Perinatal hypophosphatasia

a. Only small bony areas are apparent in the pelvis, femurs and tibias.

b. Pathognomonic metaphyseal ‘tongues’ of radiolucency, gracile ribs and long-bone deformities

Hypophosphatasia — aetiology, nosology, pathogenesis, diagnosis and treatment
Skeletal features of untreated hypophosphatasia children

Whyte MP et al. JCI Insight. 2016 Jun 16;1(9):e85971.
Odonto hypophosphatasia

premature loss of deciduous and/or permanent teeth without other skeletal HPP signs

painless loss of primary teeth < 5 yrs of age) with root intact, a hallmark of pediatric HPP.

24-year-old woman; serum ALP level was 35.0 U/L (normal range 45.0–125.0 U/L).
Radiographic severity of HPP in children

a. no abnormalities in odonto HPP

b. subtle changes in the head of the fibula in mild childhood HPP

c. characteristic “tongues of radiolucency” and metaphyseal changes in severe childhood HPP

d. survivor of perinatal HPP

*Whyte MP et al. JCI Insight. 2016 Jun 16;1(9):e85971*
Adult Hypophosphatasia with low serum AF
Hypophosphatasia (HPP)

Caused by loss-of-function mutations in alkaline phosphatase liver type (ALPL) gene which encodes tissue-nonspecific alkaline phosphatase (TNSALP).

About 275 mutations have been identified.

Europe: severe and moderately severe HPP in one of every 300,000.

Alkaline phosphatase is critical for metabolizing 3 substrates, which accumulate when not metabolized by ALP:

- **Inorganic pyrophosphate**: osteomalacia, arthropathies, recurrent (stress) fractures, joint deposition PPI crystals, chondrocalcinosis.
- **Pyridoxal 5'-phosphate** (or **vitamin B6**): seizures in children only; in HPP, ALP does not dephosphorylate and blood-liquor barrier is not crossed.
- **Phosphoethanolamine**: no clinical events.

**Biological hallmark: low alkaline phosphatase (ALP) activity**.
Age-adjusted ALP: critical to accurate diagnosis of HPP

Patients with hypophosphatasia (HPP) typically have alkaline phosphatase (ALP) activity below the age-adjusted lower limit of normal.¹ ²

---

**AGE- AND GENDER-ADJUSTED ALP REFERENCE RANGES (U/L)²³**

<table>
<thead>
<tr>
<th>Age</th>
<th>Normal age-adjusted ALP</th>
<th>Suspicion of HPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 mo</td>
<td>60</td>
<td>320</td>
</tr>
<tr>
<td>1-11 mo</td>
<td>70</td>
<td>350</td>
</tr>
<tr>
<td>1-3 y</td>
<td>125</td>
<td>320</td>
</tr>
<tr>
<td>4-6 y</td>
<td>150</td>
<td>370</td>
</tr>
<tr>
<td>7-9 y</td>
<td>150</td>
<td>440</td>
</tr>
<tr>
<td>10-11 y (M)</td>
<td>150</td>
<td>470</td>
</tr>
<tr>
<td>10-11 y (F)</td>
<td>150</td>
<td>530</td>
</tr>
<tr>
<td>12-13 y (M)</td>
<td>160</td>
<td>500</td>
</tr>
<tr>
<td>12-13 y (F)</td>
<td>110</td>
<td>525</td>
</tr>
<tr>
<td>14-15 y (M)</td>
<td>130</td>
<td>530</td>
</tr>
<tr>
<td>14-15 y (F)</td>
<td>55</td>
<td>530</td>
</tr>
<tr>
<td>16-19 y (M)</td>
<td>60</td>
<td>270</td>
</tr>
<tr>
<td>16-19 y (F)</td>
<td>40</td>
<td>120</td>
</tr>
<tr>
<td>≥20 y</td>
<td>40</td>
<td>120</td>
</tr>
</tbody>
</table>

---

Coen Netelenbos, VU University Medical Center Amsterdam, NL
In healthy bone cells, TNSALP dephosphorylates PPI, releasing inorganic phosphate (Pi) inorganic pyrophosphate (PPI).

Pi binds to calcium (Ca++) to form hydroxyapatite crystals, which mineralize bone.

When TNSALP is deficient, PPI accumulates and blocks hydroxyapatite crystal formation. Therefore, normal skeletal mineralization cannot occur and calcium and phosphate regulation is abnormal. Defective mineralization results in a wide range of systemic and functional consequences.
Burden of disease in adult patients with hypophosphatasia:

Results from two patient-reported surveys

*Thomas J. Weber et al.*
*Metabolism - Clinical and Experimental, 2016; Vol. 65, Issue 10, p1522–1530*
### History of bone and systemic manifestations of HPP in adults

