Osteoporosis International (2019) 30:469–480
https://doi.org/10.1007/s00198-018-4691-6

ORIGINAL ARTICLE

# Neurological symptoms in Hypophosphatasia

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Received: 19 July 2018 / Accepted: 26 August 2018 / Published online: 13 September 2018


## Abstract

**Summary** Hypophosphatasia (HPP) typically manifests with fractures, tooth loss, and muscle pain. Although mental health diagnoses and neurological symptoms have not been previously well documented in HPP, they occur commonly. The recognition of non-traditional symptoms may improve patient satisfaction, preempt costly evaluation and misdiagnosis, and lead to further treatment options.

**Introduction** Hypophosphatasia (HPP) is an inborn error of metabolism due to deficiency of tissue non-specific alkaline phosphatase (TNSALP). It is traditionally characterized by rickets in children and osteomalacia in adults, along with fractures, tooth loss, and muscle pain. Neurological symptoms and mental health diagnoses have not been widely reported, and we therefore report their prevalence in a cohort of patients with HPP.

**Methods** A retrospective chart review was performed on a series of 82 HPP patients. Patient charts were reviewed to identify the possible presence and onset of 13 common neurological symptoms.

**Results** Median age was 36 years (2 to 79). Seventeen had adult onset HPP (> 18 years) and 65 had pediatric onset HPP (< 18 years). Median time from symptom onset to HPP diagnosis was 8 years (0 to 67). Seventy-four percent had a family history of bone disease, while 17% had a family history of neurologic disease. Bone problems occurred in 89%, dental problems in 77%, and muscle problems in 66%. Fatigue occurred in 66%, headache in 61%, sleep disturbance in 51%, gait change in 44%, vertigo in 43%, depression in 39%, anxiety in 35%, neuropathy in 35%, and hearing loss in 33%.

**Conclusions** The extra-skeletal manifestations of HPP, specifically neurological symptoms, have not been previously well documented. However, mental health diagnoses and neurological symptoms such as headache and sleep disturbance occur commonly in patients with HPP. The recognition of non-traditional symptoms in HPP may improve patient satisfaction, preempt costly evaluation and misdiagnosis, and may lead to further treatment options.

**Keywords** Alkaline phosphatase · Hypophosphatasia · Neurological symptoms · PLP · TNSALP · Vitamin B6

The original version of this article was revised: The title was incorrect.

J.M Colazo and J.R Hu are sharing first authorship of this manuscript.

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00198-018-4691-6) contains supplementary material, which is available to authorized users.

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## Introduction

Hypophosphatasia (HPP) is an inborn error of metabolism due to loss-of-function mutation(s) of the *ALPL* gene, which encodes the tissue non-specific isoenzyme of alkaline phosphatase (TNSALP) [1]. TNSALP is a family of cell-surface phosphohydrolases expressed highly in the skeleton, liver, kidney, and developing teeth [2]. HPP involves extracellular accumulation of the natural substrates of TNSALP, including inorganic pyrophosphate (PPi), a potent inhibitor of mineralization, pyridoxal 5′-phosphate (PLP), the principal circulating form of vitamin B6, and phosphoethanolamine (PEA), a diagnostic marker. Because low alkaline phosphatase (ALP) impedes mineralization by increasing pyrophosphate levels, patients often experience rickets in childhood and osteomalacia as adults, bone fractures, and tooth loss. Hypercalcemia, hyperphosphatemia, nephrocalcinosis, chondrocalcinosis, and

muscle pain may occur [2]. Notably, diminished hydrolysis of PLP may lead to seizures that are vitamin B6-dependent in profoundly affected infants. Nonetheless, apart from pediatric onset seizures, little is known about other neurological symptoms [3].

HPP is among the most variably expressive of all skeletal disorders [4]. Autosomal dominant and autosomal recessive inheritance patterns have been detected in > 340 identified ALPL mutations, most of which are missense [2, 5]. Seven forms of HPP have been recognized (in increasing severity): odonto HPP, adult HPP, mild childhood HPP, severe childhood HPP, infantile HPP, perinatal HPP, and benign perinatal HPP [6]. Odontohypophosphatasia exhibits isolated dental problems, typically painless premature loss of deciduous teeth. Adult HPP presents after the age of 18 years and can include loss of dentition, fractures, pain, and disability. Childhood HPP, which presents after 6 months of age, can be mild or severe. Infantile HPP, which presents postnatally before 6 months of age, exhibits rickets, failure to thrive, muscle weakness, and delayed motor milestones. Perinatal HPP may include short, deformed limbs and is historically lethal in utero or soon after birth, typically due to respiratory failure [6].

Seizures are the most well described neurologic feature of HPP; they may begin soon after birth in patients with perinatal lethal or infantile HPP [7, 8]. Seizures have not been reported to occur in perinatal benign, childhood, adult HPP, or odontohypophosphatasia [7, 8]. Other reported neurological symptoms of HPP are intracranial hypertension, possibly arising from the premature closing of cranial sutures (craniosynostosis) [8], chiari malformation [9] deafness [10], and a recent report of increased prevalence of headaches [4].

To date, the association of neurologic symptoms in HPP, aside from infantile seizures, has been lacking in the scientific literature. Based on our experience at the Program for Metabolic Bone Disorders Clinic (Vanderbilt University Medical Center), we hypothesized that neurological features are prevalent in the HPP population. To explore this hypothesis, we performed a retrospective chart review to study the prevalence of common neurological symptoms in a cohort of 82 HPP patients.

