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Clinical Profiles of Children with Hypophosphatasia prior to Treatment with Enzyme Replacement Therapy: An Observational Analysis from the Global HPP Registry

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Keywords
Alkaline phosphatase · Disease burden · Enzyme replacement therapy · Hypophosphatasia

Abstract
Introduction: The objective of this study was to better understand the clinical profiles of children with hypophosphatasia (HPP) prior to treatment with enzyme replacement therapy (ERT). ***Methods:*** Pretreatment demographics and medical histories of ERT-treated children (aged <18 years) enrolled in the Global HPP Registry (2015–2020) were analyzed overall, by age at first HPP manifestation (<6 months vs. 6 months to 18 years), and by geographic region (USA/Canada, Europe, and Japan). ***Results:*** Data from 151 children with HPP were analyzed. Sex distribution was balanced overall (52.3% female; 47.7% male) but differed in Japan (63.0% female; 37.0% male). Prior to ERT initiation, common manifestations were skeletal (67.5%) and extraskeletal, with the foremost types being muscular (48.3%), constitutional/metabolic (47.0%), and neurologic (39.7%). A high proportion of children who first presented at <6 months of age (perinatal/infantile period) had a history of bone deformity (59.3%) and respiratory failure (38.3%), while those aged 6 months to 18 years at first manifestation had a predominance of early loss of primary teeth (62.3%) and gross motor delay (41.0%). Those from Japan were reported to have a younger median age overall, the highest proportion of skeletal manifestations (80.4%) and growth

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impairment, while European data reported the highest proportion of muscular manifestations (70.7%). In the USA/Canada, skeletal and muscular manifestations were reported at the same frequency (57.4%). ***Conclusion:*** Prior to ERT, skeletal and extraskeletal manifestations were commonly reported in children with HPP, with differences by age at first HPP manifestation and geographical region. Comprehensive assessments of children with HPP are warranted prior to ERT initiation.

Introduction

Hypophosphatasia (HPP) is a rare, inborn metabolic disease caused by deficient activity of tissue-nonspecific alkaline phosphatase (ALP) [1]. The most easily recognizable signs of HPP in children are persistently low ALP activity and impairment in skeletal mineralization, which can be observed on radiographs and result in bone deformity, metaphyseal radiolucent areas, and/or rickets-like growth plate abnormalities [1–6]. Given that skeletal and radiological signs are the most obvious manifestations of HPP in children, it has classically been considered a disease that primarily impacts the skeletal system [7, 8]. However, extraskeletal symptoms such as failure to thrive, seizures, muscle weakness, gross motor delay, abnormal gait, pain, early loss of primary teeth, and other dental problems have also been reported in children with HPP [1, 4, 5, 9].

While perinatal/infantile HPP (where affected patients develop their first manifestation at age <6 months) represents an extreme phenotype characterized by a high mortality rate (particularly in the neonatal period), HPP that manifests after 6 months of age is characterized by varying degrees of severity that can change over time [6, 8, 10, 11]. Strensiq® (asfotase alfa), a bone-targeting enzyme replacement therapy (ERT) approved and indicated for use in pediatric-onset HPP in the USA/Canada and Europe [12, 13], and for patients of all ages in Japan [14], has been shown to improve disease manifestations in children with HPP [1, 15–17].

Despite the lack of global treatment guidelines for initiating ERT in children with HPP, decisions to start treatment with asfotase alfa have usually relied on quantifying bone and rachitic manifestations [17, 18]. However, rickets can only be detected on radiographs in children with open growth plates, and a bone biopsy is rarely performed to confirm osteomalacia. The indication for treatment in the European Union and Canada labels is broader than rickets/osteomalacia and includes biochemical abnormalities (altered calcium and phosphate metabolism), impaired growth and mobility, respiratory compromise that may require ventilation, and vitamin B6-responsive seizures. Considering the variable clinical presentation of pediatric-onset HPP, an evaluation of the signs and symptoms of HPP in children who were initiated on ERT is warranted. Using data from the Global HPP Registry, an observational analysis was conducted to better understand the clinical profiles of children (aged <18 years) with HPP prior to initiation of ERT in regions where asfotase alfa is approved for use and whether age of HPP onset or geographical differences exist.

Materials and Methods

Data Source

Initiated in 2015, the Global HPP Registry (https://hppregistry.com/) is an observational, prospective, multinational study of patients with HPP (NCT02306720; EUPAS13514) that is sponsored by Alexion, AstraZeneca Rare Disease, Boston, MA, USA, and supervised by a scientific advisory board of clinical experts in HPP [19]. As part of routine clinical practice, healthcare practitioners collect data on patient demographics and medical history related to HPP, including signs and symptoms of HPP, age at first HPP manifestation, and ERT treatment status [19].

