DENTISTS CAN IDENTIFY HPP EARLY AND HELP SHORTEN THE PATIENT JOURNEY TO DIAGNOSIS AND APPROPRIATE CARE

HPP is frequently misdiagnosed because its presentation overlaps with other more common diseases, such as rickets, osteomalacia, and osteopenia/osteoporosis, among others. While most patients are diagnosed as children, some patients are diagnosed as adults. Early examination by dentists is key for the identification of HPP, which can shorten the patient referral pathway, time to diagnosis, and start of treatment.

If you have any questions regarding HPP in children or identifying your referral network, please contact a member of the steering committee.

Hypophosphatasia is a rare genetic disorder with significant impact on dental health

Hypophosphatasia (HPP) is caused by mutations in the tissue-nonspecific alkaline phosphatase (TNSALP) gene. Children with HPP may develop rickets-like symptoms, bone pain, skeletal deformities, fractures, muscle weakness, and premature tooth loss with the root intact. It is important for dentists to consider HPP as part of a differential diagnosis for early tooth loss where the root is mostly intact. Treatment is recommended that a dental home be established early, so that children have their first dental examination by 12 months of age.

This newsletter highlights the important role that dentists play in the early diagnosis of HPP, often seeing patients before any other healthcare professional.

The impact of HPP on dental health

Early exfoliation with minimal trauma

Radograph of patient with HPP

Exfoliated incisor from patient with HPP with root intact (left)

Exfoliated incisor from unaffected individual with root resorbed (right)

CASE REVIEW: What are common clinical presentations of HPP in your practice?

What did the dentist see?

• 3 years of age:
  > Extra-oral examination revealed unusual gait and short stature
  > Parent reported patient had lost teeth 71 and 81 due to trauma
  > Parent suspected canines on posterior teeth, unrelated to HPP

• 1 year of age:
  > Referred to Pediatric Dentist by Pediatrician for delayed tooth eruption

Teeth 71 and 81 absent

Teeth 71 and 81 present

Teeth 71 and 81 not present

If you suspect that a patient has HPP or you cannot explain the premature loss or mobility of primary teeth:
1. Refer your patient to the local children's hospital dental service or HPP medical expert to ensure further assessment, diagnosis, and management of the patient.
2. Schedule regular check-ups to monitor oral health, tooth loss, and space maintenance.

If you have any questions regarding HPP in children or identifying your referral network, please contact a member of the steering committee.

This newsletter was developed with financial support from Alexion Pharmaceuticals Inc.
**WHAT CAUSES HPP?**

HPP is a progressive disease caused by mutations that inactivate the TNSALP gene, which codes for the alkaline phosphatase (ALP) enzyme. 

ALP promotes hydroxyapatite crystal formation by converting inorganic pyrophosphate (PPi) to inorganic phosphate (Pi), which stimulates bone mineralization.

TNSALP inactivity can also lead to respiratory and neurologic complications. Perinatal cases are almost always fatal, while infantile HPP has a 50% mortality rate in the first year of life. Early detection and diagnosis of HPP is critical for patient well-being.

Asfotase alfa is an enzyme replacement therapy for patients diagnosed with pediatric-onset HPP. It replaces the defective TNSALP enzyme. It promotes hydroxyapatite crystal formation, which stimulates bone mineralization.

**CASE REVIEW (continued):**

**WHAT DOES HPP LOOK LIKE OVER TIME?**

3 YEARS OLD:
- Missing teeth 71 and 81
- Radiographs showed large molar pulp chambers and severe bone loss on teeth 51, 54, 61, 62, 71, and 74
- Skeletal survey indicated poor bone mineralization in ribs, femur, tibia, and skull
- Extra-oral examination revealed unusual gait and short stature
- Genetic testing showed mutations in the TNSALP gene
- Patient initiated on asfotase alfa enzyme replacement therapy

**AFTER 3 YEARS OF TREATMENT ENZYME REPLACEMENT THERAPY:**
- Examination indicated normal weight, height, vision, and hearing
- No bone pain or fractures
- Attended physiotherapy for help with walking and mobility
- Reported doing well in school, enjoys gym class, and did not require additional support
- Returned to visit Pediatric Dentist

**MANIFESTATIONS OF HPP TO LOOK OUT FOR:**

1. Unusual gait and/or short stature
2. Restricted mobility and/or muscle pain
3. Early mobility or exfoliation of primary teeth with or without a history of minor trauma, mostly in the anterior-canine segment with the root intact and minimal soft tissue involvement
4. Eruption disorders
5. Wide pulp chambers
6. Reduced alveolar bone height
7. Abnormal tooth surface and/or shape (e.g., enamel hypoplasia)

**HAVE YOU SEEN ANY OF THESE ANOMALIES IN YOUR PRACTICE?**

If you detect any of these dental anomalies and suspect HPP, be sure to complete the following examinations:

- Review patient medical history thoroughly to rule out other systemic conditions related to early tooth loss (e.g., take note of patient gait, height, and strength)
- Examination:
  - Pay special attention to anomalies of tooth structure and eruption
  - Assess tooth position and mobility
  - Examine periodontal health, particularly the presence of gingival recession, bone loss or loss of periodontal fibre attachment
  - Conduct a radiographic evaluation to visualize alveolar bone height
  - Extract highly mobile exfoliating tooth or acquire previously exfoliated tooth, if kept
  - Send specimen to an oral pathologist for histological analysis of cementum levels
- Rule out other possible causes for early tooth loss and other noted anomalies

**DENTISTS ARE POSITIONED AT THE BEGINNING OF THE HPP DIAGNOSTIC PATHWAY AND OFTEN HAVE FIRST CONTACT WITH THE PATIENT**

- **DENTAL**
  - Early and non-traumatic tooth loss with the root intact
- **LOW ALP ACTIVITY**
  - The diagnostic hallmark of HPP—age- and gender-adjusted ALP activity—should be evaluated
  - If confirmation is needed, test for elevated levels of serum PLP (pyridoxal-5’-phosphate; vitamin B6) and urinary PEA (phosphoethanolamine)
- **MUSCULAR, RESPIRATORY, GROWTH, & SKELETAL**
  - Prominent clinical symptoms can also be presented in these areas, which can cause devastating consequences at any age
- **GENETIC TESTING**
  - Determine if patient has mutation(s) in the TNSALP gene
WHAT CAUSES HPP?

HPP is a progressive disease caused by mutations that inactivate the TNSALP gene, which codes for the alkaline phosphatase (ALP) enzyme. ALP promotes hydroxyapatite crystal formation by converting inorganic pyrophosphate (PPi) to inorganic phosphate (Pi). When ALP activity is low, PPi accumulates and reduces hydroxyapatite formation, leading to skeletal hypomineralization, as well as altered calcium and phosphate metabolism. This leads to a decrease in tooth and bone mineralization. TNSALP inactivity can also lead to respiratory and neurologic complications. Perinatal cases are almost always fatal, while infantile HPP has a 50% mortality rate in the first year of life. Early detection and diagnosis of HPP is critical for patient well-being.

Biochemical overview of ALP enzyme activity

Asfotase alfa is an enzyme replacement therapy for patients diagnosed with pediatric-onset HPP. It replaces the defective ALP enzyme to promote hydroxyapatite crystal formation, which stimulates bone mineralization.

Manifestations of HPP to look out for

A patient with HPP may present with some, but not all of these symptoms:
1. Unusual gait and/or short stature
2. Restricted mobility and/or muscle pain
3. Early mobility or exfoliation of primary teeth with or without a history of minor trauma, mostly in the anterior-canine segment with the root intact and minimal soft tissue involvement
4. Eruption disorders
5. Wide pulp chambers
6. Reduced alveolar bone height
7. Abnormal tooth surface and/or shape (e.g., enamel hypoplasia)

If you detect any of these dental anomalies and suspect HPP, be sure to complete the following examinations:
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• Examination:
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Dentists are positioned at the beginning of the HPP diagnostic pathway and often have first contact with the patient.

Patient radiographs before and after asfotase alfa treatment

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<tr>
<th>VERTICAL BITEWINGS</th>
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<th>OCCLUSAL FILMS</th>
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Low ALP activity

The diagnostic hallmark of HPP—age- and gender-adjusted ALP activity—should be evaluated. If confirmation is needed, test for elevated levels of serum PLP (pyridoxal-5’-phosphate; vitamin B6) and urinary PEA (phosphoethanolamine).

Genetic testing

Determine if patient has mutation(s) in the TNSALP gene.

Dental anomalies

Enlarged pulp chambers and abnormal tooth shape

Eruption disorders

Increased mobility or early exfoliation of primary teeth, mostly in the anterior-canine segment with the root intact and minimal soft tissue involvement

Enlarged pulp chambers and abnormal tooth shape

Genetic testing

Determine if patient has mutation(s) in the TNSALP gene.
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8. Whyte M. Hypophosphatasia (HPP): A rare genetic disorder with significant impact on dental health. Hypophosphatasia (HPP) is caused by mutations in the tissue-nonspecific alkaline phosphatase (TNSALP) gene. Children with HPP may develop rickets-like symptoms, bone pain, skeletal deformities, fractures, muscle weakness, and premature tooth loss with the root intact. 99% of all patients with HPP experience early tooth loss with the root intact, before the age of 5. It is important for dentists to consider HPP as part of a differential diagnosis for early tooth loss where the root is mostly intact. To receive appropriate preventative and routine oral health care, it is recommended that a dental home be established early, so that children have their first dental examination by 12 months of age.

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  > Parent explained patient had lost teeth 71 and 81 due to trauma
  > Parent suspected canines on posterior teeth, unrelated to HPP
  > The second left primary mandibular incisor presented with 1–2 mm mobility with minimal root resorption
  > Tooth eruption pattern normal

Teeth 71 and 81 absent

• 1 year of age:
  > Referred to Pediatric Dentist by Pediatrician for delayed tooth eruption

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