## Methods

### Study design

This study was approved by the Institutional Review Board (IRB) of Vanderbilt University Medical Center (VUMC). A retrospective chart review was performed on a series of 82 HPP patients followed in the Program for Metabolic Bone Disorders Clinic between 2015 and 2017. Patients were included if they had a diagnosis of HPP via low age- and sex-associated serum alkaline phosphatase levels, elevated vitamin B6 levels, and/or elevated urine phosphoethanolamine levels [11] (Simplified diagnoses guideline: < 150 U/L alkaline phosphatase for pediatric patients or < 50 U/L alkaline phosphatase for adult patients (Table S5), > 125 nmol/L vitamin B6, > 200 nmol/mg urine phosphoethanolamine) with traditional HPP-associated symptoms (musculoskeletal abnormalities, dental problems, etc.). Of note, reference laboratory values depend upon multiple variables such as, but not limited to, age, gender, and body mass index (BMI) [12–16]. Some patients had known ALPL genetic mutations, but not all patients underwent genetic testing. Patients who were followed for less than 1 year were excluded from the study.

### Data collection

The chart review was conducted by a single adjudicator to identify the medical history as well as the presence and onset of a variety of symptoms. All available electronic medical records from the years of 2015–2017 were reviewed based on provider documentation in notes and ICD (International Classification of Diseases) codes for the diagnosis of HPP. Patient data that were collected included age, sex, race, current medications, family history of bone disease (same symptoms as "bone problems" described below as well as any other official bone metabolism disease diagnosis), family history of neurological disease (headache, seizure, syncope, attention-deficient/hyperactivity disorder (ADHD), sleep disturbances, depression, anxiety, fatigue, memory loss, or other official neurologic disease diagnosis), age of onset of symptoms consistent with HPP (see below), age of diagnosis of HPP, genetic testing results (if performed) and other medical diagnoses. Previous diagnosis of myasthenia gravis, multiple sclerosis, Parkinson's disease, and fibromyalgia were collected due to the possibility of misdiagnosis in the HPP population. We reviewed for bone problems [defined as bone/spine pain, fracture history, or uncommon fracture occurrences (multiple fractures at once, break upon light activity, rare fracture locations)], muscle problems (myalgias, weakness, muscle fatigue, or tears), and dental problems (abnormal tooth loss, fracture of teeth, multiple cavities) as part of core symptoms expected in HPP. We also examined medical records for hypothesized extraskeletal manifestations of HPP, including headache, seizure, syncope, ADHD, sleep disturbances, depression, anxiety, fatigue, memory loss, hearing loss, tinnitus, vertigo/dizziness, gait change, and neuropathy/paresthesia. Psychiatric factors, other than depression and anxiety, were not collected given the inconsistent collection of such data. Data from all electronic medical record (EMR) medical labs were also examined, including history of serum alkaline phosphatase, vitamin B6, and calcium levels. We examined the first recorded, last recorded, and highest-ever laboratory value for serum vitamin B6. We examined the first recorded, last

recorded, and lowest-ever laboratory value for serum alkaline phosphatase. We examined serum calcium levels evident for hypocalcemia or hypercalcemia. Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at VUMC.

### Statistical analysis

Baseline continuous variables were summarized by median and interquartile range as they were non-normally distributed. Baseline categorical variables and prevalence were summarized by number and percent of population. Baseline characteristics and prevalence were reported as a whole group and in disaggregate by pediatric or adult onset, defined as onset before or after (and including) age 18 years, respectively. Four patients were taking vitamin B6 and/or alkaline phosphatase supplementation prior to their first available laboratory measurement and were excluded from the summary statistics of baseline alkaline phosphatase and vitamin B6 levels. Correlations were examined between all possible symptom-pairs and displayed in a correlogram. In the correlogram, correlations whose $p$ values did not meet the Bonferroni-adjusted threshold were removed. In exploring the relationship between symptoms, lab values, family history, and age, two-tailed Student's $t$ tests were performed to evaluate continuous outcomes with categorical predictors. Two-tailed chi-square tests were performed to evaluate categorical outcomes with categorical predictors. All laboratory values were log transformed before analysis. All statistical analyses were performed in the statistical software R (https://www.r-project.org/).

### Comparison to prevalence estimates in the general US population

For each symptom, we systematically searched Scopus for prevalence studies that had highest generalizability to the general population in the United States. The hierarchy of selection of prevalence studies was as follows: meta-analyses of prevalence studies was the most preferred, followed by symptom-specific prevalence studies of multiple communities, followed by symptom-specific prevalence studies of the National Health and Nutrition Examination Surveys (NHANES). Prevalence studies were excluded from consideration if they were conducted on a single community, conducted on a limited and non-generalizable patient population, or used questionnaires that were not validated. For headache, we used the headache-specific prevalence study by Kalaydjian (2008), based on 31,126 participants in the 1999–2004 NHANES [17]. For tinnitus, we used the tinnitus-specific prevalence study by Shargorodsky (2010), based on 14,178 participants in the 1999–2004 NHANES [18]. For neuropathy, we used the neuropathy-specific prevalence study by Gregg (2004), based on 2873 participants in the 1999–2000 NHANES [19]. For dental problems, we used periodontitis-specific prevalence study by Eke (2015), based on 141,000,000 participants in the 2009–2012 NHANES [20]. For other symptoms which constitute disease diagnoses, such as seizure, memory loss, ADHD, depression, anxiety, and hearing loss, we used the national disease prevalence estimates calculated by the Global Burden of Diseases, Injuries, and Risk Factors Study by Vos (2017) through aggregation of all available national surveys [21]. For symptoms which did not constitute disease diagnoses, we used reference prevalence estimates from the Epidemiologic Catchment Area Program study by Kroenke (1993) [22]. This was a mental health survey conducted in four communities of 13,538 community individuals using the Diagnostic Interview Schedule to systematically determine the prevalence of 38 physical symptoms germane of concern in primary care and psychiatry. Prevalence ratios were calculated by dividing the symptom prevalence in our HPP cohort over the prevalence of the symptom in the identified study of the general population (symptom prevalence in HPP/symptom prevalence in general population).