Approval of the Global HPP Registry study protocol was obtained from the Institutional Review Board or local equivalent at each participating investigative site. Data collection and analyses complied with the World Medical Association Declaration of Helsinki, the European Medicines Agency good pharmacovigilance practices (GPV), and the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices (GPP). Prior to enrollment, legal guardians of all patients provided written informed consent and authorized the release of medical record data. For this analysis of the Global HPP Registry, data collected through September 7, 2020, were used.

Patient Population

Children (aged <18 years at ERT initiation) with prior or current ERT treatment who were enrolled in the Global HPP Registry and who had low serum ALP activity under the age- and sex-adjusted reference range and/or a genetic test indicating at least 1 *ALPL* variant were eligible for inclusion in this analysis. Patients were required to have a valid enrollment date, data on age at enrollment or date of birth, known sex (male or female), treatment with ERT, and known treatment start date. Patients were also required to have at least 1 prespecified sign or symptom of HPP prior to ERT initiation. To account for regulatory differences and access limitations associated with asfotase alfa globally, the signs and symptoms of HPP in children who went on to ERT were assessed in the 3 geographical regions where the drug is approved (USA/Canada, Europe, and Japan).

Demographics and Medical History

Demographic and medical history data from eligible children prior to ERT initiation were analyzed overall, by age at first HPP manifestation (aged <6 months vs. aged 6 months to 18 years), and by geographical region (USA/Canada, Europe, or Japan; the European subgroup included data from Austria, Belgium, France, Germany, Italy, and the UK). The reasoning behind this proposed age stratification was that children who present at <6 months of age (perinatal/infantile onset HPP) have a distinctly different disease course and severity (such as high mortality rate, vitamin B6-dependent seizures, respiratory failure) than those who manifest the disease after 6 months of age.

Statistical Analysis

Descriptive statistics (*n*, percentage, mean, standard deviation, median, and minimum [min] and maximum [max]) were calculated for demographic and medical history data, as appropriate. The relative frequency of HPP manifestations in children based on age at first HPP manifestation was quantified with prevalence ratios and 95% confidence intervals. Prevalence ratios were calculated as the ratio of the proportion of children in the <6-month age group to the proportion of children in the ≥6-month to 18-year age group with a given manifestation; 95% confidence intervals were determined using the binomial approximation. Statistically significant differences in continuous variables by geography were determined using the Kruskal-Wallis test (alpha = 0.05). All analyses were performed using SAS Life Science Analytics Framework 5.2.1.

Results

Demographic and Clinical Characteristics of ERT-Treated Children with HPP prior to ERT Initiation

A total of 151 children with HPP who were treated with ERT were included in this analysis of the Global HPP Registry. Demographics and clinical characteristics of the study population prior to ERT initiation are shown in Table 1. Overall, females made up 52% of the population, and 48% were males. The median age at first HPP manifestation was 0.2 years (min, max: −0.5, 17.0), and the median age at the time of HPP diagnosis was 0.8 years (min, max: −0.5, 17.3). A negative value for age indicates prenatal age.

When grouped by region, study participants who had initiated treatment with ERT had some notable differences in demographic factors between regions. More females (63%) than males (37%) were reported in Japan, whereas in the USA/Canada and Europe, the proportions of females and males were more evenly divided. Participants from Japan were also younger prior to treatment initiation (median age: 1.6 years, min, max: 0.0, 17.9) than the 2 other regions (p = 0.0009). When assessing age at HPP diagnosis, participants from the USA/Canada had a median (min, max) age of 2.4 (–0.1, 17.3) years, which is around 2.0 years older than the median age of participants in Europe and 2.5 years older than the median age of participants in Japan ($p < 0.0001$). Consistent with this finding, those in the USA/Canada were also more likely to be aged 6 months or older at first HPP manifestation (65%) compared with participants from Europe (32%) and Japan (22%), where the majority were aged <6 months at first HPP manifestation ($p < 0.0001$). Thus, there was a high proportion of patients with first HPP manifestation before 6 months of age in Japan and Europe. In addition, the median number of signs and symptoms per patient prior to ERT initiation were fewer in Japan (median: 2, min, max: 1, 7) than in the USA/Canada (median: 4, min, max: 1, 12) or Europe (median: 5, min, max: 1, 18) ($p < 0.0001$).

