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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 within the gene encoding tissue-nonspecific ALP¹
- HPP is a heterogenic disease with a wide range of signs, symptoms, and complications reported in the literature, including bone deformities, fractures, bone/muscle pain, respiratory problems, tooth loss, impaired mobility, seizures, and, in some cases, death^{1,2}
- The natural history of HPP is poorly understood³
- Patients and their caregivers often question whether specific signs and symptoms are manifestations of the natural course of the disease or are unrelated

OBJECTIVE

 A group of US patients and caregivers completed a survey that aimed to explore their perceptions of signs and symptoms of HPP

METHODS

- A questionnaire developed by Alexion Pharmaceuticals, Inc., was completed by patients with HPP or their caregivers during a patient focus group convened at the 2016 annual meeting of the American Society for Bone and Mineral Research
- The questionnaire asked the patient/caregiver to describe signs and symptoms that were experienced and/or observed at specific age periods (birth to 5 years; 6–12 years; 13–21 years; 22–35 years; ≥36 years)
- The patient/caregiver was also asked to identify the sign or symptom that is the 'most urgent/difficult/problematic' during each age period and to identify any sign or symptom that they or their physician 'questioned regarding its relatedness to HPP'
- Participants were not asked to relate observed signs or symptoms to time of HPP diagnosis
- All information regarding signs and symptoms of HPP were handwritten by patients/ caregivers in blank spaces on the questionnaire
- Patient/caregiver reports of HPP diagnoses or signs and symptoms were not confirmed with the diagnosing physician, by review of medical records, or by any other means

RESULTS

Demographics

- Overall, a total of 14 participants completed the questionnaire, including 9 patients, 4 caregivers, and 1 respondent who identified as both patient and caregiver
- Ages of patients ranged from 6 to 68 years (mean: 40 years; median: 44 years; N=14)
- Based on age of onset of signs and symptoms, 9 patients had childhood HPP (signs) and symptoms appeared between age 7 months and 18 years) and 5 had perinatal/ infantile HPP (signs and symptoms appeared between birth and age 6 months)
- Patients/caregivers reported that diagnosis occurred during the perinatal/infantile period for 5 patients, in childhood for 3 patients, and in adulthood for 2 patients; 3 patients were reported to be carriers; and 1 patient reported the diagnosis as "other pending atypical symptoms"

Signs and Symptoms

• Signs and symptoms reported for ≥ 6 patients were fatigue (n=10), fractures (n=10), bone deformity (n=9), general pain (n=8), early tooth loss (n=7), joint pain (n=7), scoliosis (n=7), anxiety (n=6), asthma (n=6), attention issues (n=6), bone pain (n=6), high pain tolerance (n=6), and weight gain (n=6) (**Table 1**)

Table 1. Signs

Category Signs and Sy **Bone/skeleton** Fracture(s) Bone deformit Gait issue Bone cracking Bow legs Short statu General pai Pain in joints Bone pain High pain tolera Muscle pain Denying pair Pain in legs Dental Early tooth los **Dental caries Dental problen Central nervous** Balance issue Low body temp Numbness Seizure(s)-other emperature s Gastrointestina Weight gain Failure to thrive Irritable bowel Pofluy **Musculoskeletal** Muscle weaknes *Ivpermobility* -atigue Attention issue Mental "foggine Abnormal spine espiratory Asthma **Psychiatric** Anxiety Immune relate Allergy **Developmenta** Missed develop **Reproductive sy** Yeast infection connective tiss Curata Vascular Edema

Patient-Reported Symptomatology in Hypophosphatasia

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and symptoms reported by ≥3 patients/caregivers		
oms Reported ^a	n (%)	
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	$\frac{10(71)}{0(64)}$	
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	D (30)	
pping	3 (21)	
	3 (21)	
	3 (21)	
	14 (100)	
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	7 (50)	
	6 (43)	
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	3 (21)	
	3 (21)	
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	4 (29)	
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	5 (36)	
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^aSigns and symptoms reported during ≥ 1 age period in ≥ 3 patients.