## Results

### Baseline characteristics

A total of 82 patients were included in this retrospective chart review. Among the study population, 65 had pediatric onset HPP, with a median age of onset of 4.0 years (interquartile range [IQR]: 1.0, 10.0), and 17 had adult onset HPP, with a median age of onset of 57.0 years (IQR: 25.0, 59.0) (Table 1). The current age of the pediatric onset patients is a median of 30.0 years (IQR: 15.0, 49.0), while the median current age of the adult onset patients is 60.0 years (IQR: 44.0, 65.0). Among the entire study population, 29% were male, 96% were Caucasian, 74% had a family history of bone disease, and 17% had a family history of neurological disease. Pediatric onset patients had a higher prevalence of family history of bone disease than adult onset patients ($p = 0.01$). Sixty-five percent of patients were taking psychiatric and/or pain medication. There were no differences between pediatric onset and adult onset patients in sex, race, family history of neurological disease, or use of a psychiatric medication.

### Prevalence of symptoms

The most prevalent symptoms were bone (89%), dental (77%), and muscle (66%) problems (Fig. S1). Among extraskeletal symptoms, the most prevalent symptoms were fatigue (66%), headache (61%), and sleep disturbance (51%) (Table 2). Other symptoms assessed included gait change (44%), vertigo (43%), depression (39%), neuropathy (35%),

**Table 1** Baseline characteristics of study participants

| | Overall | Pediatric onset | Adult onset | *p* |
|---|---|---|---|---|
| *N* | 82 | 65 | 17 | |
| Age of symptom onset, years (median [IQR]) | 6.50 [2.00, 16.00] | 4.00 [1.00, 10.00] | 57.00 [25.00, 59.00] | < 0.001 |
| Age at diagnosis of HPP, years (median [IQR]) | 29.50 [4.25, 52.00] | 23.00 [2.00, 44.00] | 57.00 [43.00, 62.00] | < 0.001 |
| Current age, years (median [IQR]) | 36.00 [20.00, 54.00] | 30.00 [15.00, 49.00] | 60.00 [44.00, 65.00] | < 0.001 |
| Male sex (%) | 24 (29.3) | 20 (30.8) | 4 (23.5) | 0.78 |
| Race (%) | | | | 0.67 |
| Caucasian | 79 (96.3) | 62 (95.4) | 17 (100.0) | |
| African-American | 2 (2.4) | 2 (3.1) | 0 (0.0) | |
| Latino-American | 1 (1.2) | 1 (1.5) | 0 (0.0) | |
| Family history of bone disease (%) | 61 (74.4) | 53 (81.5) | 8 (47.1) | 0.01 |
| Family history of neurologic disease (%) | 14 (17.1) | 9 (13.8) | 5 (29.4) | 0.25 |
| Psychiatric or pain medication use (%) | 53 (64.6) | 42 (64.6) | 11 (64.7) | 1.00 |
| Antidepressant use (%) | 27 (32.9) | 22 (33.8) | 5 (29.4) | 0.96 |
| Antipsychotic use (%) | 1 (1.2) | 1 (1.5) | 0 (0.0) | 1.00 |
| Anxiolytic/hypnotic use (%) | 14 (17.1) | 11 (16.9) | 3 (17.6) | 1.00 |
| Mood stabilizer use (%) | 9 (11.0) | 5 (7.7) | 4 (23.5) | 0.15 |
| Stimulant use (%) | 6 (7.3) | 6 (9.2) | 0 (0.0) | 0.44 |
| Pain medication use (%) | 40 (48.8) | 33 (50.8) | 7 (41.2) | 0.67 |
| First serum vitamin B6 level, nmol/L * (median [IQR]) | 162.40 [92.55, 324.25] | 159.25 [83.15, 297.98] | 231.70 [118.85, 404.95] | 0.26 |
| First serum alkaline phosphatase level, U/L**(median [IQR]) | 31.00 [20.50, 39.00] | 30.00 [17.00, 39.00] | 32.00 [26.00, 38.00] | 0.34 |

*IQR* interquartile range

*Serum vitamin B6: normal range 20–125 nmol/L [14]. One patient was excluded due to taking vitamin B6 supplementation at the time of first serum vitamin B6 measurement at Vanderbilt

**Serum alkaline phosphatase: normal ranges can be found on Table S5 [14]. Three patients were excluded due to taking alkaline phosphatase supplementation (Strensiq) at the time of first alkaline phosphatase measurement at Vanderbilt

anxiety (35%), hearing loss (33%), seizure (16%), memory loss (12%), tinnitus (9%), syncope (7%), and ADHD (6%).

## Comparison of symptom prevalence in adult onset and pediatric onset patients

Seizures occurred in 20% of pediatric onset patients (Fig. 1a) but did not occur in any of the adult-onset patients (Fig. 1b). ADHD did not occur in any of the adult-onset patients but occurred in 8% of pediatric-onset patients. There were no statistically significant differences in symptom prevalence between adult onset and pediatric onset patients (Table 2).