Children with HPP Who Presented with both Skeletal and Extraskeletal Disease Manifestations prior to ERT

Figure 1 shows the body systems impacted by specific signs and symptoms of HPP in children in the overall population who went on to ERT (N = 151). Skeletal signs and symptoms were most common, recorded in 68% of children, with bone deformity alone experienced by 45% of children and rickets-like deformity occurring in 32% of children. Muscular manifestations were frequently reported in up to 48% of children. Specifically, 34% reported muscle weakness, 30% reported gross motor delay, and 13% reported abnormal gait. In terms of constitutional/metabolic manifestations (47%), 33% experienced failure to thrive, and 19% experienced fatigue. When assessing neurological signs and symptoms, which were experienced by 40% of children, the most common manifestations were craniosynostosis (19%) and cognitive or developmental delay (17%). Other manifestations of HPP were dental (37%), renal symptoms (36%), respiratory issues (28%), and pain (26%) (shown in Fig. 1). Children who went on to ERT in Japan were also more likely to be shorter (z score median: −3.1) than those in the USA/Canada (z score median: −0.8) or Europe (z score median: −1.7) both $p < 0.0001$ (Table 1). Similarly, weight z scores for those in Japan (median: −1.9) were less than those in the USA/Canada (median: 0.1) or Europe (median: −0.4) (p = 0.0015).

Children Initiated on ERT Had Different Clinical Profiles if the First HPP Manifestation Was in the Perinatal/Infantile Period

Signs and symptoms of HPP among children who went on to ERT were compared among those who had their first manifestation of HPP at age <6 months

Table 1. Demographics and clinical characteristics of ERT-treated children in the Global HPP Registry prior to ERT initiation: overall and by geographical region

Characteristic	All ERT-treated children (*N* = 151)	USA/Canada (*n* = 54)	Europe[a] (*n* = 41)	Japan (*n* = 46)
Sex, *n* (%)				
Males	72 (47.7)	26 (48.1)	22 (53.1)	17 (37.0)
Females	79 (52.3)	28 (51.9)	19 (46.3)	29 (63.0)
Age at ERT initiation, years				
n	151	54	41	46
Median (min, max)	3.4 (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, years				
n	139	49	35	45
Median (min, max)[b]	0.2 (−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, years				
n	149	53	41	46
Median (min, max)[b]	0.8 (−0.5, 17.3)	2.4 (−0.1, 17.3)	0.5 (−0.5, 15.1)	0.0 (−0.5, 12.8)
Age group at first HPP manifestation, *n* (%)	151	54	41	46
<6 months	81 (53.6)	15 (27.8)	24 (58.5)	35 (76.1)
6 months to 18 years	61 (40.4)	35 (64.8)	13 (31.7)	10 (21.7)
Unknown	9 (6.0)	4 (7.4)	4 (9.8)	1 (2.2)
Number of signs/symptoms per patient				
Median (min, max)	4.0 (1.0, 18.0)	4.0 (1.0, 12.0)	5.0 (1.0, 18.0)	2.0 (1.0, 7.0)
Length/height				
n	69	17	12	37
z score, median (min, max)	−2.2 (−12.6, 2.2)	−0.8 (−3.1, 1.4)	−1.7 (−4.2, 0.7)	−3.1 (−12.6, −0.1)
z score, mean (SD)	−2.2 (2.4)	−0.8 (1.4)	−1.4 (1.8)	−3.4 (2.5)
<3rd percentile, *n* (%)	37 (53.6)	5 (29.4)	5 (41.7)	27 (73.0)
Weight				
n	77	18	18	37
z score, median (min, max)	−1.2 (−14.9, 2.4)	−0.1 (−3.7, 2.4)	−0.4 (−7.1, 1.2)	−1.9 (−14.9, 2.0)
z score, mean (SD)	−1.6 (2.8)	−0.2 (1.6)	−1.2 (2.2)	−2.6 (3.2)
<3rd percentile, *n* (%)	28 (36.4)	4 (22.2)	4 (22.2)	18 (48.6)

ERT, enzyme replacement therapy; HPP, hypophosphatasia; max, maximum; min, minimum; SD, standard deviation; USA, United States. [a]Europe included data from Austria, Belgium, France, Germany, Italy, and the United Kingdom. [b]Negative values for age represent prenatal manifestation and diagnosis.

versus those who had their first manifestation of HPP between 6 months and 18 years of age. Among those aged <6 months at first HPP manifestation, skeletal, renal, and respiratory body systems were more affected than in those aged 6 months to 18 years, with bone deformity (59%), hypercalcemia (44%), and respiratory failure (38%) being the most prevalent signs and symptoms (shown in Fig. 2). In contrast, children aged 6 months to 18 years at first HPP manifestation experienced more dental, muscular, and pain manifestations than in those aged <6 months, with early loss of primary teeth (62%), gross motor delay (41%), and chronic bone pain (36%) being the most prevalent signs and symptoms (shown in Fig. 2).

