common adverse reactions occurring in 100% or a lot of patients embrace injection site reactions, lipodystrophy, posture calcifications, and hypersensitivity reactions. Alkaline phosphatase is sensitive to magnesium; in some cases, magnesium acts as a co-factor, while in others it actually stimulates activity of the enzyme. On this basis, orally or systemically administered magnesium has been tried in patients with hypophosphatasia. The value of this therapy remains to be determined (18).

Dental treatment

As for dental treatment for hypophosphatasia patients, periodontal management is very important for teeth with mobility. Although that may not recover a healthy condition, it helps maintaining the stability of the current condition, thus enabling preservation of affected teeth as long as possible. In addition, application of a partial denture is a useful treatment modality for cases with tooth loss, as it solves not only aesthetic but also functional problems, such as mastication and speech (19). Many studies have been done in patients affected with hypophosphatasia. One of the studies done by Beumer *et al.,* in seven children with hypophosphatasia from six families over a period of several years, showed results of excessive amounts of PEA in the urine and had low levels of serum alkaline phosphatase activity (20, 21). Prior to and during the course of exfoliation of teeth, there was no clinical evidence of inflammatory periodontal disease. In some instances, the teeth appeared to be extruded. Upon exfoliation, the teeth examined were noted to have minimal apical root resorption. All these seven patients were diagnosed with childhood hypophosphatasia. In all seven patients, age of onset,

physical characteristics, and chemical findings were consistent with the diagnosis of "childhood" hypophosphatasia. The results indicated that this condition was a symptom complex with variable signs; however premature loss of teeth appeared to be an invariable essential feature. Most of the clinical cases of hypophosphatasia reported in the dental literature are of childhood type, i.e., when the condition was first diagnosed in children after 6 months of age. In all of these reported cases, the patient's serum alkaline phosphatase levels were at subnormal value or at the lower end of the normal range. The other consistent findings include the elevation of PEA in the urine and premature exfoliation of primary teeth. However, bony abnormality is only an occasional finding. Other dental abnormalities related to the condition-embody enlarged pulp chambers, hypocementosis and loss of alveolar bone.

In another study done by Okawa *et al.*, (22), two patients were diagnosed with hypophosphatasia. Both of the patients presented with exfoliation of primary anterior teeth before the age of 4 years and the roots of those teeth appeared to have no root resorption, both of the signs should be regarded as typical dental findings in hypophosphatasia cases (23). The patients were ultimately diagnosed with odonto type and no treatments were performed by the attending pediatricians (24). Mild forms of hypophosphatasia, such as odonto type, are thought to occur most often, with a frequency of 37% reported. Although no medical approaches for cases with odonto kind are reported, affected patients may develop possible problems in the jaw bones. Thus, we tend to think about the necessity to develop some choices for improvement of the condition and its associated symptoms. In addition, communication between paediatric dentists and pediatricians is very important to higher treat patients with hypophosphatasia (25). Hence hypophosphatasia is one of common disease associated with early exfoliation of both primary and permanent teeth to occur most commonly from birth to adulthood. It requires early recognition by the dentist and proper management of the disease.

CONCLUSION

Unexplained premature loss of permanent teeth of young patients always causes anxiety and frustration to the concerned parents. As there are many causes for this phenomenon it the prime duty of the dentist to carefully determine the exact cause of the problem. A chief complaint of such should not be taken lightly. The dental surgeon and especially the pediatric dentist are at the heart of the challenges associated with the diagnosis, management, and follow-up of patients with hypophosphatasia.

