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Prevalence of Transient Hyperphosphatasemia among Healthy Infants and Toddlers

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Abstract

Objective—To describe the prevalence and clinical characteristics of transient hyperphosphatasemia (TH) in a cohort of healthy infants and toddlers.

Patients and Methods—We performed a secondary data analysis of children enrolled in a study examining the epidemiology of vitamin D deficiency among healthy infants and toddlers. Children aged 8 to 24 months were enrolled at well-child visits conducted from 2005 - 2007 in an urban primary care pediatric clinic. Children with a chronic disease or using medications known to affect bone metabolism were excluded. At enrollment, we collected data regarding child age, gender, height, and weight; and maternal race/ethnicity. We measured serum levels of alkaline phosphatase, 25-hydroxyvitamin D, parathyroid hormone (PTH), calcium, magnesium and phosphorus. We divided participants into three categories, based on serum AP levels at enrollment: normal (AP 110 to 400 U/L), intermediate (AP >400 to 1000 U/L), and TH (AP >1000 U/L). We used the Fisher exact test and analysis of variance to evaluate differences in clinical characteristics among the three groups.

Results—Nine of 316 children (2.8%) had an AP > 1000 U/L (mean 2165 U/L, range 1006 to 4293 U/L). Sixteen children (5.1%) had an intermediate serum AP (mean 544 U/L, range 423 to 835 U/L). Mean weight-for-age z-score, length-for-age z-score and weight-for-length z-scores were similar across all three AP groups. Compared to the 291 children without TH, children in the intermediate AP and TH groups had similar mean serum levels of 25-hydroxyvitamin D, PTH, calcium, magnesium, and phosphorus.

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What's known on this subject: Transient hyperphosphatasemia is characterized by a temporary elevation of serum alkaline phosphatase in the absence of bone or liver disease. Retrospective data have suggested that viral infection, failure-to-thrive, or vitamin D status may be associated with risk of transient hyperphosphatasemia.

What this study adds: Transient hyperphosphatasemia appears to be a relatively common condition among healthy infants and toddlers. In this prospective cohort, the prevalence of transient hyperphosphatasemia was not associated with seasonal clustering, anthropometric measures, vitamin D status, or biochemical markers of bone turnover.

Conclusions—TH appears to be a relatively common condition among healthy infants and toddlers. TH was not associated with anthropometric measures, vitamin D status, PTH, or serum minerals. Recognition of this benign condition is important to avoid unnecessary investigations.

Introduction

Transient hyperphosphatasemia (TH) is a condition characterized by a temporary elevation of serum alkaline phosphatase (AP) in the absence of bone or liver disease. Characteristic features of TH defined by Kraut[1] et al. include: age of presentation less than five years; no other evidence for bone or liver disease on physical examination or laboratory findings; elevation in both bone and liver AP isoenzymes; and a return to normal serum AP values within four months.

Not all reported cases have met Kraut's definition, and the epidemiology of TH is not well-understood. Most published studies are retrospective chart reviews of patients evaluated for specific symptoms or medical conditions,[2-4] often at a tertiary care center.[5-7] The sole prospective study, a 1966 study of healthy Finnish infants and toddlers, reported a 1.5% incidence of TH.[8] Some authors have proposed risk factors associated with TH, including antecedent viral infection,[2, 4] failure-to-thrive,[2, 4] or recent changes in vitamin D status.[7] However, these risk factors were identified from retrospective data usually lacking a control group, raising the possibility that selection bias could account for the findings.

Our study aim was to describe the prevalence and clinical characteristics of TH in a prospectively-enrolled cohort of healthy infants and toddlers. We hypothesized that season of presentation (a possible marker for viral infection), child anthropometric measures, and child vitamin D status would be associated with TH prevalence.

Patients and Methods

Study Participants

Study enrollment occurred between October 2005 and June 2007, and has been previously described.[9] Briefly, we performed a secondary data analysis of children aged 8 to 24 months who had prospectively enrolled into a study examining the epidemiology of vitamin D deficiency. Children were considered study-eligible if they presented to the Children's Hospital Primary Care Center, an urban primary care clinic, for a well-child visit with a planned routine blood draw. We excluded children with a chronic disease or using medications known to affect bone metabolism.