Geographical Differences in the Clinical Profiles of Children with HPP prior to ERT Initiation

Data from Japan showed the highest percentages of patients with skeletal (80%) and respiratory (35%) manifestations, whereas data from the USA/Canada showed the lowest percentages for these body systems (skeletal, 57%; respiratory, 15%) (shown in Fig. 3). In contrast, data from

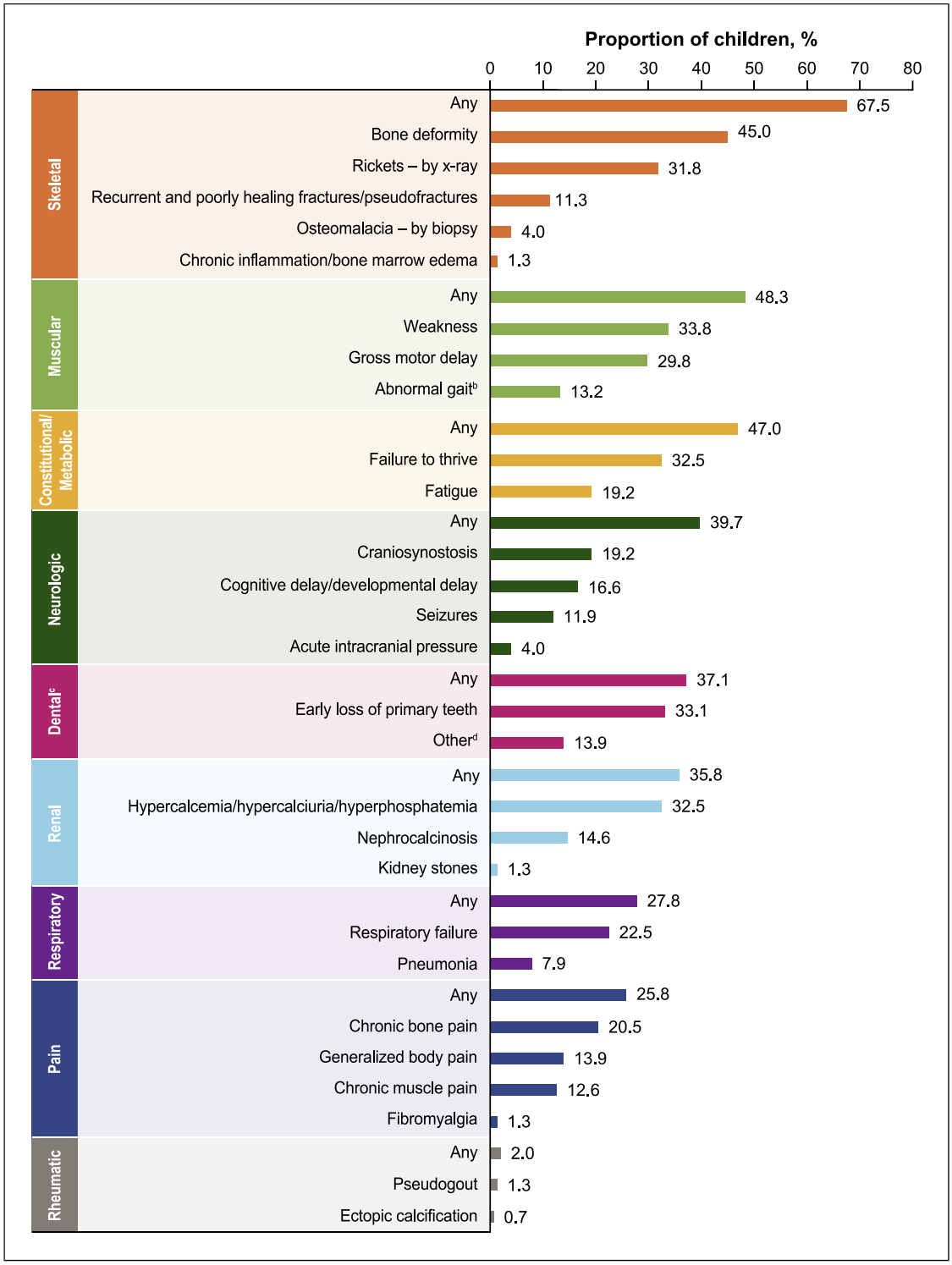

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Fig. 1. History of specific signs and symptoms of HPP within each body system[a] prior to ERT initiation in children in the overall ERT-treated population (N = 151). [a]Patients may have more than 1 sign and symptom within each body system. [b]Excludes patients <2 years of age at ERT initiation. [c]Excludes patients <6 months of age at ERT initiation. [d]This category includes loss of permanent teeth, loose teeth, poor dentition, hypodontia, dental implants, dental bridges, and dentures. ERT, enzyme replacement therapy; HPP, hypophosphatasia.

