P1-16

Diverse presentations of hypophosphatasia in paediatric patients: a review of the case literature

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INTRODUCTION

- Hypophosphatasia (HPP) is a rare inherited metabolic disease, caused by loss-of-function mutation(s) within *ALPL*, the gene that encodes tissue-nonspecific alkaline phosphatase (TNSALP)[1]
  - Deficient TNSALP activity results in elevated extracellular levels of key substrates:
    - Inorganic pyrophosphate: an inhibitor of bone mineralisation
    - Pyridoxal 5′-phosphate: the major circulating form of vitamin B_6
- Historically, HPP has been classified by the presence of skeletal symptoms and age at presentation[1,2]
  - **Perinatal-onset**: *in utero* and at birth
  - **Infantile-onset**: <6 months of age
  - **Juvenile-onset**: ≥6 months to 18 years of age
  - **Adult-onset**: ≥18 years of age
  - **Odonto-HPP**: presentation of dental symptoms (e.g., premature tooth loss) without accompanying skeletal or systemic disease
- HPP may present with a wide range of clinical manifestations, including:
  - **Skeletal defects**: e.g., skeletal deformities, bowing, rickets, fractures, craniosynostosis
  - **Growth/development impairment**: e.g., short stature, failure to thrive, impaired motor skills
  - **Muscular strength/function impairment**: e.g., muscular/joint pain, waddling gait, difficulty walking, fatigue
  - **Dental defects**: e.g., premature or nontraumatic tooth loss with root intact
  - **Systemic manifestations**: e.g., respiratory complications, vitamin B_6-responsive seizures, nephrocalcinosis
- The varied presentation of HPP presents challenges for the recognition and diagnosis of the disease. Understanding of the presentation of HPP is largely based on single case reports in the literature

OBJECTIVE

- To better understand disease presentation in patients under the age of 18 years with HPP through review and summary of available data from the case literature

METHODS

- A PubMed literature search of all HPP case reports published in English was conducted (search last updated on 24th April 2015)
  - Search terms were: "**hypophosphatasia**" and "**case report**"
  - Reference lists from identified articles were used to identify further cases
  - Articles must have contained sufficient individual information to be used as a case report
    - Aggregate reports of cases without information on individuals were not included
- Individual cases were reviewed and, where information was available, the following data were captured:
  - First reported symptom
  - Patient age
  - Systemic complications of interest, including nephrocalcinosis, pain, muscle weakness, seizure, fractures/pseudofractures, respiratory complications, early tooth loss
  - Method of diagnosis
  - *ALPL* mutational analysis genetic mutation
  - Age of death, if applicable
- Cases were filtered to include only publications reporting patients <18 years of age

RESULTS

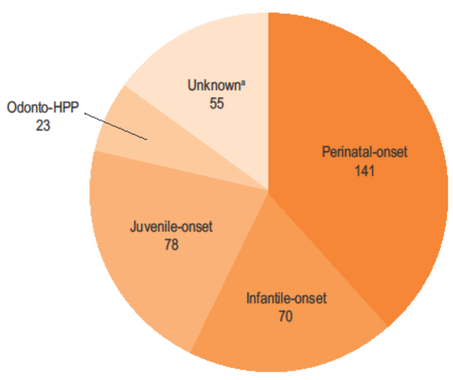
HPP cases

- 175 publications (ranging from 1939 to November 2014) were identified as meeting the specified criteria, providing 367 cases of patients <18 years of age with HPP (**Figure 1**)

Mortality

- 142 deaths were reported, of which 112 had known age at death
  - **Perinatal-onset**: 63% of patients died (87/139)
  - **Infantile-onset**: 40% of patients died (27/67)
  - **Juvenile-onset**: 1% of patients died (1/70)
  - **Odonto-HPP**: no deaths reported
- 20% of deaths occurred within the first 7 days of life. Where reported, these deaths were typically associated with hypomineralisation and/or respiratory failure

Figure 1. Reported cases of HPP in the literature by age of onset



[a]Includes cases where information was not specified, or it was not possible to determine from the available information.
HPP, hypophosphatasia.