## Comparison of symptom prevalence in hypophosphatasia patients and the general US population

Compared to prevalence studies in the general US population, all neurological symptoms occurred at a higher prevalence in our cohort of HPP patients, except for syncope (PR: 0.62) (Table 3). Symptoms that were most greatly elevated in prevalence in HPP compared to the general population were seizure (PR: 32.91), depression (PR: 9.92), memory loss (PR: 9.04), ADHD (7.63), and anxiety (PR: 6.07). Several symptoms, despite being quite common in the general population, still exhibited elevated prevalence's in our HPP population, including headache (PR: 2.68), sleep disturbance (PR: 2.67), fatigue (PR: 2.79), neuropathy (PR: 2.39), and hearing loss (PR: 1.60). Of note, headache has a general population prevalence of 22.7%, compared to the 61.0% prevalence in our HPP population.

## Symptom association with other symptoms

Some symptoms occurred independently while others occurred in combination (Fig. 3). Depression and anxiety were moderately correlated ($r = 0.51$). Fatigue was mildly correlated with numerous other symptoms, including gait change ($r = 0.22$), anxiety ($r = 0.26$), vertigo ($r = 0.28$), muscle problems ($r = 0.24$), and neuropathy (0.32) (Fig. 3). Sleep disturbance

**Table 2** Prevalence of symptoms

| Symptom | All HPP patients ($n = 82$) | Pediatric onset ($n = 65$) | Adult onset ($n = 17$) | Prevalence ratio† | Chi-square | $p$‡ |
|---|---|---|---|---|---|---|
| Bone problems | 73 (89.0%) | 60 (92.3%) | 13 (76.5%) | 1.21 | 3.12 | 0.08 |
| Dental problems | 63 (76.8%) | 51 (78.5%) | 12 (70.6%) | 1.11 | 0.61 | 0.43 |
| Muscle problems | 54 (65.9%) | 44 (67.7%) | 10 (58.8%) | 1.15 | 0.20 | 0.66 |
| Fatigue | 54 (65.9%) | 44 (67.7%) | 10 (58.8%) | 1.15 | 0.20 | 0.66 |
| Headache | 50 (61.0%) | 41 (63.1%) | 9 (52.9%) | 1.19 | 0.01 | 0.91 |
| Sleep disturbance | 42 (51.2%) | 35 (53.8%) | 7 (41.2%) | 1.31 | 0.88 | 0.35 |
| Gait change | 36 (43.9%) | 31 (47.7%) | 5 (29.4%) | 1.62 | 1.02 | 0.31 |
| Vertigo | 35 (42.7%) | 28 (43.1%) | 7 (41.2%) | 1.05 | 0.04 | 0.84 |
| Depression | 32 (39.0%) | 26 (40.0%) | 6 (35.3%) | 1.13 | 0.00 | 1.00 |
| Anxiety | 29 (35.4%) | 23 (35.4%) | 6 (35.3%) | 1.00 | 0.03 | 0.86 |
| Neuropathy | 29 (35.4%) | 23 (35.4%) | 6 (35.3%) | 1.00 | 0.00 | 1.00 |
| Hearing loss | 27 (32.9%) | 21 (32.3%) | 6 (35.3%) | 0.92 | 0.00 | 1.00 |
| Seizure | 13 (15.9%) | 13 (20.0%) | 0 (0.0%) | Inf* | 2.05 | 0.15 |
| Memory loss | 10 (12.2%) | 9 (13.8%) | 1 (5.9%) | 2.34 | 1.03 | 0.31 |
| Tinnitus | 7 (8.5%) | 4 (6.2%) | 3 (17.6%) | 0.35 | 0.24 | 0.63 |
| Syncope | 6 (7.3%) | 4 (6.2%) | 2 (11.8%) | 0.53 | 0.24 | 0.63 |
| ADHD | 5 (6.1%) | 5 (7.7%) | 0 (0.0%) | Inf* | 0.22 | 0.64 |

*ADHD* attention deficit/hyperactivity disorder

*Inf denotes infinity, for prevalence ratio calculations in which the denominator was zero, i.e., the symptom was absent in the adult onset group

† Prevalence ratio is the ratio of the prevalence in the pediatric onset group over the prevalence in the adult onset group

‡ $p$ value refers to the significance of the two-tailed chi-square test for the symptom and the age of onset group

was mildly correlated with numerous other symptoms, including fatigue ($r = 0.33$), headache ($r = 0.22$), vertigo ($r = 0.4$), depression ($r = 0.28$), anxiety ($r = 0.26$), muscle problems (0.22), memory loss (0.29), and neuropathy (0.31). Neuropathy was mildly correlated with sleep disturbance ($r = 0.31$), vertigo (r = 0.24), headache ($r = 0.23$), fatigue ($r = 0.32$), tinnitus ($r = 0.23$), depression (r = 0.3), anxiety ($r = 0.25$), and seizure (r = 0.31). The only significant negative correlation was between ADHD and fatigue ($r = -0.25$).

## Time from onset of any symptom to diagnosis of HPP

The median time from onset of HPP symptoms to diagnosis of HPP was 8 years (IQR: 0.0, 30.0 years), although there was wide variability within the population (Fig. 2).

## Symptom association with serum levels of alkaline phosphatase and vitamin B6

There was no difference in serum log alkaline phosphatase levels (first recorded, lowest ever, or last recorded) between patients with and without each of the symptoms, nor was there a difference in serum B6 levels (Table S2). There was no difference in log serum alkaline phosphatase levels between male and female patients; patients with a family history of bone disease and without; or patients with a family history of neurological disease (Table S3). There was no difference in log serum B6 levels between these groups.