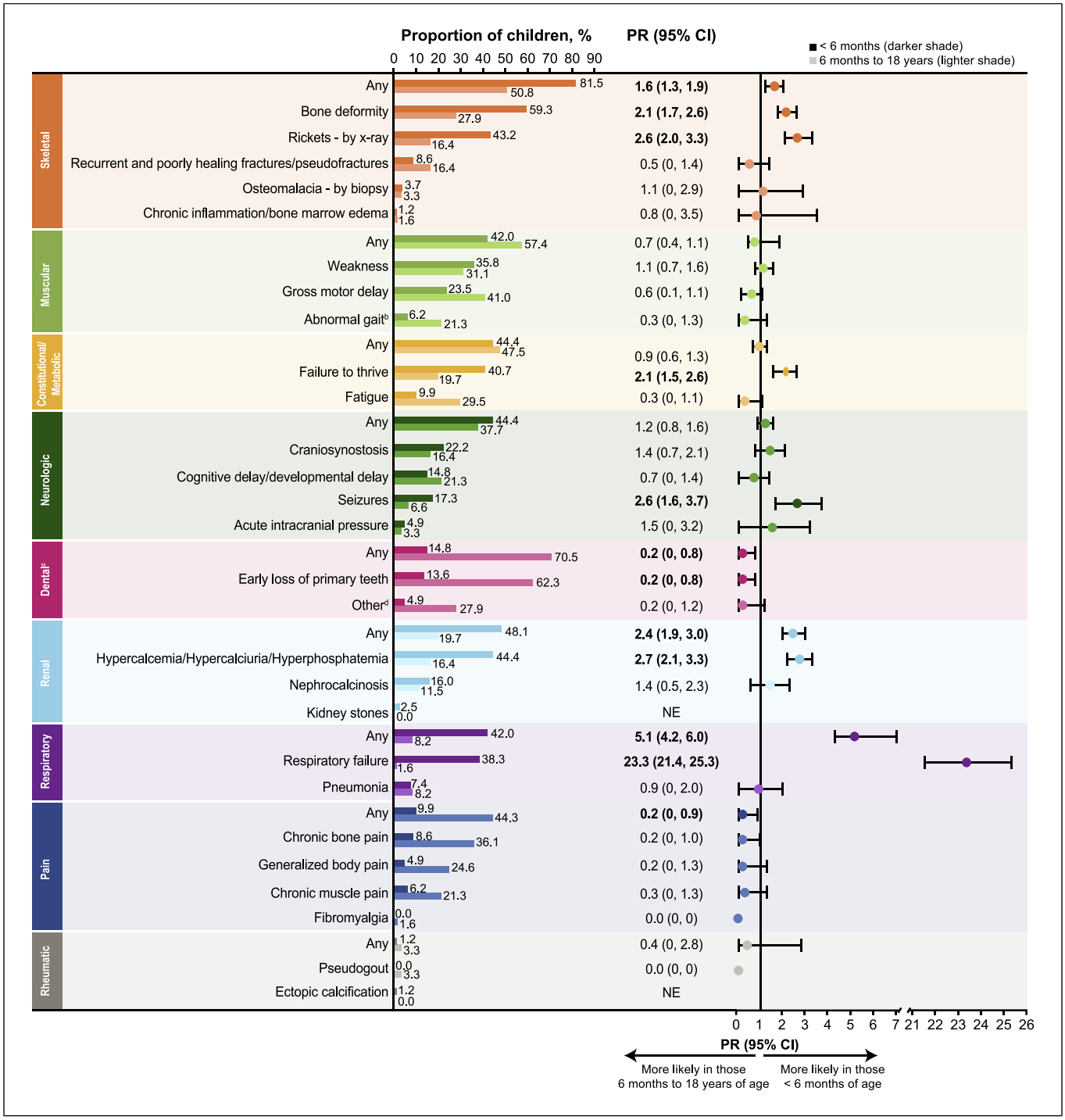

Fig. 2. History of specific signs and symptoms of HPP within each body system[a] prior to ERT initiation in children by age at first HPP manifestation: aged <6 months (n = 81) versus aged 6 months to 18 years (n = 61). Each body system is color-coded with the darker shade indicating data from children aged <6 months and the lighter shade for the children aged 6 months to 18 years. Bold font for PR (95% CI) values indicates statistical significance based on CIs that do not overlap 1. [a]Patients may have more than 1 sign and symptom within each body system. [b]Excludes patients <2 years of age at ERT initiation. [c]Excludes patients <6 months of age at ERT initiation. [d]This category includes loss of permanent teeth, loose teeth, poor dentition, hypodontia, dental implants, dental bridges, and dentures. CI, confidence interval; ERT, enzyme replacement therapy; HPP, hypophosphatasia; NE, not estimable; PR, prevalence ratio.

