Dental Implications of Hypophosphatasia: A Case Report

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Background and Pathophysiology

Hypophosphatasia (HPP) is a rare, inherited skeleto-dental metabolic disorder with an incidence of approximately 1 in 100,000 births. It is characterized by defective mineralization of bones and teeth, leading to a wide spectrum of clinical manifestations, ranging from stillbirth to isolated dental symptoms. One of the earliest signs of HPP is early exfoliation of primary teeth, which may sometimes prompt a diagnosis in milder cases. Some patients may reach adulthood without being diagnosed, despite experiencing ongoing dental issues.

HPP is caused by inactivating mutations in the *ALPL* gene, which encodes the enzyme tissue-nonspecific alkaline phosphatase (TNSALP). This enzyme plays a critical role in the mineralization process by degrading inorganic pyrophosphate (PPi), a known inhibitor of mineralization, and producing inorganic phosphate, which is essential for bone and dental tissue formation. In HPP, reduced TNSALP activity results in the accumulation of PPi, preventing phosphate production. As a consequence, calcium and phosphate cannot effectively bind to form hydroxyapatite, disrupting the mineralization of bone, dentin, enamel, and cementum. This leads to the characteristic skeletal and dental defects seen in the disorder.

Dental manifestations of HPP are primarily related to the impaired mineralization of teeth and surrounding tissues. A hallmark feature is the early exfoliation of primary teeth, particularly the incisors, which occurs due to poor mineralization of the cementum. These teeth often have reduced bone support, making them more prone to loss, and are typically single-rooted, which further increases their vulnerability to exfoliation. In addition to early loss, affected teeth show reduced dentin thickness, enlarged pulp chambers, and higher caries risk, which contribute to compromised dental health.

There are also notable changes in the enamel, including enamel hypoplasia and discoloration, which result from defective mineralization. One of the critical features in HPP is the reduced or absent acellular cementum, which weakens the attachment between the teeth and the alveolar bone. The cementum and alveolar bone are normally connected through the periodontal ligament, but in HPP, this connection is compromised due to cementum dysplasia, leading to a failure in the retention of teeth. As a result,, even minor external forces can cause increased tooth mobility, ultimately leading to early exfoliation. Anterior teeth are especially vulnerable, as they experience more lateral forces compared to the vertical forces on posterior teeth, and they have less bone support, further exacerbating the risk of premature loss.

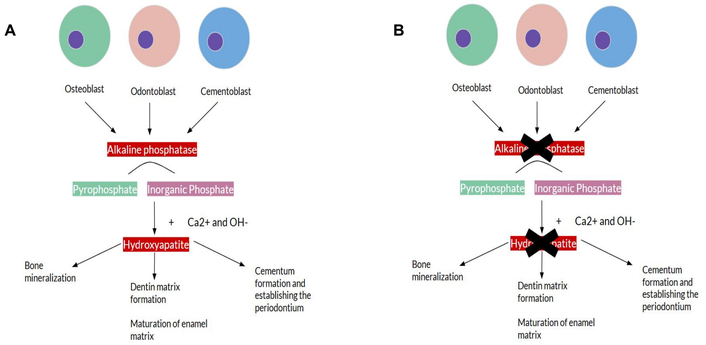
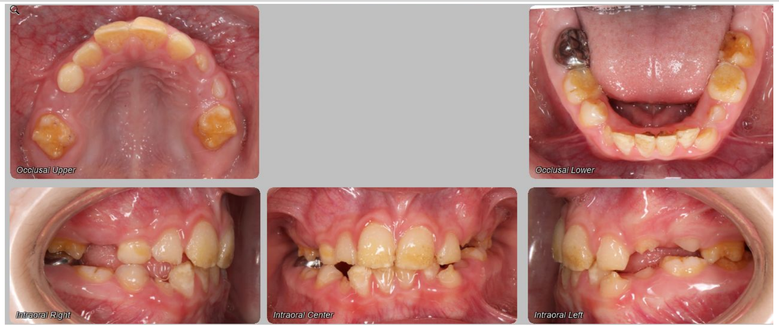


