

Disease Severity in Children and Adults with Hypophosphatasia

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Introduction

Hypophosphatasia (HPP) is a rare inherited form of rickets and osteomalacia caused by inactivating mutations in the gene encoding tissue-nonspecific alkaline phosphatase (TNSALP). Birth incidence of severe patients is about 1:100,000. The biochemical hallmarks of this inborn error of metabolism are low circulating levels of ALP with elevated serum or urine levels of TNSALP substrates. The disease manifests as a broad clinical spectrum. There is no approved treatment although clinical trials of a bone-targeted enzyme replacement therapy are underway.

Methods

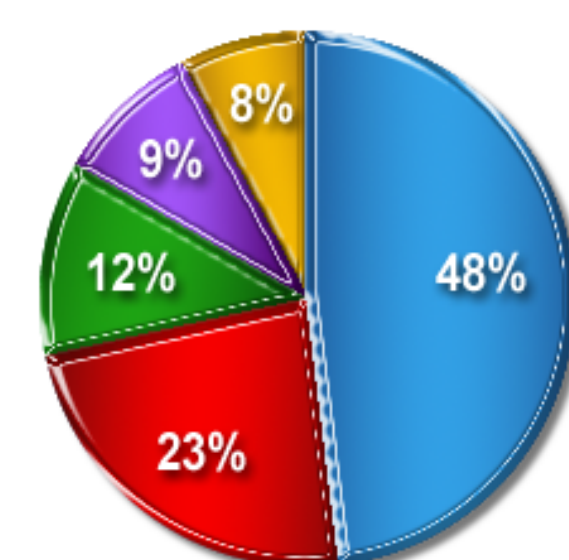
An online survey was developed to assess self-reported disease burden and quality of life in children and adults with HPP. Translations were available in English, French, German and Japanese. Respondents were recruited through patient advocacy groups and small donations were made for each completed survey. Data from 90 respondents who reported age at symptom onset are presented. Respondents were stratified into three subgroups based on age of symptom onset: infancy (≤ 1 year), childhood (2-12 years) and adolescence/adulthood (> 12 years) of age.

Results

Of the 90 respondents, 46 (51%) reported symptom onset in the first year of life, 27 (30%) in childhood and 17 (19%) in adolescence/adulthood. Skeletal abnormalities were more common in patients who presented in the first year of life. Poorly healing fractures severe enough to require surgical repair occurred in the majority of patients regardless of age at symptom onset. Use of walking aids and prescription pain medication to manage symptoms was common. The majority of respondents reported worsening of HPP signs and symptoms over the past 5 years regardless of age at symptom onset. Pain and limited mobility/physical activity were among the top rated symptoms that interfered most with daily function. Quality of life scores suggested diminished physical health and function and significant pain.

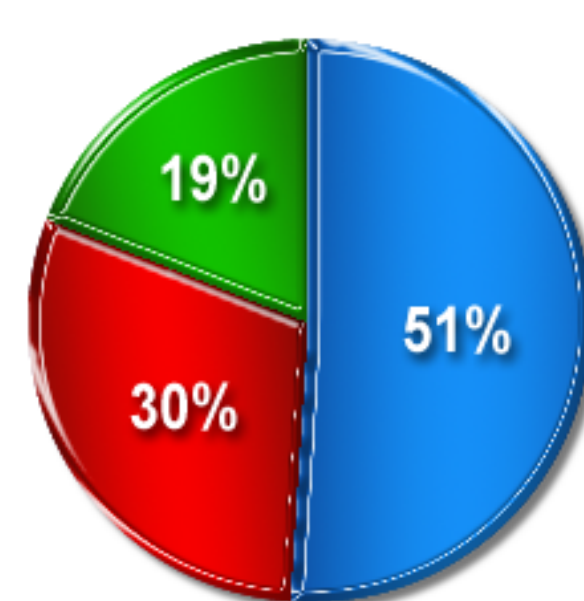
Respondents by Country

United States Germany France Canada Other



Classification Based on Age of Symptom Onset

Infantile (≤ 1 year) Childhood (2-12 years) Adult (> 12 years)



