Transient Benign Hyperphophatasemia

*Gianluca Gualco, *Sebastiano A.G. Lava, *Luca Garzoni, †Giacomo D. Simonetti, ‡Alberto Bettinelli, §Gregorio P. Milani, ‡Maria Cristina Provero, and *Mario G. Bianchetti

ABSTRACT

Background and Aim: Sometimes, a temporary increase in alkaline phosphatase level is found in healthy infants and toddlers without evidence of liver or bone disease. The condition is customarily termed transient benign hyperphosphatasemia of infancy and early childhood. Most textbooks do not refer to the condition. The aim of the study was to promote broader awareness of transient benign hyperphosphatasemia.

Methods: We completed a systematic review of the literature using the principles underlying the UK Economic and Social Research Council guidance on the conduct of narrative synthesis and the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.

Results: The 142 reports retained for analysis included 813 cases (male:female ratio 1.1:1.0): 80 in subjects older than 18 years and 733 in subjects 18 years or younger. The alkaline phosphatase ratio, calculated by dividing the measured level by the upper limit of normal, was $\geq$5.0 in $\approx$70% and the duration of the elevation was $\leq$4 months in 80% of the cases. Transient benign hyperphosphatasemia often followed a benign infection, but available data fail to demonstrate a causal link. The prevalence of transient benign hyperphosphatasemia ranged from 1.1% to 3.5% in infants 2 to 24 months of age.

Conclusions: Transient benign hyperphosphatasemia is likely the most common cause of hyperphosphatasemia among healthy infants and toddlers. Sometimes it also occurs in older children and adults, indicating that the traditional term transient benign hyperphosphatasemia of infancy and early childhood may not be correct. The elevation in alkaline phosphatase persists for >4 months in $\approx$20% of the cases. Recognition of this benign condition is crucial to avoid unnecessary investigations.

Key Words: alkaline phosphatase, bone disease, isoenzymes, liver disease, transient benign hyperphophatasemia

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From the *Integrated Department of Pediatrics, Ente Ospedaliero Cantonale Ticinese, and University of Bern, the †Pediatric Nephrology, University Children's Hospital Bern and University of Bern, Bern, Switzerland, the ‡Division of Pediatrics, San Leopoldo Mandic Hospital, Merate-Lecco, Italy, and the §Pediatric Emergency Unit, Clinica De Marchi, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

Address correspondence and reprint requests to Mario G. Bianchetti, MD, San Giovanni Hospital, 6500 Bellinzona, Switzerland (e-mail: mario.bianchetti@pediatrician.ch).

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The alkaline phosphatase test measures the amount of this enzyme in blood. Most of the alkaline phosphatase is produced in the liver, bone, and placenta during the third trimester of pregnancy (1,2). The amount of alkaline phosphatase in blood varies with age, being generally higher in children and adolescents because of physiologically high osteoblastic activity (1,2). This test is performed to detect diseases of the skeleton or the hepatobiliary system (1,2). Sometimes a marked increase in alkaline phosphatase values is found in infants and toddlers without evidence of liver or bone disease and may be persistent or, more frequently, transient (1–4). The temporary increase in alkaline phosphatase resolves without intervention within 16 weeks (3,4). The condition, which is frequently an incidental finding, is termed transient benign hyperphosphatasemia of infancy and early childhood (3,4). It is customarily assumed that it was first reported in 1954 by Bach in Germany (5).

Existing textbooks do not refer to transient benign hyperphosphatasemia or mention it only in passing. Because broader awareness of transient benign hyperphosphatasemia is crucial to prevent complex and largely unnecessary testing and apprehension, we completed a systematic review of the available literature.

METHODS

Between August and October 2012, we performed a computer-based search of the terms ''alkaline phosphatase temporary elevation,'' ''alkaline phosphatase transient elevation,'' and ''hyperphosphatasemia'' in the US National Library of Medicine database and of the term ''transient benign hyperphosphatasemia'' in the Web-based search engine Google Scholar. For this purpose, we used the principles underlying the UK Economic and Social Research Council guidance on the conduct of narrative synthesis and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (6). Reports available as an article or as a letter in English, French, German, Italian, Portuguese, or Spanish, including cases of transient benign hyperphosphatasemia, which were described individually, were retained for analysis. The diagnosis of transient benign hyperphophatasemia was made in subjects with a markedly increased total alkaline phosphatase level without other evidence for bone or liver disease on physical examination or laboratory findings and a tendency to return to normal values (7,8).

