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Real-world Clinical Profiles of Children With Hypophosphatasia From the Global HPP Registry

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INTRODUCTION

- Hypophosphatasia (HPP) is a rare, inherited, metabolic disease caused by deficiency of tissue-nonspecific alkaline phosphatase (TNSALP) that can lead to musculoskeletal and systemic manifestations in children[1,2]
- Classically, HPP is considered a disease primarily of the skeletal system[3,4]; however, children with HPP have a heterogeneous clinical presentation with varying degrees of disease severity, which often delays diagnosis and treatment[1,2,5,6]
  - The current observational study was conducted to better understand the clinical features of children with HPP in the real world and to evaluate the clinical profiles and body systems impacted at initial assessment (baseline) for the total population and for those who eventually received treatment with enzyme replacement therapy (ERT) with asfotase alfa (STRENSIQ®, Alexion Pharmaceuticals, Inc.)

METHODS

The Global HPP Registry, an observational, prospective, multinational study (NCT02306720; EUPAS13526), was initiated in 2015 to enable healthcare practitioners to collect data on patient demographics and medical history related to HPP, including disease signs and symptoms, age at first manifestation, and ERT treatment status

Patients <18 years of age at baseline from the Global HPP Registry were included in this study if they had:

- ☑ Low serum alkaline phosphatase (ALP) activity under the lower limit of the age- and sex-adjusted reference range and/or genetic testing results indicating at least one *ALPL* mutation
- ☑ Valid enrollment date, data on age at enrollment or date of birth, known sex (male or female), known ERT treatment status (treated or untreated), and treatment start date, if ever treated
- ☑ History of at least one prespecified sign or symptom of HPP at baseline

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Medical history data from eligible children were analyzed for:

- The overall population*
- Ever-treated patient subgroups based on geographic region:

Separate analyses of the most common signs and symptoms of HPP in children with ≥3 baseline signs and symptoms, excluding those presenting with only dental manifestations, were also performed

*The never-treated population included regions where coverage may not be available and thus, a meaningful assessment of the data was not possible in this subgroup

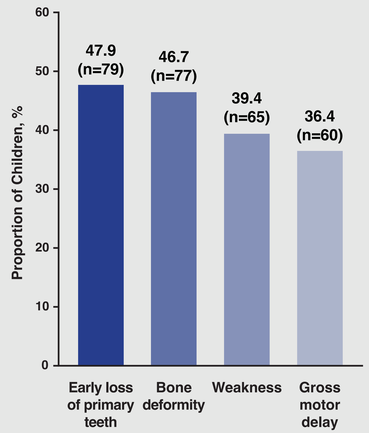
RESULTS

Baseline demographics and clinical characteristics of study participants overall and by region

	All children	Ever-treated children (N=141)[a]		
		US/Canada	Europe[b]	Japan
	N=323	n=54	n=41	n=46
Sex, n (%)	Male 153 (47.4) / Female 170 (52.6)	Male 26 (48.1) / Female 28 (51.9)	Male 22 (53.7) / Female 19 (46.3)	Male 17 (37.0) / Female 29 (63.0)
Age at study baseline, y				
Mean (SD)	6.2 (4.8)	6.8 (5.2)	4.7 (5.4)	3.5 (4.7)
Median (min, max)	5.4 (0.0, 17.9)	5.4 (0.0, 17.4)	2.7 (0.0, 17.0)	1.6 (0.0, 17.9)
Age at first HPP manifestation, y				
n	285	49	35	45
Mean (SD)	1.9 (2.7)	2.4 (3.6)	0.8 (1.6)	0.41 (1.2)
Median (min, max)	1.0 (−0.5, 17.0)	1.2 (−0.1, 17.0)	0.2 (−0.4, 6.9)	0 (−0.5, 7.1)
Age at HPP diagnosis, y				
n	313	52	41	46
Mean (SD)	3.7 (4.1)	4.7 (5.2)	1.4 (2.6)	1.7 (3.6)
Median (min, max)	2.4 (−0.5, 17.6)	2.5 (0.0, 17.3)	0.5 (−0.5, 15.1)	0.01 (−0.5, 12.8)
Duration of delay in diagnosis, y				
n	279	47	35	45
Mean (SD)	1.6 (2.9)	1.7 (2.8)	0.6 (2.3)	1.3 (3.3)
Median (min, max)	0.5 (−7.5, 15.6)	0.6 (−23.0, 12.3)	0.3 (−7.5, 10.5)	0.01 (−0.0, 12.3)
Age group at first HPP manifestation, n (%)				
<6 months	99 (30.7)	15 (27.8)	24 (58.5)	35 (76.1)
6 months to <16 years	195 (60.4)	35 (64.8)	13 (31.7)	10 (21.7)
Unknown	29 (9.0)	4 (7.4)	4 (9.8)	1 (2.2)
Number of baseline[c] signs/symptoms per patient				
n	323	54	41	46
Mean (SD)	3.4 (2.7)	4.6 (2.6)	6.0 (3.3)	2.5 (1.5)
Median (min, max)	3.0 (1.0, 18.0)	4.0 (1.0, 12.0)	5.0 (1.0, 18.0)	2.0 (1.0, 7.0)
Height				
n	175	17	12	37
Z-score, mean (SD)	−1.2 (2.1)	−0.8 (1.4)	−1.4 (1.8)	−3.4 (2.5)
Z-score, median (min, max)	−0.9 (−12.6, 3.1)	−0.8 (−3.1, 1.4)	−1.7 (−4.2, 0.7)	−3.1 (−12.6, −0.1)
<3rd percentile, n (%)	58 (33.1)	5 (29.4)	5 (41.7)	27 (73.0)
Weight				
n	180	18	18	37
Z-score, mean (SD)	−0.8 (2.2)	−0.2 (1.6)	−1.2 (2.2)	−2.6 (3.2)
Z-score, median (min, max)	−0.5 (−14.9, 2.7)	−0.1 (−3.7, 2.4)	−0.4 (−7.1, 1.2)	−1.9 (−14.9, 2.0)
<3rd percentile, n (%)	36 (20.0)	4 (22.2)	4 (22.2)	18 (48.6)
ALP < LLN				
n	287	48	34	33
n (%)	273 (95.1)	48 (100)	33 (97.1)	25 (75.7)