Demographics

	Infantile Onset (n = 46)	Childhood Onset (n = 27)	Adulthood Onset (n = 17)
Gender			
Male	25 (54%)	17 (63%)	13 (76%)
Female	21 (46%)	10 (37%)	4 (24%)
Current Age Category			
Adult	23 (50%)	21 (78%)	17 (100%)
Child	23 (50%)	6 (22%)	0 (0%)
Mean Current Age			
Years (SD)	20.6 (17.4)	37.8 (20.5)	52.9 (13.1)
Mean Age at Symptom Onset			
Years (SD)	0.4 (0.5)	4.2 (3.2)	36.9 (12.4)
Family History of HPP			
Yes	15 (33%)	13 (48%)	10 (63%)

Disease History

	Infantile Onset (n = 46)	Childhood Onset (n = 27)	Adult Onset (n = 17)
Developmental			
Difficulty gaining weight	28 (61%)	7 (26%)	3 (18%)
Delayed walking	31 (67%)	12 (44%)	3 (18%)
Delayed talking	9 (20%)	1 (4%)	0 (0%)
Short stature	30 (65%)	8 (30%)	2 (12%)
Bone			
Abnormally shaped chest	22 (48%)	7 (26%)	2 (12%)
Abnormally shaped head	22 (48%)	7 (26%)	1 (6%)
Bowing of legs	24 (52%)	9 (33%)	0%
Bowing of arms	18 (39%)	3 (11%)	0%
Knock knees	19 (41%)	5 (19%)	0%
Dental/Oral			
Premature tooth loss	37 (80%)	21 (78%)	6 (35%)
Excessive cavities	12 (26%)	12 (44%)	10 (59%)
Loss of adult teeth	10 (22%)	14 (52%)	8 (47%)
Mobility			
Currently using wheelchair or walking device	23 (50%)	12 (50%)	11 (92%)

