**Manifestation in the Oral Cavity Caused by Hypophosphatasia**

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**Abstract**

The aim of the review is to raise awareness of the hypophosphatasia and highlight the clinical findings in the oral cavity that would make pediatric dentists to doubt in this rare disease and to establish the diagnosis.

The main source of information were found on www.pubmed.gov where using keyword search hypophosphatasia we received 949 papers which discuss about the problems and changes in this rare congenital metabolic bone disease.

Hypophosphatasia (HP) is a rare inherited disorder characterized by a wide spectrum of defects in mineralized tissues and caused by deficiency in the tissue non-specific alkaline phosphatase gene (ALPL). Six clinical types of hypophosphatasia are currently recognized as in the forms of perinatal lethal, benign, prenatal, infantile, childhood, adult and odontohypophosphatasia.

Odontohypophosphatasia seems to represent a form of the disease with only a dental phenotype. This form is characterized by spontaneous exfoliation of fully rooted deciduous teeth, enlarged pulp chambers and root canals, not associated with abnormalities of the skeleton.

**Conclusion:** The severity of hypophosphatasia varies widely, depending on the mode of inheritance, and the structural consequences of more than 200 individual ALPL mutations associated with this rare inborn-error-of-metabolism. As premature loss of primary teeth is often the first, and sometimes the only visible symptom of the milder forms, the pediatric dentist plays a critical role in the detection and diagnosis of the disease.

**Keywords:** Hypophosphatasia; Rare; Inherited; Mineralized Tissues; Non-Specific Alkaline Phosphatase (ALPL); Exfoliation

**Introduction**

Hypophosphatasia (HP) is a rare inherited disorder characterized by a wide spectrum of defects in mineralized tissues and caused by deficiency in the tissue non-specific alkaline phosphatase gene (ALPL). Hypophosphatasia result in accumulation of the extracellular pyrophosphate that inhibits skeletal and dental mineralization [1]. Hypophosphatemia (hypophosphatasia) is a hereditary disease characterized by a deficiency of the tissue enzyme alkaline phosphatase and its activity in the serum [2]. Laboratory serum testing revealed a low concentration of alkaline phosphatase with an increased presence of phosphoethanolamines in the serum and urine. In serum there is a low level of vitamin B6 and pyridoxine phosphate [3,4].

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Inheritance is carried out through autosomal recessive genes, but there are reports of autosomal dominant transmission through the encountered gene that is located on the X chromosome, so that it is twice as likely to occur in boys. This disease occurs very rarely, with an incidence of 1: 100 000.

Hypophosphatasia is divided into neonatal, infantile, hypophosphataemia in childhood, and hypophosphataemia of adults, over time when it occurs. In children with neonatal and infantile hypophosphataemia, general development is disrupted due to insufficient mineralization of the bone skeleton, and craniosynostosis, intracranial hypertension, and various eyes disorders are present [5].

Six clinical types of hypophosphatasia are currently recognized as in the forms of perinatal lethal, benign, prenatal, infantile, childhood, adult and odontohypophosphatasia [6]. In the last clinical type odontohypophosphatasia all dental mineralized tissues from enamel, dentin and cementum to alveolar bone are affected in a gradient proportional to the severity of the disease [7]. The clinical signs and symptoms of juvenile hypophosphatasia HPP are very heterogeneous in their presentation, severity and course. The bone malformations can be manifested as impaired bone mineralization, leg deformations, pain, rickets, growth abnormalities and dental as premature loss of deciduous teeth [8].

Hypophosphatemia in childhood, which occurs in the 2nd or 3rd year of life, is characterized by daring growth and curvature of the lower limbs in the shape of the letter O [2].

Gurevich E and Landau D claim that there are no case reports of infantile hypophosphatasia in Israel [9].

Rodrigues TL., et al. suggest that pulp cells in the patients with hypophosphatasia have compromised ability to mineralize and disrupted function of the odontoblast. Their conclusion provides one step further toward understanding of the molecular mechanism for dentin phenotypes observed in patients with hypophosphatasia [10].

Dental Defects

Oral manifestations: Dentition tarda and premature teeth loss are the main oral features of hypophosphatasia. Usually incisal teeth are affected. Dental changes can sometimes be the only symptom of the disease, and then this condition is called odontohypophosphatasia [11]. The process of teeth exfoliation is relatively painless and is not accompanied by inflammatory changes in the periodontium. On the radiograph, alveolar bone loss and pulp chamber changes accompanied by minor defects in the dentine can be seen, of cement, which is the main feature and cause of teeth loss. Early exfoliation of the primary teeth is not a result of resorption, but because of the aplasia of cement. Sometimes there is a complete lack of cement, cellular and acetal, on the surface of the root of the tooth while the enamel is unchanged. Exfoliated teeth show significant loss [12,13].

Changes in the oral cavity occur in the form of delayed tooth growth and pronounced periodontitis, which passes without inflammatory changes of the gingiva. Parodontopathy is transmitted by a premature lose of primary teeth and permanent dentition. Early exfoliation of mammary teeth usually occurs on the anterior teeth, and this can sometimes be the first clinical signs of the disease. Spontaneous loss of teeth or as a result of minor trauma are very often in children [2].