ALP, alkaline phosphatase; LLN, lower limit of normal.
[a]10 ever-treated children were not part of the prespecified regions and were not captured.
[b]European countries with ever-treated children include Austria, Belgium, France, Germany, Italy, and United Kingdom.
[c]For treated patients, baseline refers to the time prior to the initiation of ERT; for untreated patients, baseline refers to the time of data collection after registry enrollment.

Most common signs and symptoms of HPP in children with ≥3 baseline signs and symptoms, excluding those presenting with only dental manifestations (n=165)



History of specific signs and symptoms of HPP within each body system at baseline

[a]This category includes loss of permanent teeth, loose teeth, poor dentition, hypodontia, dental implants, dental bridges, and dentures. [b]Scaling of results was used to increase readability; HPP, hypophosphatasia.

LIMITATIONS

- The Global HPP Registry is observational. Because data were derived from medical records, the data may reflect variations in the reported severity of the disease from patient to patient and in standard of care across practices and geographic regions
- The manifestations of HPP in the Global HPP Registry were based on a predetermined set, and therefore all manifestations may not be represented in this analysis
- The differences in median age between geographic regions was a major biasing factor in this study
- Clinical histories of HPP signs and symptoms taken from medical records may be subject to recall bias for events that were reported by the patient and parents to the provider if recall intervals were long and therefore accuracy was potentially reduced, particularly for less severe disease manifestations
- The definitions of clinical manifestations may have been subject to physicians' interpretation; for example, failure to thrive may not have been based on a standardized definition, thus potentially introducing variability in the data

CONCLUSIONS

- This analysis from the Global HPP Registry assessed baseline real-world clinical profiles of children with HPP and to our knowledge is the largest cohort of children with HPP studied to date
- We found that 51% of the children aged <18 years experienced ≥3 signs and symptoms of HPP
- Regional differences in clinical presentation were noted:
  - Japan had the largest reported population of patients diagnosed at less than 6 months, largest percentage of patients with skeletal and respiratory manifestations, and maximum percentage of patients in the <3rd percentile in height
  - The United States/Canada had the largest percentage of patients with dental and pain manifestations
  - Europe had the largest percentage of patients with muscular and neurologic manifestations
- A comparison of HPP signs and symptoms in children with varying baseline characteristics highlights the importance of understanding differences in clinical presentation of HPP, particularly differences based on geographic region
- Additionally, non-skeletal manifestations, such as muscle weakness, gross motor delay, fatigue, and failure to thrive, commonly occur and should be considered in the diagnosis and the decision to treat HPP patients with ERT
- These findings may facilitate recognition of common HPP signs and symptoms and thus reduce delays in diagnosis

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DISCLOSURES

GAMM, AL, CRG, KMD, LS, KO, and **WH** are consultants for, and have received research funding and honoraria from, Alexion, AstraZeneca Rare Disease. **PSK** is a clinical study investigator and has received consulting fees and travel support from Alexion, AstraZeneca Rare Disease for consulting and participation on advisory boards. **AP** and **SF** are employees of Alexion, AstraZeneca Rare Disease, the study sponsor, and may own stock options in the company.