From each report dealing with transient benign hyperphosphatasemia, 2 of us (G.G. and S.A.G.L.) independently excerpted data on sex, age, preexisting chronic disease, reasons underlying the initial determination of the alkaline phosphatase level, general physical examination, laboratory tests, course of alkaline phosphatase level, and the tissue source of increased alkaline phosphatase. Because the normal range for total alkaline phosphatase must be adjusted for age, sex, and laboratory's own normal values, we calculated the alkaline phosphatase ratio by

dividing the measured level by the corresponding upper limit of normal (1,2).

Numerical data were presented as median and interquartile range, and categorical data as relative frequency. The 2-sided Wilcoxon-Mann-Whitney and the 2-sided Fisher exact test were performed for analysis. Significance was assumed when $P < 0.05$.

RESULTS

The article, written in German and published by Ursula Bach, has often been quoted as the original description of transient benign hyperphophatasemia (5). Interestingly, we did not find any subject with a temporary and unexplained elevation of the alkaline phosphatase level in that report.

Search Results

The flowchart of the literature search process (Fig. 1) indicates that the initial search revealed 448 publications, of which 329 remained after excluding duplicates (ie, publications found with both search terms). A total of 195 of them were reviewed in detail and 116 were retained for the final analysis. Twenty-six pertinent reports were found in the references of the mentioned reports. Hence, a total of 142 reports were included in the final analysis (9–150) (references 51–150 are online only: *http://links.lww.com/MPG/A215*): 84 in English (9–92), 8 in French (93–100), 5 in German (101–105), 18 in Italian (106–123), 1 in Portuguese (124), and 26 in Spanish (125–150). They had been reported from Italy (N = 22), Spain (N = 21), the United States (N = 19), Great Britain (N = 14), Germany (N = 11), France (N = 9), Czech Republic (N = 7), Argentine (N = 6), Belgium (N = 3), Canada (N = 3), Japan (N = 3), Australia (N = 2), Brazil (N = 2), Croatia (N = 2), Denmark (N = 2), Israel (N = 2), Ireland (N = 2), Scotland (N = 2), Switzerland (N = 2), Venezuela (N = 2), Finland (N = 1), Greece (N = 1), China (N = 1), Poland (N = 1), Sweden (N = 1), and Turkey (N = 1). The aforementioned 142 reports included 813 cases of transient benign hyperphophatasemia: 733 (90%) in subjects 18 years or younger and 80 (10%) in subjects older than 18 years.

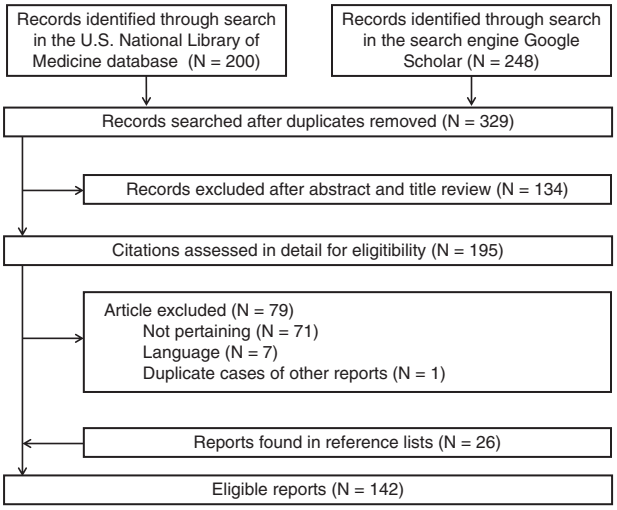

FIGURE 1. Flowchart of the literature search process. Twenty-one of the 142 reports included in the final analysis had been identified exclusively from the Web-based search engine Google Scholar.