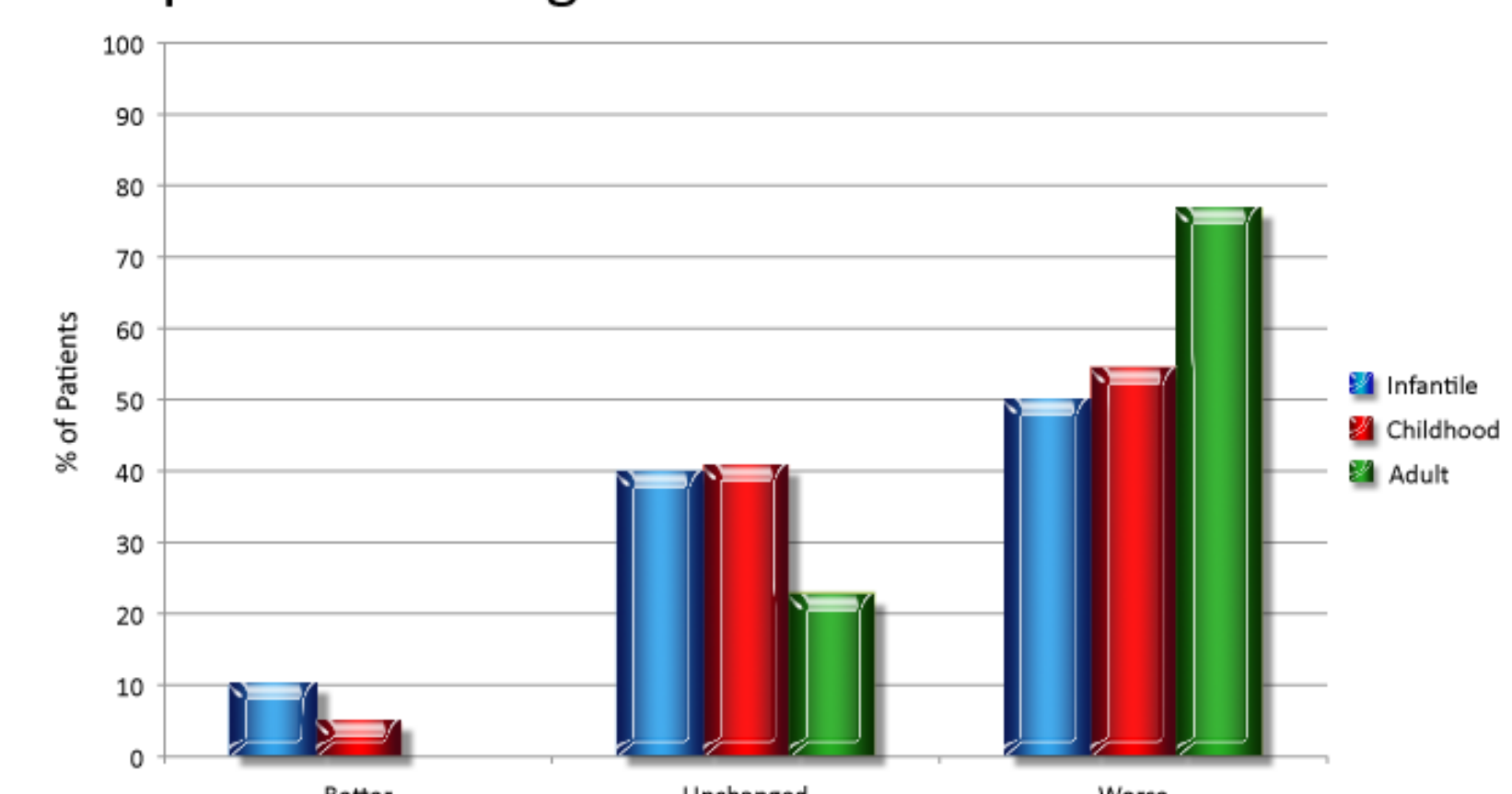
Fractures

	Infantile Onset (n = 31)	Childhood Onset (n = 25)	Adult Onset (n = 16)
Any Fracture	31 (67%)	17 (68%)	14 (88%)
Number of Fractures			
Median (SE)	5 (4)	7 (1)	4 (3)
Range	1-100	1-15	1-30
First Fracture			
Childhood	22 (71%)	4 (23%)	2 (14%)
Adolescence	6 (19%)	3 (18%)	0 (0%)
Adulthood	3 (10%)	10 (59%)	12 (86%)
Surgical Repair for Fractures			
Cranectomy	5 (16%)	2 (12%)	2 (14%)
Rods	14 (45%)	9 (53%)	8 (57%)
Plates	11 (36%)	6 (35%)	5 (36%)
Osteotomy	9 (29%)	5 (29%)	0 (0%)
Joint Replacement	4 (13%)	1 (6%)	2 (14%)
Fracture Characteristics			
Caused by Trauma	26 (84%)	11 (65%)	7 (50%)
Complete	21 (68%)	9 (53%)	7 (50%)
Poorly healing fractures	14 (45%)	12 (71%)	10 (71%)
Mobility/Medication			
Wheelchair	14 (45%)	0 (0%)	2 (14%)
Walking Device	13 (42%)	7 (41%)	4 (29%)
Prescription Pain Medication	12 (39%)	12 (71%)	11 (79%)