Hypoplastic changes occur on the teeth of primary and permanent dentition. The most characteristic finding of the teeth is the increase of coronary pulp with horns spreading to the enamel-dentin boundary, as well as the presence of a large amount of interglobular dentine due to a defect in mineralization. The roots of teeth often have lack cement, while in the apical part of the tooth can be observed a wide layer of predentin, which prevents the apexification and closure of the root's apex.

On the radiographs, pronounced destruction of the alveolar bone can be noticed, which can sometimes be confined only to the frontal region, with characteristic absence or diminution of the lamine dure around the roots of the teeth, as well as an increase in the coronary or radicular pulp chamber of the tooth [2].

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The thin, usually hypomineralized enamel is rapidly abraded and exposure of the pulp occurs as well as abscesses and fistulas over clinically healthy primary and permanent teeth. Abscesses are present in primary dentition in about 25% of patients.

The dental finding is characterized by premature loss of primary teeth which may be important in the process of detection and diagnosis of milder forms of the disease [14], and in the so-called odontohypophosphatasia a key finding for diagnosing the condition.

The sedimentation of the dentin is slow and significantly reduced accompanied by the appearance of interglobular dentine and osteodentin [15].

A deficiency in acellular cementum, delay and defects in dentin mineralization are characteristic signs of the hypophosphatasia [1]. The only condition which affect cementogenesis is hypophosphatasia which disrupts the formation of acellular cementum caused by inhibition of mineralization. Luder in his article stated that disruption of this process entails taurodontism, single-rooted posterior teeth, and misshapen furcations [16].

Reibel A., et al. in their study present 5 patients with known genotype and investigated the genotype-phenotype correlations [17].

Treatment

Therapy consists of a diet rich with calcium and phosphorus, giving of high doses of vitamin D, as well as parathyroid hormone (PTH), but the results are poor [18].

Asfotase alfa (AA) has been recently developed to treat HPP complications [19,20]. Thirteen patients (9 females, 4 males) ages 0 days to 34 years at baseline were enrolled and treated with AA (2 mg/kg three times weekly subcutaneously in all but one patient). All had ALPL gene mutations. HPP forms were perinatal (n = 6), infantile (n = 5), childhood (n = 1) and adult (n = 1). Results from a Japanese clinical trial give support to the safety and efficacy of asfotase alfa therapy for HPP patients [20].

The existence of enzymatic replacement treatment for this disease makes it important to diagnose this problem as soon as possible [9]. Early results of enzyme replacement therapy are encouraging [21]. However, a multidisciplinary approach remains the core of the treatment including nutritional support, monitoring of vitamin D, calcium and phosphate levels, physical therapy and regular dental care.

McKee MD., et al. provide evidence that this enzyme-replacement therapy, applied early in post-natal life could prevent the tooth loss seen in individuals with hypophosphatasia HPP [1].

Bone marrow and stem cell transplantation have very small effect on the overall clinical outcome [22]. The use of the bisphosphonates is contraindicated because they are chemically analogue to one of the mineralization inhibitor, pyrophosphate, which accumulated in patients with hypophosphatasia. Lately there have been attempts for the involvement of the gene therapy for the treatment of hypophosphatasia [23].

Clinical Reports

Bağış B., et al. in their clinical report described the prosthetic rehabilitation of 22 year old female Turkish patient with hypophosphatasia. Because of the corrupted occlusal relations, missing of many teeth, patient’s age and motivation, metal ceramics fixed partial denture was done, after appropriate non-surgical periodontal treatment and obtaining of the oral hygiene habits with the help of her family [24].

Few conditions associated with a low serum alkaline phosphatase are Wilson’s disease, hypophosphatasia, pernicious anemia and untreated hypothyroidism. The diagnosis of hypophosphatasia in the case reported by Shajani-Yi Z., et al. was complicated by a serum ceruloplasmin concentration at the lower end of the reference interval leading to the genetic testing for Wilson’s disease [3].

Herasse M., et al. report in their molecular study three cases of odontohypophosphatasia where the disease was the result of heterozygosity for TNSAL P gene mutations [25].
Clinical, experimental and laboratory trials of humans and animals are still being done in order to discover the exact mechanisms of the occurrence of the disease and to detect appropriate treatment of this disease [26,27]. Micro-computed tomography was used for measurement of the enamel and dentin mineral densities [26].

**Dental Treatment**

Dental treatment can normally be performed in children undergoing medication treatment. Endodontic treatment of teeth with exposed pulp is mainly performed with permanent teeth. Saarnisto., et al. (1999) suggested making prosthetic golden crowns to prevent pulp infection [28]. The lack of teeth, after their loss, is resolved prosthetic [24].

**Conclusion**

The severity of hypophosphatasia varies widely, depending on the mode of inheritance, and the structural consequences of more than 200 individual \( ALPL \) mutations associated with this rare inborn-error-of-metabolism. As premature loss of primary teeth is often the first, and sometimes the only visible symptom of the milder forms, the pediatric dentist plays a critical role in the detection and diagnosis of the disease.

**Bibliography**


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