Cases in Subjects Ages 18 Years or Younger

Characteristics of the Affected Subjects

The age of the 733 subjects (male:female ratio 1.1:1.0; not significant) 18 years or younger with transient benign hyperphosphatasemia retained for the final analysis ranged from 2 months to 17 years, median 18 months, as depicted in Figure 2. Eighteen percent of the cases were observed in subjects ages 37 months or older. In these subjects, the highest alkaline phosphatase ratio ranged from 2.0 to 71, median 9.2. The highest alkaline phosphatase ratio was ≥5.0 in 520 subjects (71%). A tendency to return to normal alkaline phosphatase values was documented in all cases. The duration of the elevation of the alkaline phosphatase level, documented in 569 cases (male:female ratio 1.1:1.0; not significant), ranged from 2 weeks to 4 years, median 10 weeks. The duration of the elevation was ≥17 weeks in 108 (19%) of the 569 subjects.

Transient benign hyperphosphatasemia was suspected and subsequently confirmed by means of further diagnostic procedures in the context of a regular checkup in 92 patients (13%) with a preexisting chronic disease (male:female ratio 1.0:1.0). Forty-three subjects were solid organ transplant recipients (liver, N = 27; kidney, N = 11; heart, N = 5), the remaining 49 subjects were affected by malignancy (N = 12), by immunodeficiency (N = 4) or by other, mostly congenital chronic conditions. In the 641

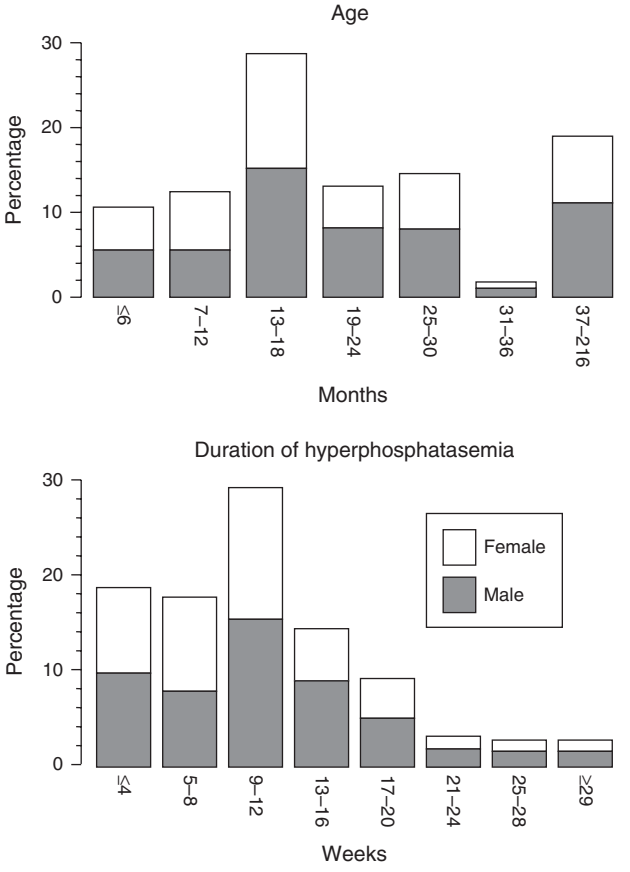

FIGURE 2. Age, sex (upper panel), and duration (lower panel) of the transient elevation of the alkaline phosphatase level in 733 subjects (male:female ratio 1.1:1.0) ages 18 years or younger. The duration of the elevation of the alkaline phosphatase level was documented in 569 cases (male:female ratio 1.1:1.0).

subjects (87%) without any underlying chronic condition (male:-female ratio 1.1:1.0; not significant), the initial determination of the alkaline phosphatase level was made either in the context of a checkup or in the context of likely infectious illnesses (Table 1). Transient benign hyperphosphatasemia patients with a chronic underlying condition were significantly older than subjects without any underlying chronic condition by 9 months (26 [17–40] vs 17 [14–30] months; $P < 0.0005$). On the contrary, the highest alkaline phosphatase ratio (7.9 [4.3–17] vs 9.8 [4.7–18]) and the duration of the elevation of the alkaline phosphatase level (10 [7–14] vs 10 [5–18] weeks) were similar in subjects with and without any underlying condition.