## Misdiagnoses analysis

To explore potential misdiagnosis in our cohort, we reviewed charts for a previous diagnosis of myasthenia gravis (0/82, 0%), multiple sclerosis (3/82, 3.7%), Parkinson's disease (0/82, 0%), or fibromyalgia (10/82, 12.2%).

## Genetic testing and symptoms

Genetic testing was performed in 28 patients (Table S4). The most common mutation was the Asp378Val mutation, which occurred in 6 subjects (6/28, 21%). Presence of the Asp378Val mutation did not confer increased or decreased susceptibility to any of the HPP symptoms (data not shown).

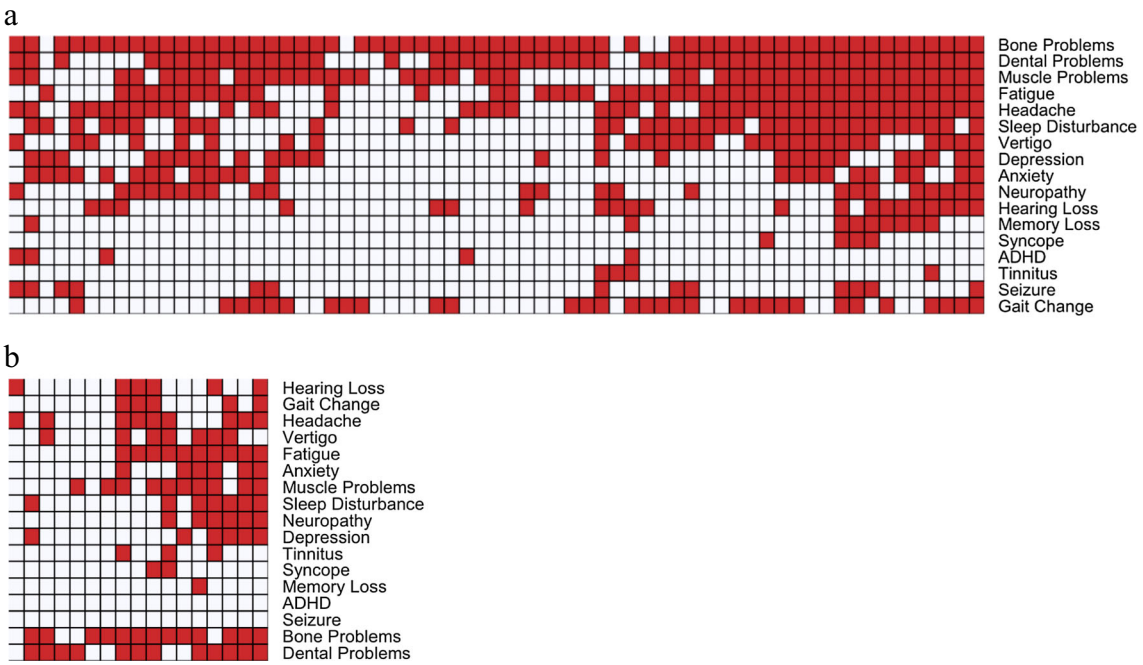


**Fig. 1** **a** Symptom prevalence in pediatric onset (< 18 years old at onset) patients. Each column represents a single patient. Red indicates positive for the symptom; white indicates negative for the symptom or unknown. **b** Symptom prevalence in adult onset (≥ 18 years old at onset) patients. Each column represents a single patient. Red indicates positive for the symptom; white indicates negative for the symptom or unknown

## Discussion

In this cross-sectional study, we quantified the prevalence of neurological symptoms in a registry of hypophosphatasia patients and found that neurological symptoms are present at a higher prevalence compared to the general US population. The most prevalent symptoms were the cardinal musculoskeletal manifestations of HPP, including bone (89%), dental (77%), and muscle (66%) symptoms. Certain extra-skeletal symptoms were expressed highly, with fatigue in 66%, headache in 61%, and sleep disturbance in 51%. Additionally, symptoms that were present in less than half of HPP patients were still present at a higher prevalence than that of the general US population, including seizure, depression, memory loss, ADHD, and anxiety. This suggests that fatigue, headache, sleep disturbance, and other symptoms may comprise a constellation of neurological symptoms in HPP hitherto uncharacterized.

Although the pathogenesis of headache in HPP is unclear, craniosynostosis [8] and chiari malformation [9] can occur in patients with HPP, both of which may manifest with headaches. Sleep disturbance may be related to headaches. Bieske et al. (2013) reported increased odds of headache and headache frequency in subjects with sleep disturbance, independent of obstructive sleep apnea, as compared to general population controls [23]. Consistent with these findings, we report a correlation in our patients between sleep disturbance and headaches ($r = 0.33$, Fig. 3). Sleep disturbance may also be due to pain [24] or other symptoms. In accordance, we report positive correlations between sleep disturbance and headache, neuropathy, fatigue, anxiety, depression, muscle problems, and memory loss. However, it is important for providers to recognize that sleep disturbance may be more common in patients with HPP than the general population. Sleep disturbance is related to multiple serious health concerns, including obesity, heart disease, diabetes, and it shortens life expectancy [25]. Similarly, the high prevalence of fatigue found in our HPP patients may represent an independent symptom or a consequence of sleep disturbance or musculoskeletal pain.