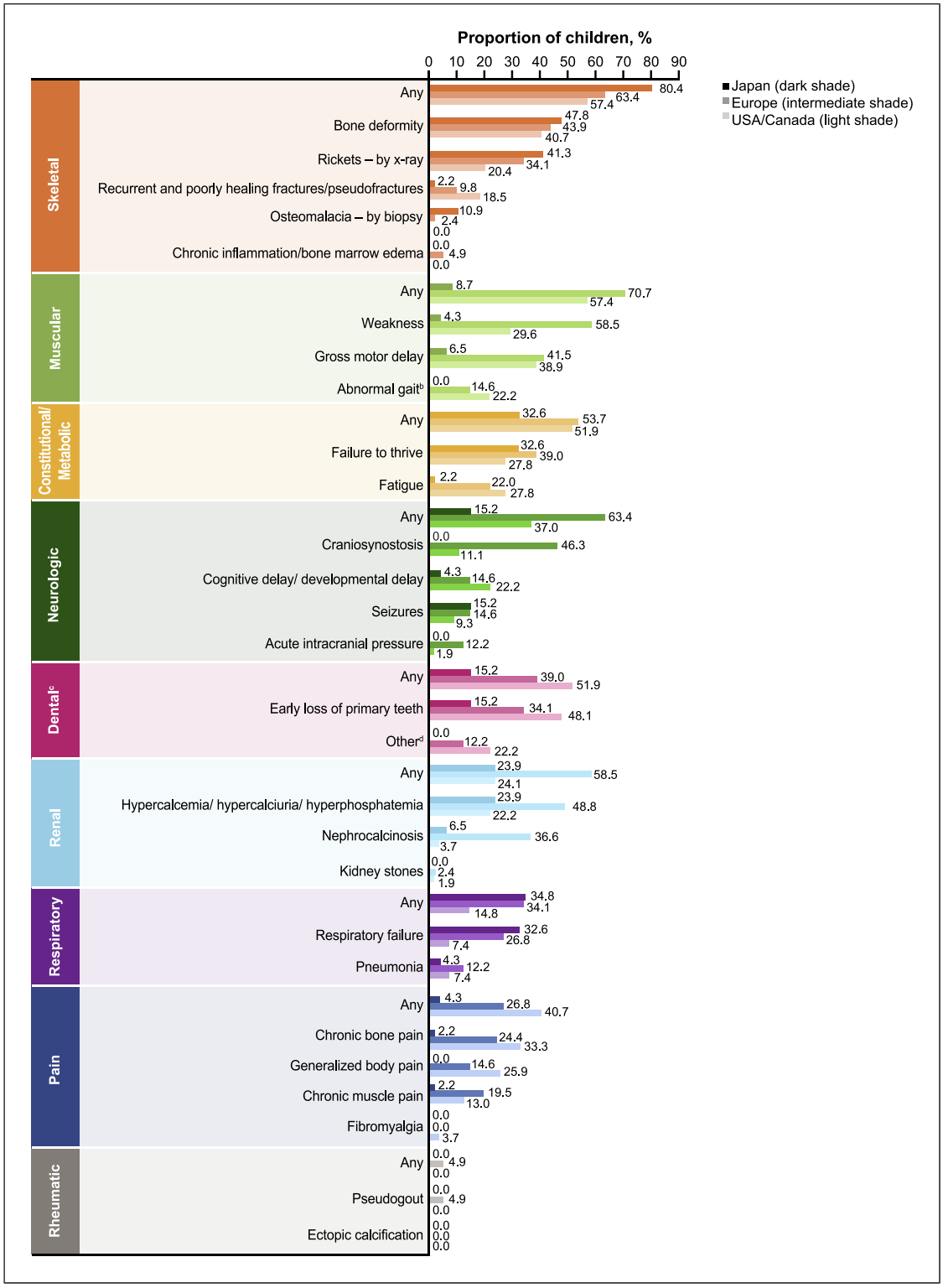

Fig. 3. History of specific signs and symptoms of HPP within each body system[a] prior to ERT initiation in children by geographical region (USA/Canada: $n = 54$; Europe: $n = 41$; Japan: $n = 46$). Each body system is color-coded with the darkest shade indicating data from Japan, the intermediate shade for Europe, and the lightest shade for the USA/Canada. [a]Patients may have more than 1 sign and symptom within each body system. [b]Excludes patients <2 years of age at ERT initiation. [c]Excludes patients <6 months of age at ERT initiation. [d]This category includes loss of permanent teeth, loose teeth, poor dentition, hypodontia, dental implants, dental bridges, and dentures. ERT, enzyme replacement therapy; HPP, hypophosphatasia; USA, United States.

