MON 335

Fracture Burden in Patients With Probable Hypophosphatasia Identified in an Electronic Health Record Database

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*Potential conflict of interest may exist. Refer to the ENDO 2017 Meeting App.

INTRODUCTION

- Hypophosphatasia (HPP) is a rare, inherited, systemic, metabolic disease characterized by low serum alkaline phosphatase (ALP) activity and poor skeletal mineralization resulting from mutations of the gene encoding tissue-nonspecific ALP[1-3]
- Signs and symptoms of HPP are heterogeneous, ranging from severely impaired bone mineralization, seizures, and hypercalcemia in infants to multiple fractures, severe pain, impaired mobility, and disability in adults[3-6]
- HPP is often misdiagnosed and underdiagnosed because of a lack of awareness of this rare disease, which is characterized by signs, symptoms, and complications associated with well-recognized diseases such as nutritional rickets, osteogenesis imperfecta, X-linked hypophosphatemic rickets, and osteoporosis[6,7]
- As with other rare diseases, knowledge about the burden of disease in HPP is limited

OBJECTIVE

- To document the frequency of fractures among pediatric and adult patients with probable HPP identified within the electronic health records (EHR) database of an academic medical center

METHODS

Database

- Retrospective longitudinal study using the University of Utah Healthcare EHR database, which consists of the following:
  - Health records of more than 1.5 million individuals
  - Current and historical EHRs, patient demographics, hospital and professional billing accounts, pharmacy data, laboratory findings, radiology and inpatient and outpatient encounters, diagnoses, procedures, and clinical data

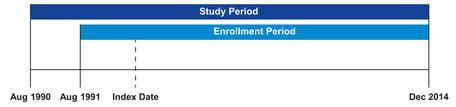
Population

- Patients with records in the EHR database that include diagnosis, procedure, or lab codes from August 1990 to December 2014 documenting the following were considered probable HPP patients and were included in the study:
  - Disorders of phosphorous metabolism noted by ICD-9 code 275.3 **or**
  - Persistently low age-/sex-adjusted ALP activity noted by CPT 84705 (≥2 measurements, low/never normal activity levels, and no bisphosphonate use) **and**
  - Clinical, biochemical, and radiographic evidence of HPP noted by ≥1 of the following:
    - Seizures/respiratory failure in children aged <5 years
    - Elevated serum pyridoxal-5'-phosphate
    - Elevated urine phosphoethanolamine
    - Family history
    - Radiographic evidence of hypomineralization, osteopenia, or rickets-like features
    - Osteomalacia
    - History of nontraumatic and/or multiple fractures, premature tooth loss, or craniosynostosis

Study Definitions (Figure 1)

- Index date was defined as the date of a diagnosis of a disorder of phosphorus metabolism and/or the second finding of a low ALP activity level
- Post-index period (i.e., follow-up) varied and had no minimum duration but did not extend beyond December 31, 2014
- Incident fractures were defined as the first fracture at a given anatomic site noted in the EHRs
  - ICD-9 codes for fractures included 800.xx–829.xx
- Subsequent fractures were defined as fractures occurring ≥8 weeks post-incident fracture (i.e., a fracture code reported every 4 weeks for 4 months would result in a total of 2 subsequent fractures)

Figure 1. Overall study design



Study period: August 1, 1990, to December 31, 2014
Index date: Date of diagnosis of disorder of phosphorus metabolism and/or the second low ALP activity finding
Pre-index period: 12 months prior to index date
Enrollment period: August 1, 1991, to December 31, 2014
Post-index period: Follow-up period after index date through whichever occurs first: patient death, last patient record in the EHR database, or December 31, 2014
EHR=electronic health record.

Analysis

- Probable HPP patients were further identified as patients with all ALP values low for age and gender (certain HPP) and a majority of ALP values low for age and gender (uncertain HPP)
- Probable HPP patients' records were extracted, and those with codes for bone fractures were identified by ICD-9 codes
- All patients with ≥1 fracture code were flagged; for each of these patients, EHRs were assessed and all codes for fractures were identified and recorded per patient
- For each patient, number of fractures and dates of fractures (based on dates of code in EHR databases) were recorded
- All potentially disease-related comorbidities were identified and tabulated including:
  - Skeletal complications, pain, depression/anxiety, respiratory failure, seizures, neurologic complications, vitamin D deficiency, nutritional deficiency, premature tooth loss, and craniosynostosis
- Incident fracture and number of subsequent fractures per patient were identified as described above
- Fracture burden was assessed by Kaplan-Meier analysis as:
  - Time from first activity date (i.e., first visit to the physician recording in the EHR database) to incident fracture
  - Time from first activity date to subsequent fractures