For these analyses, of the 380 participants who enrolled into the primary study, we excluded 44 children with vitamin D deficiency (serum 25-hydroxyvitamin D $\leq$ 20 ng/mL),[9] as this deficiency can result in secondary hyperparathyroidism with an associated increase in alkaline phosphatase secretion. Another 15 children did not undergo a serum AP measurement due to inadequate sample. Thus, the final sample size was 316 children. Parents or guardians of all participants provided informed consent at enrollment. The study protocol was approved by the Committee on Clinical Investigation at Children's Hospital Boston.

Data Collection

At the enrollment interview, we collected data regarding child age, gender, height, and weight; and maternal race/ethnicity and highest level of education attained. We calculated length-for-age, weight-for-age, and weight-for-length z-scores using national reference standards.[10] Serum levels of AP, calcium, magnesium and phosphorus were measured in the Children's Hospital Clinical Laboratory using an end point assay in a multichannel analyzer (Roche Diagnostics, IN). Serum 25-hydroxyvitamin D levels were measured at ARUP laboratories (Salt Lake City, UT) using a DiaSorin chemiluminescent assay (LIASON, DiaSorin Inc,

Stillwater, MN). Intact PTH was measured by a 2-site chemiluminescence immunoassay (Nichols Institute, San Clemente, CA). Samples were analyzed in multiple assays. Interassay coefficients of variation were 5.4 - 7% for PTH, 8.6-10.0% for 25-hydroxyvitamin D, 0.67% for AP, and 1.5 - 2.2% for the cations.[9]

For each participant with TH, we contacted the primary care pediatrician to request a follow-up serum AP level. We collected data regarding medical conditions and follow-up lab values from the electronic medical record.

We divided participants into three categories, based on serum AP levels at enrollment: normal (AP 110 to 400 U/L), intermediate (AP >400 to 1000 U/L), and high (AP >1000 U/L). We defined TH as a serum AP >1000 U/L (high AP group).[6]

Statistical Analysis

We compared differences in maternal and child characteristics among the three AP groups using the Fisher exact test for categorical variables, and one-way ANOVA for continuous variables. We defined presentation during the fall and winter season as an enrollment date between the months of October and March.[9] For anthropometric measures, we compared differences in mean weight-for-age, length-for-age, and weight-for-length z-scores; we also compared the proportion of children in each AP group with z-scores < -2.0, a commonly used definition of failure-to-thrive.[11] We conducted all data analyses using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of the three AP groups are noted in Tables 1 and 2. Nine of 316 children (2.8%) had TH, with a serum AP > 1000 U/L (range 1006 to 4293 U/L). Sixteen children (5.1%) had an intermediate serum AP, with a mean value of 544 U/L (range 423 to 825 U/L). Children with TH ranged in age from 9.0 to 19.0 months. Maternal race/ethnicity and education level were similar among all three groups.

Mean length-for-age, weight-for-age, and weight-for-length z-scores did not differ by serum AP level. None of the participants in the TH group, and only one child in the intermediate AP group, had a weight-for-length z-score lower than -2.0, compared with 7 children (2.5%) of the normal AP group. None of the children in the intermediate AP or TH groups had a weight-for-age z-score or length-for-age z-score of less than -2.0. Mean 25-hydroxyvitamin D levels, PTH, calcium, magnesium, and phosphorus were similar in the normal, intermediate AP, and TH groups.

In the TH group, 6 of 9 children (67%) had a history of upper respiratory symptoms (n=3), rash (n=2), or diarrhea (n=1) in the month preceding diagnosis of TH. A slightly higher proportion of children in the intermediate AP (62.5.0%) and TH (55.6%) groups enrolled during the fall and winter months (October through March), compared with the normal AP group (50.9%), but these differences were not statistically significant. (p=0.69).

For 6 of the 9 children with TH, we confirmed that a follow-up serum AP level was normal. The shortest reported interval for a return to a normal AP was 35 days.

Discussion

In this prospectively-enrolled cohort of healthy infants and toddlers, we found a TH prevalence of 2.8%. The childhood incidence of TH may exceed 2.8%, as indicated by the 5.1% prevalence of an intermediate elevation in serum AP between 400 and 1000 U/L. This intermediate AP

group may represent children in whom TH is developing or resolving. Our data suggest that TH is a relatively common condition; recognition of this condition by pediatricians is important to avoid unnecessary investigations.