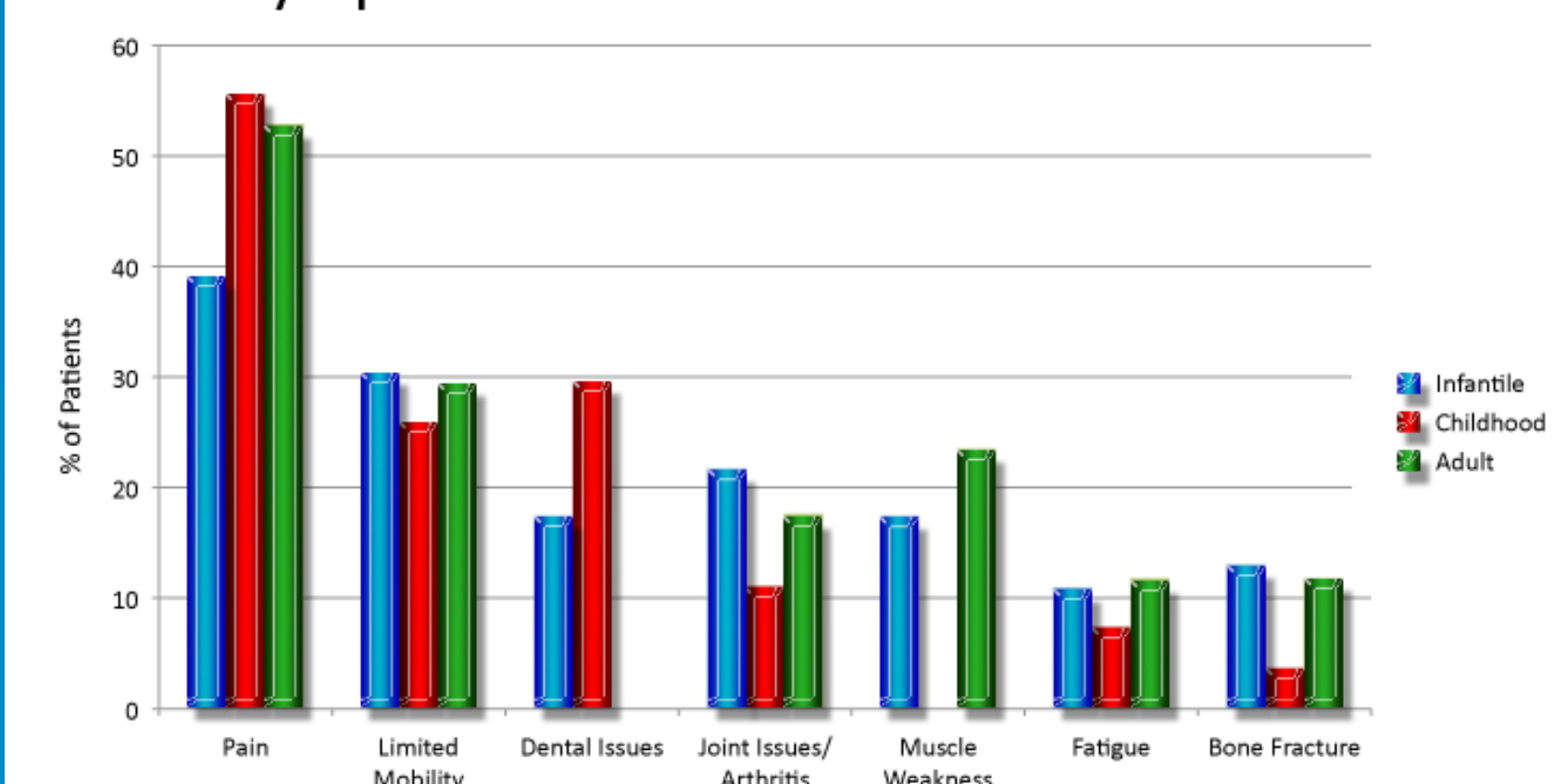
Acknowledgement

The Hypophosphatasia Impact Patient Survey was developed by Enobia Pharma, Inc., Montreal, QC, Canada.