RESULTS

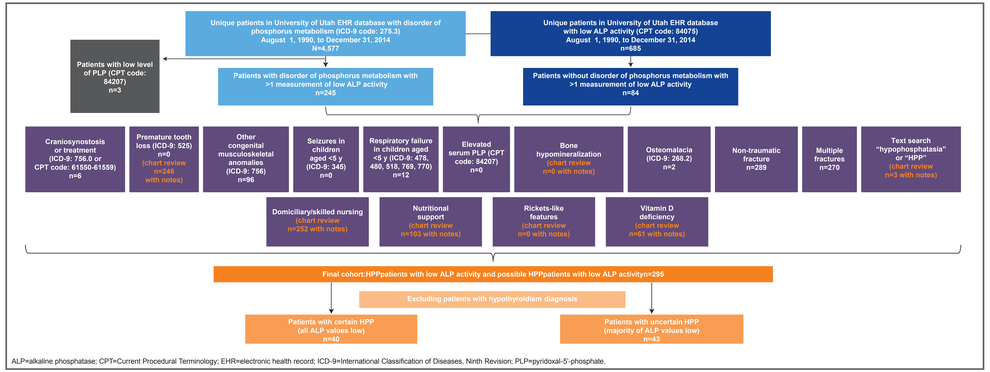
Patients

- 83 patients met inclusion criteria and were identified as probable HPP patients (**Figure 2**)
  - 29 children aged ≤17 years
    - 2 had notation of HPP diagnosis in record
  - 54 adults aged ≥18 years
    - 1 had notation of HPP diagnosis in record
- Baseline demographics and clinical characteristics are presented in **Tables 1** and **2**
- Median number of serum ALP tests per patient was 7 (range: 2–85)
- Mean follow-up for the total population was 9.9 years

Fractures

- Overall, 78 (94%) patients had ≥1 fracture (cumulative total: 447), with a mean (SD) of 5.4 (7.3), median of 3 (25th percentile: 2; 75th percentile: 6), and range of 0–55 (**Table 3**)
  - 5 patients (3 adults and 2 infants [aged 0–6 months]) had no evidence of fractures
- The incidence of fracture was 54.5/100 person-years in this population
- Median time to first fracture determined by Kaplan-Meier analysis was 2.9 years (**Figure 3**) and third fracture was 7.3 years (**Figure 4**)

Figure 2. HPP diagnostic algorithm



ALP=alkaline phosphatase; CPT=Current Procedural Terminology; EHR=electronic health record; ICD-9=International Classification of Diseases, Ninth Revision; PLP=pyridoxal-5'-phosphate.

Table 1. Baseline demographics

	Certain HPP n=40				Uncertain HPP n=43			
Age:	0–6 mo	7 mo–5 y	6–17 y	18+ y	0–6 mo	7 mo–5 y	6–17 y	18+ y
Demographic	(n=2)	(n=4)	(n=6)	(n=28)	(n=2)	(n=5)	(n=10)	(n=26)
Age at time of diagnosis, y, mean (median)	0 (0)	4 (5)	10 (10)	52 (52)	0 (0)	3 (3)	10 (11)	51 (55)
Mortality, n (%)	0 (0)	0 (0)	1 (16.7)	3 (10.7)	0 (0)	0 (0)	1 (10.0)	6 (23.1)
Gender, n (%)								
Female	0 (0)	1 (25.0)	2 (33.3)	16 (57.1)	1 (50.0)	2 (40.0)	3 (30.0)	16 (61.5)
Ethnicity, n (%)								
White	1 (50.0)	4 (100)	3 (50.0)	26 (92.9)	0 (0)	4 (80.0)	5 (50.0)	19 (73.1)
Hispanic or Latino	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Black or African American	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.9)
Native American or American Indian	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Asian/Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	3 (50.0)	2 (7.1)	1 (50.0)	1 (20.0)	5 (50.0)	5 (19.2)
Unknown	1 (50.0)	0 (0)	0 (0)	0 (0)	1 (50.0)	0 (0)	0 (0)	1 (3.9)

HPP=hypophosphatasia.