In the sole other study estimating the frequency of TH among healthy infants and toddlers, 260 healthy Finnish infants born in 1963 were enrolled into a trial of vitamin D supplementation and followed prospectively through age 15 months.[8] Each participant had serum alkaline phosphatase measured at three time points: ages 2 to 4 months, 4 to 7 months, and 11 to 15 months. The study reported substantial loss to follow-up: of the 260 infants seen at age 2 to 3 months, 186 (71.5%) infants were followed-up at age 4 to 7 months, and 85 (32.6%) infants were followed-up at age 11 to 15 months. The number of new TH cases detected at each time point was 3/260 (1.2%) at 2 to 4 months, 2/186 (1.1%) at 4 to 7 months, and 3/85 (3.5%) at 11 to 15 months. The overall TH incidence was 1.5%; however, the substantial loss to follow-up and the absence of data between ages 7 to 11 months suggest that the study may have underestimated the true TH incidence in this cohort.

Two other small prospective studies of 20-50 children admitted to hospital failed to detect any cases of TH;[4, 12] the small sample sizes of those reports may have led to sampling error. Children under the age of two appear to account for the majority of reported cases,[4] and both our study and the Finnish study were restricted to children under the age of 2 years. Our findings likely underestimate the TH prevalence in children up to age 5 years, as defined by Kraut; furthermore, TH has been reported in children older than 5 years, and rarely, in adults.[13-15]

Prevalence estimates also depend upon the degree of elevation of AP used to define TH. Consistent with a recent report,[6] we defined TH as a serum AP >1000 U/L, a level 2.5-fold the age-related upper reference limit; we also identified an intermediate AP group with serum AP levels between 400 and 1000 U/L. In the study of Finnish infants and toddlers, TH was defined as a serum AP > 20 Bessey-Lowry-Block units (range 25 to 53 Bessey-Lowry-Block units).[8] The methodologic differences in the alkaline phosphatase assays preclude a direct comparison of our TH definition with that used in the Finnish study.[16] Many reports do not describe an *a priori* definition of TH, but report cases identified with serum AP levels of more than 2-fold the age-related upper reference limit. [4, 5] In most studies it is not clear whether children with elevated serum AP levels less than 2-fold the age-related upper reference limit were not detected, or not reported. If the intermediate AP group identified in our study represents children in whom TH is developing or resolving, then studies excluding this group would underestimate TH prevalence.

Our findings do not support an association between failure-to-thrive and TH, as proposed in several retrospective reports.[2, 4, 17] Comparisons across studies are difficult because most studies do not define the term “failure-to-thrive” using objective anthropometric criteria, but rely on clinician diagnoses that are usually not clearly defined.[2, 4, 17] We found that child anthropometric measurements, standardized against U.S. national reference data, did not differ among children with normal, intermediate, or high AP levels. Our findings are consistent with an observational study of 40 Czechoslovakian children showing a normal mean weight-for-age z-score of -0.65 and length-for-age z-score of -0.84 at the time of TH diagnosis.[18] We speculate that the previously reported association of failure-to-thrive with risk of TH may be explained in part by a selection bias, as children with failure-to-thrive are more likely to have blood drawn for investigations.

The theory that viral infection is associated with the development of TH is supported by a clustering of TH diagnoses during the autumn[5, 7] or winter,[6] as well as laboratory investigations confirming recent viral or protozoal infection.[2] Behulova[5] et al. found a seasonal clustering of cases, with 43% of 194 TH cases in Slovakia presenting between September and November;

a similar pattern was seen in a British study of 35 cases.[7] In an Australian study of 21 TH cases, cases clustered during winter.[6] Our study is the first to examine this theory by comparing the season of presentation in healthy infants and toddlers with and without TH, and we were unable to confirm the seasonal predilection previously reported in retrospective reviews of TH cases.

During the month prior to enrollment, two-thirds of our study participants with TH had symptoms consistent with a possible viral infection. This symptom prevalence estimate should not be affected by recall bias, because these symptom data were reported prior to the diagnosis of TH. Although this symptom prevalence may appear high, there is likely to be a high prevalence of respiratory and gastrointestinal symptoms among all infants and toddlers attending well-child visits. Data suggest that infants and toddlers experience 2 to 8 episodes of acute respiratory infection per year,[19, 20] with the highest incidence occurring in the first year of life.[21] The incidence of acute diarrheal disease in children under age 2 has been estimated at 1-3 episodes per child per year.[22]