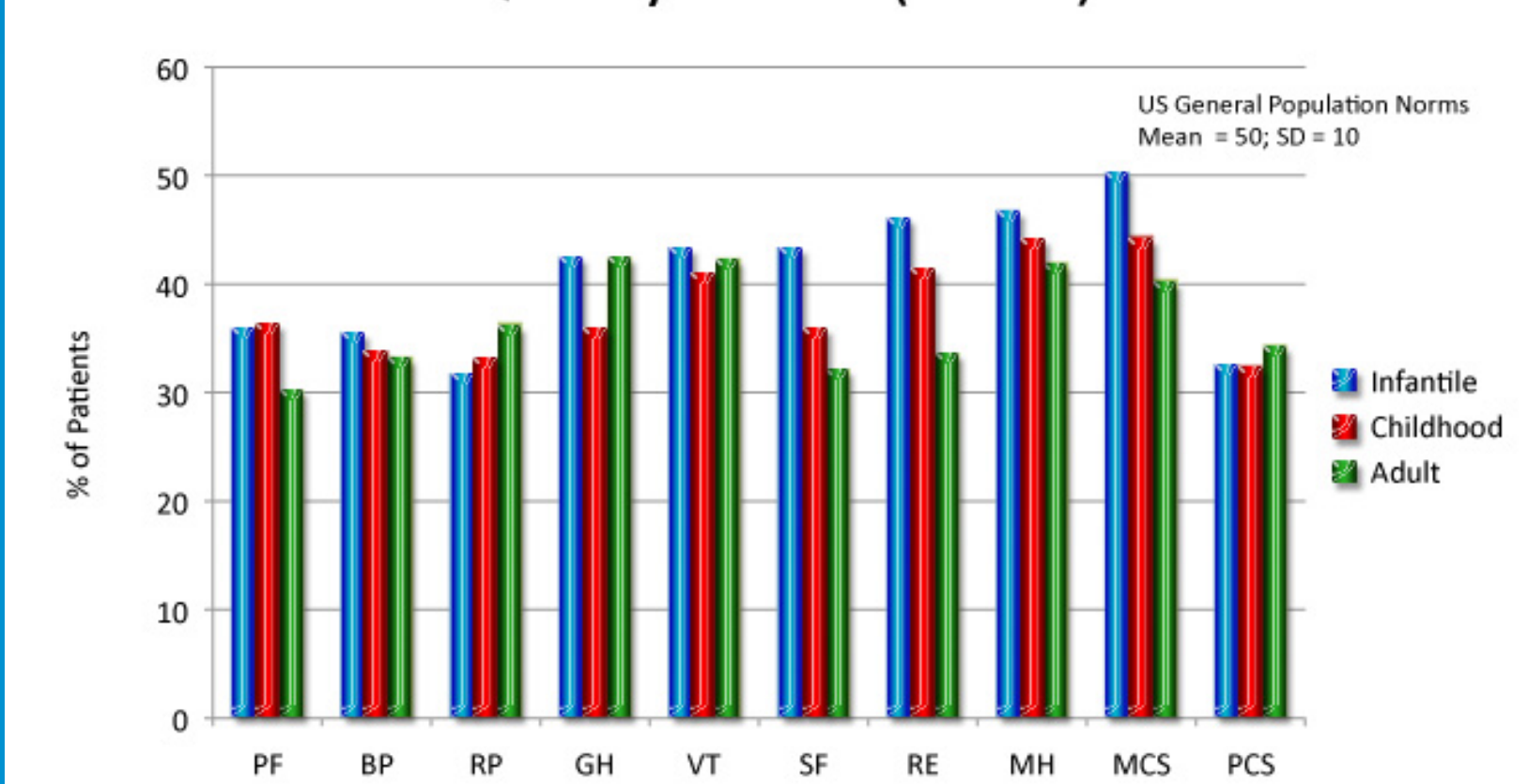
Perception of Change in Health Status in Past 5 Years



Symptoms that Interfere Most with Life



Quality of Life (SF-36)



Conclusions

Findings suggest that HPP is associated with debilitating symptoms, particularly fractures as well as physical disability, pain and diminished quality of life regardless of age at symptom onset.