<table>
<thead>
<tr>
<th>Systemic manifestations</th>
<th>All ≥ 18 Years (n = 125)</th>
<th>Pediatric-onset (n = 84)</th>
<th>Adult-onset (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle weakness</td>
<td>77/124 (62%)</td>
<td>53/83 (64%)</td>
<td>22/34 (65%)</td>
</tr>
<tr>
<td>Unusual gait</td>
<td>46/89 (52%)</td>
<td>38/62 (61%)</td>
<td>8/22 (36%)</td>
</tr>
<tr>
<td>Delayed walking</td>
<td>44/117 (38%)</td>
<td>39/78 (50%)</td>
<td>4/32 (13%)</td>
</tr>
<tr>
<td>Short stature</td>
<td>45/125 (36%)</td>
<td>37/84 (44%)</td>
<td>7/34 (21%)</td>
</tr>
<tr>
<td>Flexible joints</td>
<td>38/125 (30%)</td>
<td>30/84 (36%)</td>
<td>7/34 (21%)</td>
</tr>
<tr>
<td>Difficulty gaining weight</td>
<td>33/124 (27%)</td>
<td>26/83 (31%)</td>
<td>6/34 (18%)</td>
</tr>
<tr>
<td>Difficulty breathing</td>
<td>24/89 (27%)</td>
<td>17/62 (27%)</td>
<td>7/22 (32%)</td>
</tr>
<tr>
<td>Seizuresb</td>
<td>8/89 (9%)</td>
<td>8/62 (13%)</td>
<td>0/22 (0%)</td>
</tr>
<tr>
<td>Nephrocalcinosib</td>
<td>7/89 (8%)</td>
<td>5/62 (8%)</td>
<td>2/22 (9%)</td>
</tr>
<tr>
<td>Kidney stonesb</td>
<td>6/89 (7%)</td>
<td>4/62 (6%)</td>
<td>2/22 (9%)</td>
</tr>
<tr>
<td><strong>Bone manifestations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowing of legs</td>
<td>38/125 (30%)</td>
<td>34/84 (40%)</td>
<td>3/34 (9%)</td>
</tr>
<tr>
<td>Abnormally shaped chest</td>
<td>27/125 (22%)</td>
<td>24/84 (29%)</td>
<td>2/34 (6%)</td>
</tr>
<tr>
<td>Abnormally shaped head</td>
<td>26/116 (22%)</td>
<td>24/82 (29%)</td>
<td>1/27 (4%)</td>
</tr>
<tr>
<td>Knock knees</td>
<td>26/125 (21%)</td>
<td>22/84 (26%)</td>
<td>3/34 (9%)</td>
</tr>
<tr>
<td>Bowing of arms</td>
<td>19/125 (15%)</td>
<td>18/84 (21%)</td>
<td>0/34 (0%)</td>
</tr>
</tbody>
</table>

**most common: musculoskeletal pain**


Coen Netelenbos, VU University Medical Center Amsterdam, NL
Toal fractures in adults with HPP

Percentage of Patients

Total Fractures Sustained Over Lifetime

0 1 2-5 6-10 >10

10% 11% 10% 6% 6% 13% 26% 32% 26% 24% 22% 24% 21% 26% 24% 29%

NB most common sites: foot and femur

Adaptive strategies for disability of HPP in adults


Coen Netelenbos, VU University Medical Center Amsterdam, NL
"Atypical Femoral Fractures" during bisphosphonate exposure in adult hypophosphatasia

49 yr old woman with pain left shin and ankle (stress periostitis)
Dxa T-score -2.5 at the L2-4 spine and -2.0 hip
serum AF 40 U/L
alendronate treatment
later zoledronic acid
1 yr later stress fracture right which healed

Shortly thereafter fall:

Case report

69-year-old woman; history of 9 (stress) fractures age 9-67 years

- Age 61: T-score -4.9 lumbar spine, -2.0 femoral neck R \ risedronate, Ca/D
- Age 67: stress fracture left collum femoris; R \ denosumab

Laurent MR et al. ASBMR 2016: First case report of a denosumab-related atypical femoral fracture in HPP
Hypophosphatasia

Enzyme Replacement Therapy Brings New Opportunities and New Challenges

Michael P Whyte

Journal of Bone and Mineral Research, 13 Jan. 2017 online
Asfotase alfa is a recombinant, bone-targeted, human TNSALP developed to treat hypophosphatasia

2012: First report that infants and young children (<3 years of age) with life-threatening perinatal and infantile hypophosphatasia showed substantial radiographic healing of rickets, improved respiratory status, and better physical function during 1 year of asfotase alfa treatment.

Asfotase alfa is a recombinant, bone-targeted, human TNSALP developed to treat hypophosphatasia

2016: 5 years asfotase alfa treatment in cohort of older children (6–12 years of age) with either infantile- or childhood-onset hypophosphatasia effects on their skeletal manifestations, growth, physical function, and quality of life.

Whyte MP et al. Asfotase alfa therapy for children with hypophosphatasia. JCI Insight. 2016 Jun 16;1(9):e85971
Asfotase alfa is a recombinant, bone-targeted, human TNSALP developed to treat hypophosphatasia

2015: Asfotase alfa (Strepsiq; Alexion Pharmaceuticals) became available in Japan for hypophosphatasia, and then in Canada, the European Union and the USA for paediatric-onset hypophosphatasia.

About $300,000 annually
Cost-benefits
Asfotase alfa treatment children

Better stature and improved strength and agility accompanied by significant healing of the skeletal manifestations and persisted through 5 years of treatment.

The treatment was well tolerated and seemed safe, with a favorable benefit-risk profile

*Whyte MP et al. JCI Insight. 2016 Jun 16;1(9):e85971*

About $300,000 annually

Costs benefits reimbursement

In 2015, asfotase alfa (Strepsiq; Alexion Pharmaceuticals, USA) became available in Japan for hypophosphatasia, and then in Canada, the European Union and the USA for paediatric-onset hypophosphatasia.
Treatment of adults with HPP

- No established treatment
- Inconsistent results with teriparatide
- Cave bisphosphonates, zoledronic acid, denosumab and high dose vitamin D
- Before treatment of atypical osteoporosis patient: check always serum AF!
- Phase 2 trial report with asfotase with improved walk tests outcomes (abstract)
- How in Benelux?
HPP in Benelux

- 15 children known with HPP; to be expected > 100
- Better attention for assessment serum AP in lower range with regard to age
- No children with HPP are treated with strensiq
- No reimbursement available
- 3 adults HPP patients in Leuven treated with strensiq (compassionate use)
Thanks