We did not find an association between vitamin D status and risk of TH. We found similar mean 25-hydroxyvitamin D levels in all 3 AP groups, consistent with a study that reported normal 25-hydroxyvitamin D levels in 7 children with TH.[23] Our findings contrast with those of Crofton,[7] who reported that children with TH presenting between October and January had a higher mean 25-hydroxyvitamin D level (55.4 nmol/L or 22.1 ng/mL) than a control group of hospitalized children (mean 30.9 nmol/L or 12.4 ng/mL). When we restricted our analyses to 109 children enrolled between October and January, we found no difference in 25-hydroxyvitamin D levels among the three AP groups (p=0.42, data not shown). In Crofton's study, the control group's low mean 25-hydroxyvitamin D level is consistent with vitamin D deficiency, and their clinical status is not described in detail.[7] The control group's lower vitamin D levels in that study might be explained by selection bias resulting from control children with clinical conditions severe enough to limit their sun exposure or vitamin D intake.

The mechanism of elevation in AP remains controversial. Four isoenzymes of AP have been identified in humans: tissue-non-specific, found in liver, bone, and kidney; placental; intestinal; and germ cell.[24] In TH, the liver and/or bone isoenzyme levels appear to be increased.[1, 2, 7] The serum AP elevation in TH might arise from a temporary increase in release of AP from liver and bone, or an increase in sialylation of the enzyme, resulting in reduced hepatic clearance from the circulation.[7, 18] Serum bone-specific AP correlates directly with osteoblastic activity, although it can also be elevated in conditions with low bone formation, such as rickets.[25] Serum osteocalcin, another marker of bone formation, has also been reported to be normal in TH.[26] Elevated levels of urine hydroxyproline, a marker of bone resorption, were reported in 1 of 5 subjects with TH in a German study,[26] 3 of 5 subjects with TH in a Czechoslovakian study,[27] and in 11 of 33 children with TH in another report.[28] None of these studies appears to have controlled for dietary collagen intake, which can influence urinary hydroxyproline levels.[29] Among children who developed TH after liver or kidney transplantation, PTH levels were normal in 5 of 6 children,[30] and normal urine hydroxyproline/creatinine ratio was reported in one 5 year old boy.[31] In our study, the similar mean levels of calcium, magnesium, phosphorus and PTH across AP groups did not support increased bone resorption among children with TH.

Additional, larger studies using more specific bone biomarkers may help elucidate whether bone turnover contributes to the serum AP elevation in TH. For bone formation, serum levels of procollagen type I carboxy-terminal (PICP) or amino-terminal propeptides, reflect synthesis of new collagen; specific markers of bone resorption include urinary excretion of specific collagen metabolites not influenced by dietary collagen intake, such as peptide-bound alpha-1 to alpha-2 N-telopeptide crosslinks, or the c-telopeptide crosslink (ICTP).[32] In one analysis of 33 children with TH, serum PICP and ICTP were either normal or mildly elevated.[28]

Strengths and limitations of this study must be acknowledged and considered. Study strengths include a design with prospective data collection, available anthropometric data and biochemical markers of calcium and vitamin D metabolism, including 25-hydroxyvitamin D, PTH and serum minerals. We rigorously examined the association between specific hypothesized risk factors and prevalence of TH, including seasonal clustering, failure-to-thrive, and vitamin D status. Our study also had some limitations. The original enrollment protocol did not include isoenzyme analyses or measurement of other liver enzymes or liver function tests. However, the TH cases did not have obvious symptoms or signs suggestive of other liver or bone disease, and met all other commonly accepted criteria for the diagnosis of TH.[1] The study enrollment exclusion criteria and normal follow-up serum AP levels also supported the diagnosis of TH. Another study limitation was the relatively small number of TH cases, which may explain our inability to confirm a seasonal predilection in presentation. We were unable to obtain follow-up serum AP levels for most of the intermediate AP group, limiting our ability to describe the natural history of these children. Further prospective studies in larger population-based datasets would be helpful to determine the natural history of the intermediate AP group and the incidence of TH.

In conclusion, TH appears to be a relatively common condition among healthy infants and toddlers. The prevalence of TH was not associated with anthropometric measures or biochemical markers of calcium and vitamin D metabolism. This condition resolves without intervention. Therefore, among healthy infants and toddlers, we would not recommend routinely measuring serum AP to screen for TH. If a high serum AP is incidentally detected in a healthy infant or toddler without clinical features suggestive of liver or bone disease, we recommend a repeat serum AP level within a few months to confirm resolution of the condition. Recognition of this benign condition is important to avoid additional unnecessary investigations.