Seizures were noted to occur in 21% of patients with pediatric-onset HPP and in no patients with adult-onset HPP. Our cohort has a prevalence ratio of 32.9 compared with the general population, reinforcing the known occurrence of seizures in pediatric-onset HPP [26]. Seizures are presumed to be due to vitamin B6 depletion in the CNS. TNSALP is required for pyridoxal 5′-phosphate (PLP) to be dephosphorylated to cross the blood-brain barrier as pyridoxal (PL), before being re-phosphorylated in the CNS [27]. Once rephosphorylation in the brain occurs, PLP can be used as a cofactor in enzymatic reactions necessary to synthesize key neurotransmitters (Fig. S2).

ADHD was also common, occurring 6% in pediatric-onset HPP but no patients with adult-onset HPP. Psychiatric illnesses occurred frequently, with 39% of HPP patients having a medical diagnosis of depression, which accounts for a

**Table 3** Prevalence of symptoms in patients with HPP and in the general U.S. population

| Symptom | Prevalence in HPP patients, % $n = 82$ | Prevalence in general U.S. population, % | Reference | Study type | Prevalence ratio* |
|---|---|---|---|---|---|
| Seizure | 15.9% | 0.5% | Vos (2017, Lancet) | Synthesis of multiple studies | 32.91 |
| Depression | 39.0% | 3.9% | Vos (2017, Lancet) | Synthesis of multiple studies | 9.92 |
| Memory loss | 12.2% | 1.3% | Vos (2017, Lancet) | Synthesis of multiple studies | 9.04 |
| ADHD | 6.1% | 0.8% | Vos (2017, Lancet) | Synthesis of multiple studies | 7.63 |
| Anxiety | 35.4% | 5.8% | Vos (2017, Lancet) | Synthesis of multiple studies | 6.07 |
| Fatigue | 65.9% | 23.6% | Korenke (1993, Arch Intern Med) | Synthesis of multiple communities | 2.79 |
| Headache | 61.0% | 22.7% | Kalaydjian (2008, Psychosom Med) | NHANES | 2.68 |
| Sleep disturbance | 51.2% | 19.2% | Korenke (1993, Arch Intern Med) | Synthesis of multiple communities | 2.67 |
| Gait change | 43.9% | 18.3% | Korenke (1993, Arch Intern Med) | Synthesis of multiple communities | 2.40 |
| Neuropathy | 35.4% | 14.8% | Gregg (2004, Diab Care) | NHANES | 2.39 |
| Vertigo | 42.7% | 23.2% | Korenke (1993, Arch Intern Med) | Synthesis of multiple communities | 1.84 |
| Dental problems | 76.8% | 46.0% | Eke (2015, J Periodont) | NHANES | 1.67 |
| Hearing loss | 32.9% | 20.6% | Vos (2017, Lancet) | Synthesis of multiple studies | 1.60 |
| Tinnitus | 8.5% | 7.9% | Shargorodsky (2010, Am J Med) | NHANES | 1.08 |
| Syncope | 7.3% | 11.7% | Korenke (1993, Arch Intern Med) | Synthesis of multiple communities | 0.62 |
| Bone problems | 89.0% | N/A | N/A | N/A | N/A |
| Muscle problems | 65.9% | N/A | N/A | N/A | N/A |

*HPP* hypophosphatasia, *ADHD* attention-deficit/hyperactivity disorder, *NHANES* National Health and Nutrition Examination Survey

*Prevalence ratio for any given symptom = symptom prevalence in our HPP cohort divided by symptom prevalence in the general population

prevalence ratio of 9.92 compared with the general population [21]. Thirty-five percent of HPP patients had a medical diagnosis of anxiety, compared with only 5.8% of adults in the US [21]. Of note, 65% of patients were actively prescribed and taking psychiatric medications, and for many, mental illness preceded the diagnosis of HPP.