Table 2. Baseline clinical characteristics

	Certain HPP n=40				Uncertain HPP n=43			
Age:	0–6 mo	7 mo–5 y	6–17 y	18+ y	0–6 mo	7 mo–5 y	6–17 y	18+ y
Characteristic, n (%)	(n=2)	(n=4)	(n=6)	(n=28)	(n=2)	(n=5)	(n=10)	(n=26)
History of HPP	1 (50.0)	0 (0)	1 (16.7)	1 (3.6)	0 (0)	0 (0)	0 (0)	0 (0)
Family history of HPP	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Osteomalacia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
History of nontraumatic fractures	1 (50.0)	4 (100)	6 (100)	28 (100)	1 (50.0)	5 (100)	10 (100)	23 (88.5)
History of multiple fractures	1 (50.0)	4 (100)	6 (100)	26 (92.9)	0 (0)	5 (100)	10 (100)	23 (88.5)
Premature tooth loss	1 (50.0)	2 (50.0)	1 (16.7)	3 (10.7)	0 (0)	0 (0)	2 (20.0)	2 (7.7)
Craniosynostosis	1 (50.0)	1 (25.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.9)
Respiratory failure	2 (100)	4 (100)	5 (83.3)	26 (92.9)	2 (100)	5 (100)	10 (100)	25 (96.2)
Seizures	0 (0)	0 (0)	0 (0)	1 (3.6)	0 (0)	0 (0)	1 (10.0)	3 (11.5)
Skeletal complications	1 (50.0)	4 (100)	6 (100)	28 (100)	1 (50.0)	5 (100)	9 (90.0)	25 (96.2)
Neurosurgical complications	2 (100)	4 (100)	5 (83.3)	26 (92.9)	2 (100)	5 (100)	7 (70.0)	23 (88.5)
Depression and anxiety	0 (0)	3 (75.0)	5 (83.3)	26 (92.9)	1 (50.0)	7 (80.0)	5 (50.0)	23 (88.5)
Vitamin D deficiency	0 (0)	0 (0)	0 (0)	5 (17.9)	0 (0)	0 (0)	0 (0)	4 (15.4)
Nutritional deficiency	0 (0)	2 (50.0)	1 (16.7)	4 (14.3)	1 (50.0)	0 (0)	0 (0)	2 (7.7)
Orthopedic surgery	0 (0)	0 (0)	0 (0)	13 (46.3)	0 (0)	0 (0)	0 (0)	8 (30.8)
Neurologic surgery	0 (0)	1 (25.0)	0 (0)	15 (53.6)	0 (0)	1 (20.0)	1 (10.0)	4 (15.4)

HPP=hypophosphatasia.

Figure 3. Kaplan-Meier curve for entire HPP cohort time to first fracture

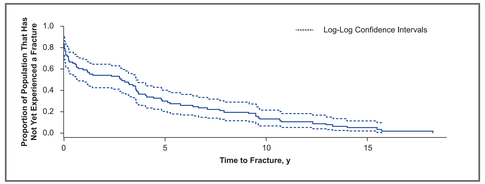


Figure 4. Kaplan-Meier curve for entire HPP cohort time to third fracture

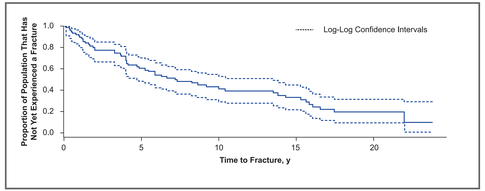


Table 3. Overall burden of disease as defined by number of fractures

	n	Mean no. of fractures	SD	Median no. of fractures	25%	75%	Min	Max	Mean follow-up, y
Certain HPP	40	7.1	9.5	3.5	2.0	10.5	0	55	11.8
Uncertain HPP	43	4.2	3.1	3.0	2.0	6.0	0	12	8.1

HPP=hypophosphatasia; SD=standard deviation.

CONCLUSIONS

- Patients with probable HPP had a significant burden of disease as evidenced by number of fractures
  - Over a mean length of follow-up of 9.9 years, the cumulative total of fractures among 78 of 83 probable HPP patients was 447, with a mean (SD) of 5.4 (7.3) fractures
- Incidence of fracture in the probable HPP population in this analysis was 54.5 per 100 person-years; to provide context for these data, in a survey of the healthy general population in England the incidence of fracture was 3.6 per 100 person-years[8]

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DISCLOSURES

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