REFERENCES

1. Album, M. M., Hope, J. W., Bongiovani, A. M., Root, A. W., Marino, J., Spencer, D. M. H.: Hypophosphatasiaa: Case report. J Dent Child. 1969; 36: 403-409.
2. Baer, P. N., Brown, N. C., Hanner, J. E. Hypophosphatasia: report of two cases with dental findings. Periodontics. 1964; 2: 209-215.
3. Casson, M. H. Oral manifestations of primary hypophosphatasia. Br Dent J 1969; 127: 561-566.
4. Eastman, J., Bixler, D. Urinary phosphoethanolamine: normal values by age. Clin Chem 1980; 2(6): 1757.
5. Tunison, W., Flores-Mir, C., El Badrawy, H., Nassar, U., El-Bialy, T. Dental arch space changes following premature loss of primary first molars: A systematic review. Pediatr Dent 2008; 30: 297-302.
6. Cuoghi, O. A., Bertoz, F. A., de Mendonca, M. R., Santos, E. C. Loss of space and dental arch length after the loss of the lower first primary molar: A longitudinal study. J Clin Pediatr Dent. 1998; 22: 117-120.
7. Lin, Y. T., Chang, L. C. Space changes after premature loss of the mandibular primary first molar: A longitudinal study. J Clin Pediatr Dent. 1998; 22: 311- 316.
8. Mithun Raja, S., Meenakshi, M., Ganesh, J. Premature loss of primary teeth and developing malocclusion - A review. Journal of Pharmacy Research. 2018; 12(2): 190-193.
9. Bianchi, M. L. Hypophosphatasia: an overview of the disease and its treatment. Osteoporos Int. 2015; 26: 2743–2757.
10. Mornet, E., Hofmann, C., Bloch-Zupan, A., Girschick, H., Le Merrer, M. Clinical utility gene card for: Hypophosphatasia an update. Eur J Hum Genet. 2014; 22: 2013.177.
11. Mornet, E. Hypophosphatasia. Orphanet J Rare Dis. 2007; 2: 40.
12. Lezot, F., Descroix, V., Hotton, D., Mauro, N., Kato, S., Berdal, A. Vitamin D and tissue non-specific alkaline phosphatase in dental cells. Eur J Oral Sci 2006; 114: 178-182.
13. Rockman-Greenberg, C. Hypophosphatasia. Pediatr Endocrinol Rev. 2013; 10: 380–388.
14. Reibel, A., Maniere, M.C., Clauss, F. Orodental phenotype and genotype findings in all subtypes of hypophosphatasia. Orphanet J Rare Dis. 2009; 4: 6.
15. Bethune, J. E., and Dent., C. E. Hypophosphatasia in the Adult, Am. J. Med. 1960; 28: 45.
16. Van den Bos, T., Handoko, G., Niehof, A., Ryan, L. M., Coburn, S. P. Cementum and dentin in hypophosphatasia. J Dent Res. 2005; 84: 1021-1025.
17. Foster, B. L., Ramnitz, M. S., Gafni, R., Burke, A. B., Boyce, A. M., Lee, J. S., *et al.*, Rare Bone Diseases and Their Dental, Oral, and Craniofacial Manifestations. J Dent Res. 2014; 93: 7S-19S.
18. Bishop, N. Clinical management of hypophosphatasia. Clin Cases Miner Bone Metab. 2015; 12: 170 -173.
19. Licatta, A. A., Radfor, N., Bartter, F. C., Bow, E. The urinary excretion of phosphor-ethanolamine in disease other than hypophosphatasia. Am J Med. 1978; 64: 133-138.
20. Rosenthal, I. M., Bonting, S. L., Hogan, W., Pirani C. L. Tissue Alkaline Phosphatase in Hypophosphatasia. Am. J. Dis. Child. 1960; 99: 185.
21. Beumer, J., Henry, O., Trowbridge, Silverman, S. Childhood hypophosphatasia and the premature loss of teeth. Oral surgery, oral medicine, oral pathology. 1973; 35(5): 631-640.
22. Okawa, R., Kituoka, T., Saga, K., Ozono, K., Nakano, K., Reports of two dental patients diagnosed with hypophosphatasia. Journal of clinical case reports.2016; 6(2): 1-5.
23. Ozono, K., Michigami, T. Hypophosphatasia now draws more attention of both clinicians and researchers: a commentary on

Prevalence of c.1559delT in ALPL, a common mutation resulting in the perinatal (lethal) form of hypophosphatasia in Japanese and effects of the mutation on heterozygous carriers. J Hum Genet. 2011, 56: 174-176.

24. Straffon, L. H., Hartsook, J. T., Corpron, R. E. Some systemic causes for the premature exfoliation of primary teeth. J Mich Dent Assoc. 1975; 57: 342-352.
25. Primstone, B., Eisemberg, E., Silverman, S. Hypophosphatasia: genetic and dental studies. Ann Intern Med. 1996; 65: 722-729.