INTRODUCTION

- Hypophosphatasia (HPP) is a rare inherited metabolic disease, caused by loss-of-function mutations within ALPL, the gene that encodes tissue nonspecific alkaline phosphatase (TN-SALP).
- Deficient TN-SALP 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 B6
- Historically, HPP has been classified by the presence of skeletal symptoms and age at presentation:
  - 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, craniostenosis
  - Growth/development impairment: e.g., short stature, failure to thrive, impaired motor skills
  - Muscle strength/function impairment: e.g., muscular/ joint pain, waddling gait, difficulty walking, fatigue
  - Dental defects: e.g., premature or nontraumatic tooth loss with root impact
  - Systemic manifestations: e.g., respiratory complications, vitamin B6-responsive seizures, nephrocalcinosis
- The varied presentation of HPP presents challenges for the recognition and diagnosis of the disease. Understanding 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 24 April 2015)
- Search terms: “hypophosphatasia” and “bone, growth plate and mineral metabolism
- 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, sepsis, 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 patients of cases <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 hyperpyrexemia and/or respiratory failure

First reported symptom
- The most frequently reported first symptom 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)

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:
  - Long bones, respiratory complications
  - In infants <6 months of age:
  - Respiratory complications, pain, muscle weakness, 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

REFERENCES


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