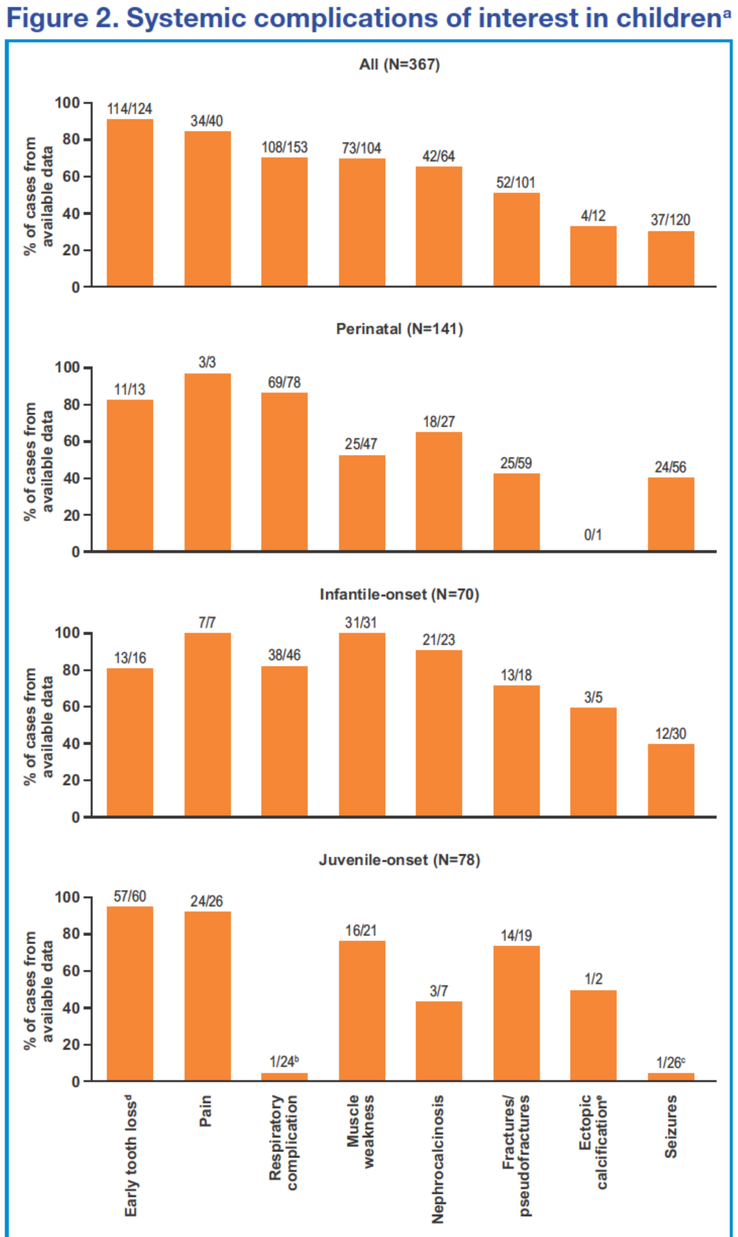
First reported symptom

- The most frequently reported first symptoms by HPP type were:
  - **Perinatal-onset**: bowing of limbs, skeletal abnormalities (ultrasound analysis), abnormally shaped head, respiratory complications
  - **Infantile-onset**: failure to thrive, vomiting
  - **Juvenile-onset**: premature tooth loss

Systemic complications

- Overall, the most frequently reported manifestations across all HPP types were early tooth loss, pain, respiratory complications, and muscle weakness (**Figure 2**)

Figure 2. Systemic complications of interest in children[a]



[a]Numbers over bars represent n/N, where n is the number of cases reporting a finding and N is the number of cases for which definite data were reported in the publication. Cases for which data were unavailable were not included in percentage calculations.
[b]Patient had repeated attacks of respiratory distress.[3]
[c]Patient presented with febrile seizure.[3]
[d]Cases where tooth loss was not applicable were not included in calculations.
[e]Ectopic calcification was identified in dura, connective tissue, gastric mucosa, and ocular locations.[4–7]