Fig 1. Pathophysiology of HPP at the cellular level. **A)** Normal **B)** HPP

Case Report



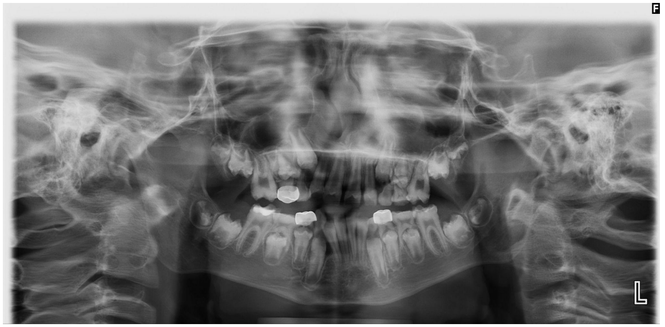


Fig 2. Clinal photographs and Panoramic radiograph of the patient at ages 12y 6mo and 10y 11m respectively

An 11-year-old male presented to the University of Michigan Pediatric Dental Clinic for a routine recall exam with no chief complaint. The patient has a known diagnosis of HPP, confirmed by genetic testing, which revealed two affected genes. The patient's past medical history includes craniosynostosis, for which he underwent a craniotomy in 2014. The patient also has a history of sleep apnea and snoring, for which he underwent an adenoiectomy. He is currently receiving treatment with Strensiq®, a recombinant human tissue-nonspecific alkaline phosphatase enzyme replacement therapy commonly used to manage HPP. Family history is significant for HPP as well. The patient's two younger twin sisters both have one affected gene and have been diagnosed with HPP. His father also carries one affected gene. The patient has been following a regular recall schedule since the age of 7. At the time of initial presentation the patient reported premature loss of #E, #F, #O, #P and #Q and had SSCs placed on #A, #S and #T at an external office. At the time of this visit, the patient reported being otherwise healthy, with no new symptoms or concerns. The patient has had several dental procedures completed at the clinic outlined in **Table 1.** The patient's dentition presents with features characteristic of HPP outlined in **Table 2**. Of note is the enamel hypoplasia noted on teeth #3, 7, 8, 9, 10, 14, 23, 24, 25, 26, 19, 30. The patient has been followed closely due to the increased caries risk associated with his presentation. Over the course of his treatment, the patient has been followed closely by both pediatric dentistry and orthodontics, commencing orthodontic screenings annually from age 8. The patient exhibits agenesis of teeth #4 and #13 and moderate crowding on the mandibular arch for which orthodontic intervention was requested. Overall, this patient presents with multiple dental findings including widespread enamel hypoplasia affecting multiple teeth, agenesis of permanent teeth, and early loss of primary teeth. Consistent follow up and coordination of care within a multidisciplinary team are essential in the management of patients with complex dental needs

Age	Treatment
7 years	- Tooth #A and#J extracted due to root resorption from eruption of #3 and #14 respectively
9 years	- Teeth #B, #I, #M, #R extracted as per orthodontic recommendation. - #30 restored with SSC due to MOD caries - #T-DO resin restoration due to enamel defect
11 years	- Caries on # 3-L, #14-L and #19- O restored with resin restorations - Commenced comprehensive orthodontic treatment after restorative treatment was complete

Table 1. Summary of dental treatments received at the clinic

Dental Presentation of Hypophosphatasia
Premature loss of teeth #E, #F, #O, #P and #Q (time of loss unknown)
Enamel defects requiring restorations (#T-DO at age 9)
Enamel hypoplasia secondary to hypophosphatasia on #3, 7, 8, 9, 10, 14, 23, 24, 25, 26, 19, 30

Table 2. Summary of dental manifestations of HPP presenting the patient

Discussion

1. Early exfoliation of primary teeth can be one of the first signs of undiagnosed HPP making the dentist's role in identifying the disease extremely important
2. Due to the poor mineralization of enamel that may occur, caries risk can be higher in HPP patients. Regular recall visits and reinforcing proper home care and OHI are extremely important
3. Early follow-up with orthodontics is recommended especially if there was premature loss of primary teeth causing space loss
4. Follow up with other dental specialties including prosthodontics may be required especially as the patient becomes older

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