the USA/Canada showed the highest proportion of patients with dental (52%) and pain (41%) manifestations; these results were considerably higher than the data reported by Japan, which showed the lowest proportion of patients with these manifestations (dental, 15%; pain, 4.3%). Data from Europe showed the largest percentage of patients with muscular (71%), neurologic (63%), and renal (59%) manifestations.

Discussion

This large, observational dataset from the Global HPP Registry confirms that children with HPP experience a wide range of HPP manifestations impacting multiple body systems, which is consistent with previously published literature [5, 9, 10]. This study reports manifestations of HPP exclusively in a pediatric population planned by their physicians to be treated prior to treatment initiation and is distinct from published data on the HPP registry as a whole [19]. Additionally, the inclusion of patients with pretreatment status leads to a heterogeneous selection of patients due to differing local treatment indications. Although the proportions of treated children who reported specific HPP signs and symptoms prior to ERT initiation varied by age of first HPP manifestation and geographic region, the aggregate data evaluated in this study show that children who went on to receive ERT in all age groups and geographies were broadly affected by HPP. However, it is important to note that treatment decisions are generally made based on a patient's unique clinical profile, the care provider's recommendation, and country-specific policy rather than aggregate trends.

This is the first study to describe the clinical profiles of ERT-treated children with HPP prior to ERT initiation outside of clinical trials. Our analysis showed that children with HPP who go on to receive treatment with ERT are more likely to experience skeletal, renal, and respiratory manifestations when first presenting at <6 months of age, whereas dental, muscular, and pain manifestations were more frequently experienced among those aged 6 months to 18 years at first HPP manifestation. Specifically, skeletal manifestations were found in most children who presented at <6 months of age, and renal and respiratory manifestations were present in nearly half of these patients. For children aged 6 months to 18 years, high proportions of extraskeletal manifestations such as early loss of primary teeth, gross motor delay, and chronic pain were seen prior to ERT initiation. When the disease manifests before 6 months of age, skeletal hypomineralization and muscular hypotonia can lead to respiratory failure, whereas elevated serum calcium and inorganic phosphate load may cause renal damage [1, 6]. Bone deformities, for example, can only manifest in children before growth plate closure.

Comparisons by geography underscored regional, data collection differences in the clinical profiles of children with HPP before treatment with ERT, such as data from Japan showing the largest population of patients diagnosed at <6 months of age, the largest percentage of patients with skeletal and respiratory manifestations, and higher degree of growth impairment. These geographical variations could be at least partly explained by the high prevalence of certain *ALPL* variants associated with perinatal and infantile onset HPP in patients in Japan [20, 21]. It is possible that the lower median age seen in the data of patients from Japan may have influenced the higher prevalence of skeletal and respiratory manifestations also observed in their data. While the data showed that skeletal manifestations were present prior to ERT initiation in 63% of ERT-treated patients in Europe and 57% in the USA/Canada, other manifestations were also common. Data from the European subgroup showed the largest percentage of patients with muscular and neurological manifestations, while data from the USA/Canada subgroup showed the largest percentage of patients with dental and pain manifestations.

Overall, these findings highlight the multitude of considerations in the clinical spectrum of managing the health of children with HPP. In many countries, the treatment indication for ERT limits physicians to skeletal manifestations, which may impact the decision to include ERT in a management plan. Although skeletal manifestations were among the most prevalent in children who went on to ERT in all regions assessed, our analysis also revealed differences in the signs and symptoms of HPP in children based on geography. Data showed that extraskeletal manifestations appear to be more frequently reported in certain geographies, such as the USA/Canada and Europe. Therefore, comprehensive assessments of both skeletal and extraskeletal manifestations of HPP in children are warranted prior to ERT initiation [22, 23]. It should also be noted that diagnostic delay from age at first manifestation is shorter than what has been previously reported [19], which likely reflects better understanding of disease manifestations and more timely testing for HPP in routine clinical practice in recent years.