- Seizures were present in approximately 40% of patients presenting with perinatal- and infantile-onset HPP
- Early tooth loss, pain, and muscle weakness were reported in the majority of juvenile-onset cases with available data
- Other complications included:
  - **Perinatal-onset**
    - Abnormally shaped head (n=16)
    - Dimples (n=18)
  - **Infantile-onset**
    - Failure to thrive (n=15)
    - Delayed walking/motor development (n=9)
    - Vomiting (n=9)
    - Developmental delay (n=6)
  - **Juvenile-onset**
    - Delayed walking/motor development (n=26)
    - Short stature (n=10)

Diagnostics

- 29% of cases were diagnosed using a combination of ALP, radiological findings, and laboratory tests (**Table 1**)

Table 1. Evidence used for diagnosis of HPP

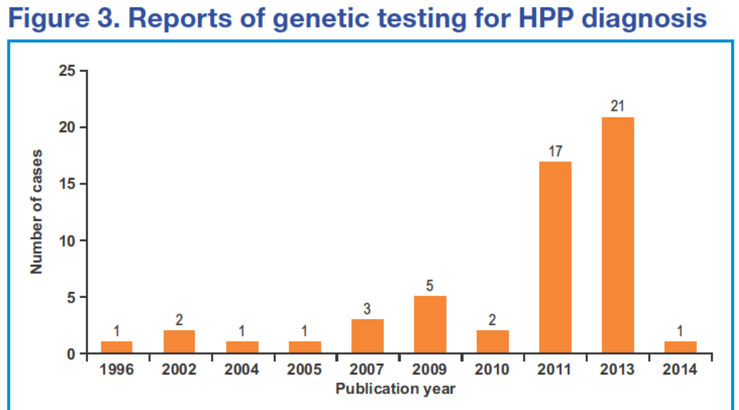
Diagnostic test	Patients diagnosed, n (%[a])
ALP only	7 (2%)
Radiological only	30 (8%)
ALP + radiological[b]	82 (22%)
ALP + labs[c]	32 (9%)
ALP + radiological + labs[d]	107 (29%)

[a]Percentages based on total case study population (N=367), which includes cases where data are unknown. [b]3 patients presented with normal radiological findings. [c]Laboratory tests included: pyridoxal 5'-phosphate, phosphoethanolamine, pyrophosphate and calcium. Laboratory tests were performed either alone or in combinations. [d]1 patient had laboratory diagnostic with normal phosphoethanolamine levels.
ALP, alkaline phosphatase.

Genetic testing

- *ALPL* genetic testing was used to confirm diagnosis for a total of 54 cases
  - 3 cases were diagnosed by genetic testing alone (all prenatal)
  - 16 cases were diagnosed by genetic testing in combination with ALP testing; for 1 case these were the only tests performed
  - 48 cases were diagnosed by genetic testing in combination with radiological examination; for 18 cases these were the only tests performed
  - 14 cases were diagnosed by genetic testing in combination with ALP and radiological examination
- 41 of the 54 cases were published in the last 5 years (**Figure 3**)
- The earliest case report for which genetic testing was used was published in 1996 (**Figure 3**)

Figure 3. Reports of genetic testing for HPP diagnosis



HPP, hypophosphatasia.

Limitations

- Case literature is subject to reporting/publishing bias: interesting or unusual cases are more likely to be published
- Cases may contain incomplete data or report findings inconsistently: not a complete picture of each patient
- This is a descriptive compilation of the literature data: not a meta-analysis or systematic review

DISCUSSION & CONCLUSIONS

- A large body of case report data is available for HPP; however, there are few data available on long-term follow-up of infants and children with HPP in this literature
- Prevalent symptoms to be aware of are:
  - *In utero* and in neonates: bowing of long bones, respiratory complications
  - In infants <6 months of age: respiratory complications, pain, muscle weakness, and nephrocalcinosis
  - In children ≥6 months of age: premature tooth loss, pain and muscle weakness
- Respiratory complications were frequently experienced by children with perinatal- and infantile-onset HPP, but infrequently by children with juvenile-onset HPP
- Most HPP-associated deaths occurred within the first year of life
- Recognition of the common symptoms that are characteristic of HPP will facilitate proper diagnosis of this rare and often fatal disease

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DISCLOSURES

EKS is an employee of Alexion Pharmaceuticals, Inc.
KA was an employee of Alexion Pharmaceuticals, Inc. when contributing to this work.

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