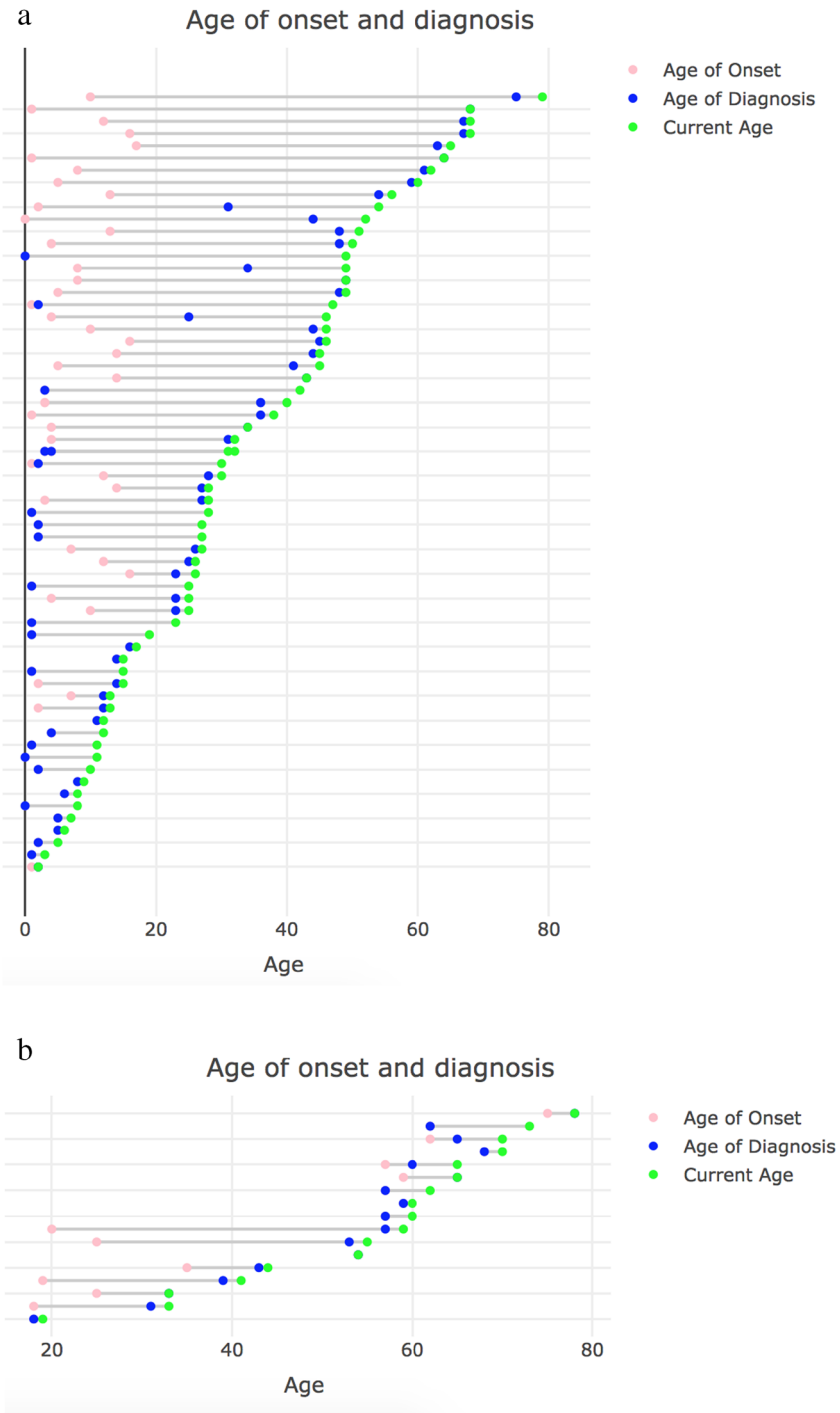


**Fig. 2** **a** Diagnosis timeline for pediatric-onset patients. **b** Diagnosis timeline for adult-onset patients

The high prevalence of gait change (44%), vertigo (43%), hearing loss (33%), memory loss (12.2%), and tinnitus (9%) are also worth noting. As balance, gait, and hearing are under the control of the vestibulocochlear system, it is possible that local or systemic phosphate and calcium imbalances may be contributing to these symptoms, especially since there have been recent reports of vestibulocochlear dysfunction in patients with other metabolic bone diseases [28]. Certainly, gait change may also be due to musculoskeletal problems.

Decreased levels of PLP in the CNS has been described in HPP (Fig. S2). Recently, Cruz et al. (2017) identified altered levels of brain metabolites cystathionine, adenosine, GABA, methionine, histidine, 3-methylhistidine, N-acetylaspartate and N-acetyl-aspartyl-glutamate in mouse models of HPP compared to wild-type control mice [29]. Cystathionine and