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Abbreviations

TH	transient hyperphosphatasemia
AP	alkaline phosphatase

Table 1

e characteristics of 9 patients with transient hyperphosphatasemia (Serum alkaline phosphatase >1000 U/L)

mographic Data			Anthropometry			Serum Biochemistry						Follow-up	
months)	Sex	Month	Length-for-age z-score	Weight-for-age z-score	Weight-for-length z-score	AP (U/L)	25-OH vitamin D (ng/mL)	PTH (pg/mL)	Calcium (mg/dL)	Mg (mg/dL)	P (mg/dL)	AP (U/L)	Days to follow-up
	F	Dec	0.86	0.15	-0.26	2987	41	39.3	10.5	2.3	5.7	235	162
	M	Aug	0.75	1.03	1.36	1405	35	21.0	10.4	2.4	6.1	237	295
	M	Sep	-1.07	-0.17	1.31	1703	47	26.8	10.6	2.5	5.6	None	---
	M	Jan	-0.49	-1.32	-0.94	1006	27	24.7	10.3	2.1	5.6	357	35
	F	Oct	-0.39	0.01	0.69	2367	40	40.5	11.1	2.3	6.0	161	90
1	M	Jul	2.16	0.97	0.09	1799	24	35.2	10.6	2.3	5.4	137	165
2	F	Apr	-0.64	-0.89	-0.10	1629	22	18.4	10.5	1.9	5.3	None	---
4	M	Mar	-1.12	-0.7	0.47	2295	30	41.1	10.3	2.7	5.3	None	---
0	F	Nov	-0.86	-1.21	-0.56	4293	25	23.2	10.9	1.9	5.9	305	590

h of enrollment. AP, alkaline phosphatase; PTH, parathyroid hormone; Mg, Magnesium; P, Phosphorus.

Table 2

Comparison of baseline characteristics among normal AP, intermediate AP and transient hyperphosphatasemia groups

	Normal (AP 100 – 400) n=291	Intermediate (AP > 400 – 1000) n=16	TH (AP > 1000) n=9	p-value
		Mean (SD) or n (%)		
Alkaline phosphatase, U/L	260.9 (60.2)	543.9 (126.9)	2164.9 (988.5)	---
Child age, months	11.7 (3.6)	12.1 (4.4)	11.7 (3.7)	0.92
Presentation October – March, n (%)	148 (50.9)	10 (62.5)	5 (55.6)	0.69
Male gender, n (%)	149 (51.2)	8 (50.0)	5 (55.6)	1.00
Maternal race, n (%)				0.54
White	29 (10.0)	2 (12.5)	1(11.1)	
Black	172 (59.1)	10 (62.5)	4 (44.4)	
Other	38 (13.1)	0.0 (0)	2 (22.2)	
Unknown	52 (17.9)	4 (25.0)	2 (22.2)	
Weight-for-age z-score	-0.1 (1.2)	-0.2 (0.7)	-0.2 (0.9)	0.91
Weight-for-age z-score ≤ 2.0, n (%)	15 (5.2)	0 (0)	0 (0)	1.00
Length-for-age z-score	-0.1 (1.0)	0.1 (0.6)	-0.1 (1.1)	0.89
Length-for age z-score ≤ -2.0, n (%)	7 (2.5)	0(0)	0(0)	1.0
Weight-for-length z-score	0.3 (1.1)	0.0 (1.1)	0.2 (0.8)	0.61
Weight-for-length z-score ≤ 2.0, n (%)	7 (2.5)	1 (6.7)	0 (0.0)	0.49
25-hydroxyvitamin D level, ng/mL	37.3 (11.6)	38.9 (14.0)	32.3 (8.8)	0.38
PTH, pg/mL	26.2 (13.5)	32.0 (28.3)	30.0 (9.0)	0.24
Calcium, mg/dL	10.5 (0.4)	10.4 (0.4)	10.6 (0.3)	0.29
Magnesium, mg/dL	2.3 (0.2)	2.3 (0.2)	2.3 (0.3)	0.34
Phosphorus, mg/dL	5.8 (0.5)	5.7 (0.6)	5.7 (0.3)	0.31

AP, alkaline phosphatase; TH, transient hyperphosphatasemia; PTH, parathyroid hormone.

P-values calculated using Fisher exact test for categorical variables, one-way ANOVA for continuous variables.