 Signs and symptoms reported in ≥3 patients during each age period are shown in Figure '

Figure 1. Signs and symptoms reported in ≥3 patients by age period during which the sign or symptom occurred (N=14). Values shown are numbers of patients



• The signs and symptoms reported to be 'most urgent/difficult/problematic' in >3 patients were fractures, bone pain, early tooth loss, fatigue, and muscle pain (Table 2)

Table 2. Signs and symptoms reported as 'most urgent/difficult/ problematic' for ≥ 2 patients (N=14)

Signs and Symptoms	'Most Urgent/Difficult/ Problematic' ^a n (%)	<pre>'Most Urgent/Difficult/ Problematic' AND 'Questioned Regarding Its Relatedness to HPP'b n (%)</pre>
Fracture(s)	8 (57)	1 (7)
Bone pain	5 (36)	0
Early tooth loss	4 (29)	0
Fatigue	4 (29)	2 (14)
Muscle pain	4 (29)	0
Asthma	3 (21)	0
Dental caries	3 (21)	0
Pain in joints	3 (21)	1 (7)
Migraine(s)	3 (21)	2 (14)
Vomiting	3 (21)	3 (21)
Attention issues	2 (14)	1 (7)
General pain	2 (14)	1 (7)
Reflux	2 (14)	1 (7)
Breathing problems	2 (14)	2 (14)

HPP=hypophosphatasia.

^aTotal number of patients/caregivers who marked the sign or symptom as being 'most urgent/difficult/ problematic

^oTotal number of patients/caregivers who marked the sign or symptom as 'most urgent/difficult/ problematic' AND 'questioned regarding its relatedness to HPP.'

• The signs and symptoms that were reported as being 'questioned regarding its relatedness to HPP' in >3 patients were breathing problems, short stature, and high pain tolerance (**Table 3**)

Table 3. Signs and symptoms reported as being 'questioned' regarding its relatedness to HPP' for ≥2 patients (N=14)

Signs and Symptoms	'Questioned Regarding Its Relatedness to HPP'a n (%)	'Most Urgent/Difficult/ Problematic' AND 'Questione Regarding Its Relatedness to HPP' ^b n (%)
Breathing problems	6 (43)	2 (14)
Short stature	5 (36)	0
High pain tolerance	4 (29)	0
Abnormal spine curvature – scoliosis	3 (21)	0
Denying pain	3 (21)	0
Dislocation	3 (21)	0
Failure to thrive	3 (21)	0
Attention issues	3 (21)	1 (7)
Fatigue	3 (21)	2 (14)
Vomiting	3 (21)	3 (21)
Bone deformity	2 (14)	0
Dental problems	2 (14)	0
Eating disorder	2 (14)	0
Edema	2 (14)	0
Fogginess	2 (14)	0
Gait issue	2 (14)	0
Low body temperature	2 (14)	0
Sleep apnea	2 (14)	0
Tremors	2 (14)	0
Fracture(s)	2 (14)	1 (7)
General pain	2 (14)	1 (7)
Pain in joints	2 (14)	1 (7)
Poor feeding	2 (14)	1 (7)
Seizure(s) – other	2 (14)	1 (7)
Reflux	2 (14)	1 (7)
Migraine(s)	2 (14)	2 (14)

HPP=hypophosphatasia.

^aTotal number of patients/caregivers who marked the sign or symptom as being 'questioned regarding its relatedness to HPP.'

^bTotal number of patients/caregivers who marked the sign or symptom as 'most urgent/difficult/ problematic' AND 'questioned regarding its relatedness to HPP.'

LIMITATIONS

- Signs and symptoms reported by caregivers were not confirmed with the patients or physicians
- Patient/caregiver reports that a physician questioned the relatedness of a sign or symptom to HPP were not confirmed with the physician and are based solely on the patients'/caregivers' perceptions
- Reported signs and symptoms of HPP were not evaluated in relation to the time of HPP diagnosis
- Recruitment of the survey participants may have been biased, and the study population may not accurately reflect the HPP patient/caregiver population

CONCLUSIONS

- Many signs and symptoms known to be associated with the natural history of HPP (e.g., fracture, bone deformity, gait issues, tooth loss) were reported
- More than 70% of the patients/caregivers reported fatigue, which supports that manifestations of HPP may extend beyond bone
- The 'most urgent/difficult/problematic' signs and symptoms reported were fractures, bone pain, early tooth loss, fatigue, and muscle pain
- Multiple signs and symptoms were also reported that previously have not been associated with the disease (e.g., migraine, attention deficit, brain fogginess/ cognition, paresthesia, asthma)
- Most of these and signs and symptoms are not bone related
- It is not clear whether these are signs and symptoms of HPP or comorbidities
- Many of the signs and symptoms 'questioned regarding relatedness to HPP' by patients/caregivers were also indicated as the 'most urgent/difficult/problematic,' suggesting a high burden imposed by these signs and symptoms
- These results expand on the current understanding of the spectrum of signs and symptoms experienced by patients with HPP during different life stages, particularly adulthood and suggest that previous descriptions of the natural history of HPP may be inadequate
- A more inclusive description of the signs and symptoms of HPP may allow for a more robust understanding of the disease by patients and caregivers, help to inform the medical management of patients with HPP, and help to define outcome measures in future clinical studies evaluating HPP therapies

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DISCLOSURES

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