The inclusion of ERT in the treatment plan therefore varies widely by age at first HPP manifestation (before or after 6 months of age), geography, and on the signs and symptoms experienced by patients. However, a variety of other factors may have played a prominent role in the

decision to initiate ERT, including patient access to healthcare, jurisdictional differences in access to reimbursed ERT, availability of genetic testing for *ALPL* variants, and parental wishes based on prognosis information provided by a healthcare professional.

Limitations

It is important to note limitations of the Global HPP Registry and this analysis. Given the observational nature of registry data collected from medical records during routine medical practice, there may have been variations in the availability of data due to differences in the standard of care from site to site and for different patients based on severity of disease. Also, the manifestations recorded in the Global HPP Registry were based on a predetermined set of signs and symptoms. Therefore, all manifestations of HPP may not be represented in this analysis. Furthermore, the definitions of clinical manifestations may be subject to the physician's interpretation (e.g., failure to thrive was not based on a standardized definition), which may have led to variability in the signs and symptoms recorded in the data.

The histories of clinical manifestations, while obtained from medical records, may also be subject to recall bias because the events may have been reported to the clinician by the patient or due to the level of documentation. Long recall intervals may have reduced the accuracy of these data, particularly for less severe disease manifestations.

Conclusion

Using the largest pediatric cohort studied to date, our results indicate that extraskeletal manifestations, such as muscle weakness, gross motor delay, fatigue, and failure to thrive, are common in children with HPP prior to ERT initiation. Our results also confirm that those who had their first HPP manifestation at <6 months of age had a different clinical profile characterized by predominant skeletal manifestations, respiratory failure, and abnormal calcium and phosphate metabolism, in contrast to those >6 months of age at first HPP manifestation. Comparisons of the data collected by geographical region underscored data reporting differences in the clinical profiles of children with HPP, such as data from Japan showing the largest population of patients diagnosed at <6 months of age and, consequently, showing predominantly growth, skeletal, and respiratory manifestations in the data. As data from the Global HPP Registry continue to mature, follow-up genetic and clinical data may shed light on the emergence of associations between phenotypic features, the regional differences, and the impact of ERT on the natural history of HPP, including treatment outcomes that are relevant to routine clinical practice.

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Statement of Ethics

Approval of the Global HPP Registry study protocol was obtained from the Institutional Review Board or local equivalent at each participating investigative site (NCT02306720; EUPAS13514). Data collection and analyses complied with the World Medical Association Declaration of Helsinki, the European Medicines Agency good pharmacovigilance practices (GPV), and the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices (GPP). The full list of participating site and ethics committees can be found at https://clinicaltrials.gov/ct2/show/NCT02306720, https://hppregistry.com, or https://www.encepp.eu/encepp/viewResource.htm?id=47907. Prior to enrollment, legal guardians of all patients provided written informed consent and authorized the release of medical record data.

Conflict of Interest Statement

This study was sponsored by Alexion, AstraZeneca Rare Disease, Boston, MA, USA, which was involved in all stages of the study and manuscript development. Anna Petryk and Shona Fang are employees of Alexion, AstraZeneca Rare Disease, Boston, MA, USA, and may own stock/options in AstraZeneca, Cambridge, UK. Priya S. Kishnani, Gabriel Ángel Martos-Moreno, Kathryn M. Dahir, Agnès Linglart, Cheryl Rockman-Greenberg, Keiichi Ozono, Lothar Seefried, and Wolfgang Högler are consultants for and have received research funding and honoraria from Alexion, AstraZeneca Rare Disease, Boston, MA, USA.

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Disease, who held roles in the conception and design of the Global HPP Registry and this study, the collection of data, the statistical analyses, the interpretation of data, and writing of the manuscript as described in the Author Contributions section.

Author Contributions

G.A.M.-M., C.R.-G., K.O., A.P., P.S.K., K.M.D., L.S., S.F., W.H., and A.L. contributed to study design. G.A.M.-M., C.R.-G., K.O., P.S.K., K.M.D., L.S., W.H., and A.L. are study investigators, enrolled patients, and collected and assembled patient data. S.F. performed the statistical analysis. G.A.M.-M., C.R.-G., K.O., A.P., P.S.K., K.M.D., L.S., S.F., W.H., and A.L. interpreted the data, critically reviewed and revised the manuscript, and approved the final manuscript.

Data Availability Statement

Alexion, AstraZeneca Rare Disease will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods such as data de-identification, pseudonymization, or anonymization (as required by applicable law) and if such disclosure was included in the relevant study informed consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at http://alexion.com/our-research/research-and-development. Link to data request form: https://alexion.com/contact-alexion/medical-information.

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