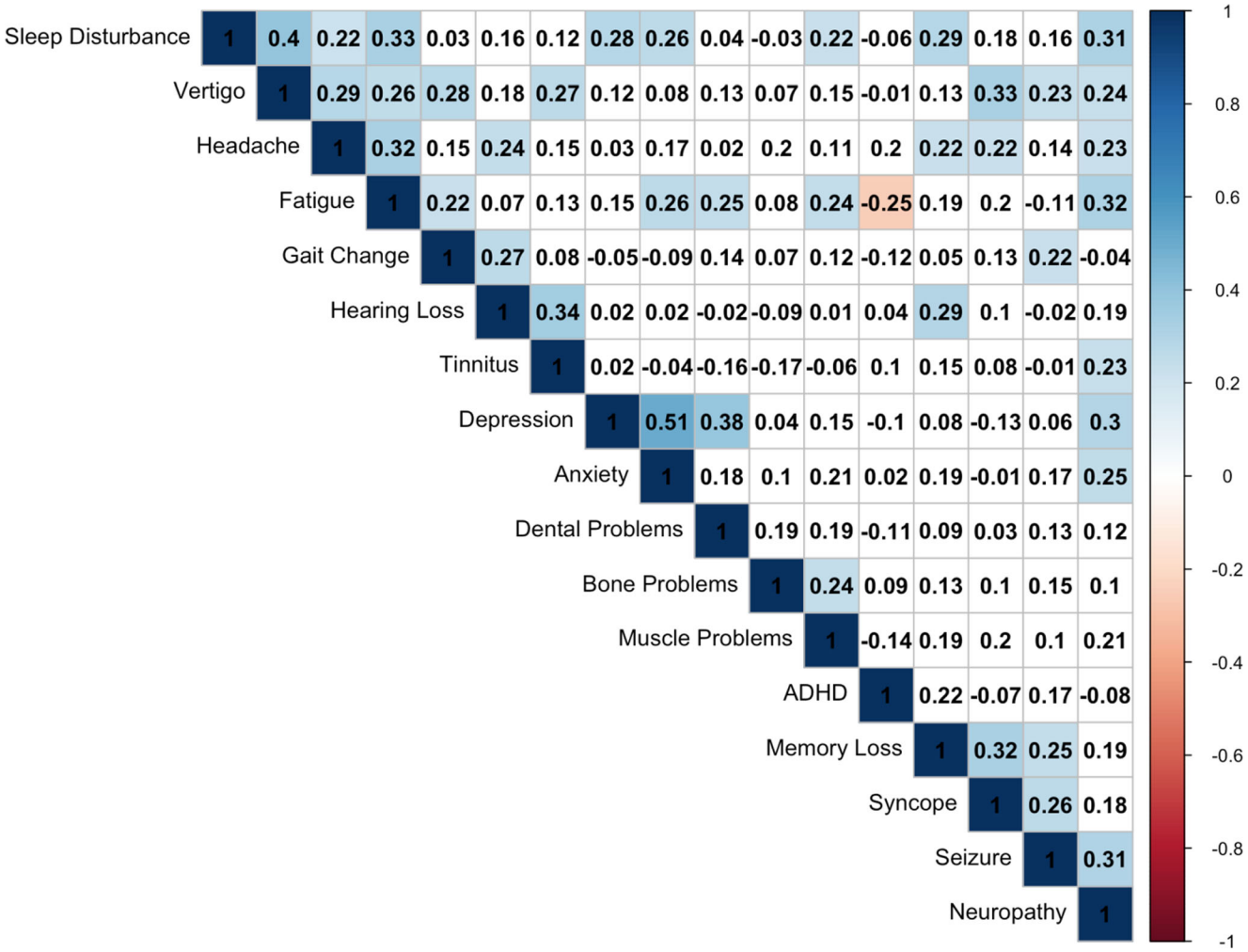


**Fig. 3** Correlation between symptoms experienced by HPP patients. Blue indicates symptom pairs that are positively correlated. Red indicates symptom pairs that are negatively correlated. Correlations that did not meet significance are blanked out for their cell background. Black text displays the Phi correlation coefficient (*R*)

adenosine levels displayed the strongest alterations with adenosine decreased and cystathionine increased. These metabolites identify several biochemical processes that directly or indirectly involve TNSALP function, through the regulation of ecto-nucleotide levels and of pyridoxal phosphate-dependent enzymes. These metabolites are also involved in neurotransmission, in myelin synthesis, and in the methionine cycle and transsulfuration pathway [29]. These findings may contribute to the proposed neurological phenotype of HPP and additional clinical studies are warranted regarding this possible disease model.

The duration from onset of HPP-associated symptoms until diagnosis is variable between patients. Patients with primary musculoskeletal abnormalities were diagnosed earlier than patients with hearing loss, tinnitus, and/or vertigo. This may suggest that hearing loss, tinnitus, and vertigo are more likely to appear together with HPP that is clinically evident at an older age; an alternative explanation is that atypical presentations of HPP cause delayed diagnosis. The latter could be due to physician unfamiliarity with the disease, as it is rare (~1/100000) and variably expressive [1]. This can also explain the relatively high diagnosis (12.8%) of fibromyalgia and a median time of 8 years from symptom onset to an official diagnosis in our cohort.

Interestingly, patients with vestibulocochlear symptoms, i.e., hearing loss, tinnitus, and vertigo have decreased values for their lowest serum alkaline phosphatase (ALP) level than those without (Table S3). It is possible that these symptoms may not occur until serum levels drop below a specific threshold. Other than this finding, there are no apparent differences in serum ALP levels or vitamin B6 levels by the presence of any other symptoms or family history. However, this result is confounded by time, as none of the lab measurements occurred systematically in relation to routine charting documentation. Future prospective cohort studies should be conducted following patients before and after treatment (i.e., asfotase

alfa, etc.) to determine the association between serum ALP and vitamin B6 levels and the presence of symptoms as well as the effects of treatment.

This was a retrospective chart review and therefore has limitations. Time of onset for each specific symptom is not routinely charted in daily clinical practice, and resolution of symptoms is not always documented. This prevents us from making inferences about the directionality of associations and associated benefits from treatments over time. Second, the study is lacking a matched control group, which prevents us from assessing the magnitude of difference between HPP patients and the general population and, thus, the only inferences we can make is by comparing our cohort to previously reported values from the general population. Furthermore, because the comparator studies were not all syntheses of the same population, the prevalence ratio of one symptom cannot be directly compared to the prevalence ratio of another symptom. Third, it is likely that we have under-reported the presence of some symptoms and diagnoses due to deficiencies in routine charting.

## Conclusion

To our knowledge, our study is the first to comprehensively describe and quantify neurologic symptoms in patients with HPP. In a HPP cohort of 82 patients, fatigue occurred in 66%, headache in 61%, sleep disturbance in 51%, gait change in 44%, vertigo in 43%, depression in 39%, anxiety in 35%, neuropathy in 35%, hearing loss in 33%, with other neurological symptoms also being common. Compared to reported literature, these symptoms occur at a greater prevalence than the US general population. From these results, a prospective case-cohort study is warranted, in which patients complete standardized surveys and undergo standardized physical examinations and laboratory tests at predefined time points to better characterize a potential neurologic phenotype. In addition, elucidating the exact molecular pathways responsible for these symptoms will allow for efficient use of current medications or the discovery of novel targeted therapies that could intervene or reduce neurological symptoms. Recognition of extra-skeletal symptoms in HPP may lead to better patient care, new therapies, and/or more efficient therapy regimens, and may prevent costly evaluation and misdiagnosis.

### Compliance with ethical standards

**Conflict of interest** Juan M. Colazo, Jiun-Ruey Hu, Kathryn M. Dahir, Jill H. Simmons declare no conflicts of interest. One of the authors (JMC) is supported by NIGMS (National Institute of General Medical Sciences) of the National Institutes of Health under award number T32GM007347. The content in this report is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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