Prevalence of the Condition in Apparently Healthy Subjects

The prevalence of transient benign hyperphosphatasemia was addressed in 2 studies. In a cohort of 321 healthy infants and toddlers ages 8 to 24 months investigated in Boston, 9 (2.8%) were found to have a transient and unexplained elevation of the alkaline phosphatase level (39). In a study estimating the frequency of transient benign hyperphosphatasemia among Finnish healthy infants born in 1963, circulating alkaline phosphatase was measured at 3 time points: ages 2 to 4, 4 to 7, and 1 to 15 months. The number of new cases detected at each time point were 3 of 260 (1.2%) at 2 to 4 months of age, 2 of 186 (1.1%) at 4 to 7 months of age, and 3 of 85 (3.5%) at 11 to 15 months of age (10).

Link With Infectious Diseases—Familial Cases—Recurrences

There is a history of a recent infection in >60% of the subjects with transient benign hyperphosphatasemia without any underlying chronic disease (Table 1). It has been therefore postulated that transient benign hyperphosphatasemia is caused by a preceding, mostly viral, infection. This assumption is supported by a clustering of transient benign hyperphosphatasemia diagnoses during fall or winter months: a seasonal clustering was noted in Slovakia, with 43% presenting between September and November; a similar pattern was observed in a British study of 35 cases and in an Australian study (16,19,22). The seasonal predilection reported in the mentioned retrospective reports, however, was not confirmed in the well-designed prospective study that addressed the frequency of transient benign hyperphosphatasemia among infants and toddlers in Boston (39). In this study, however, 6 of 9 children (67%) with transient benign hyperphosphatasemia had a history of upper respiratory symptoms (N = 3), rash (N = 2), or diarrhea (N = 1) in the month directly preceding the diagnosis (39).

Six articles reported ≥2 members of the same family (44,46,84,114,116,149) who developed simultaneously a temporary and unexplained increase in alkaline phosphatase level: they were 6 sets of twins ages 24 months or younger (monozygotic in 1 case; information not available in the remaining 5 reports). In 1 of the 6 articles, the increase in alkaline phosphatase level concurrently affected two 14-month-old female twins and their 36-month-old brother (46). Transient benign hyperphosphatasemia never recurred in childhood.

TABLE 1. Reasons underlying the initial determination of the alkaline phosphatase test in 641 subjects (male:female ratio 1.1:1.0) ages 18 years or younger affected by transient benign hyperphosphatasemia without any underlying chronic disease

Reason	N	Percentage
Checkup	226	35
Respiratory infections	120	19
Otitis media	10	1.6
Pharyngitis	10	1.6
Other upper respiratory illnesses*	62	9.7
Lower respiratory illnesses	38	5.9
Diarrheal disease	112†	17
Urinary tract infection	4	0.6
Other likely infectious diseases	90	14
Two or more infections	66	10
Convulsions (with or without fever)	23	3.6

* Other than otitis media or pharyngitis.
† Rotavirus detected in 20 cases.

Cases in Subjects Older Than 18 Years

A temporary and unexplained elevation of the alkaline phosphatase level was reported in 80 subjects older than 18 years. The diagnosis of transient benign hyperphosphatasemia was addressed in 8 small reports for a total of 7 female and 7 male healthy subjects ages 19 to 68 years, median 46 years. The remaining 66 cases were included in a report published >20 years ago (67). This study addressed the cause of raised alkaline phosphatase level in 204 acute medical admissions in which hyperphosphatasemia was found. Liver and bone disease accounted for 98 (48%) of the established diagnoses, other diseases accounted for 9 (4.4%), and the diagnosis was not established in 31 (15%) cases. Transient hyperphosphatasemia occurred in the aforementioned 66 (32%) cases (67). A 29-year-old man affected by a combined immunodeficiency developed a transient increase in alkaline phosphatase activity that recurred 30 months later (25).

Tissue Source of Increased Alkaline Phosphatase Level and Biochemical Bone Turnover Markers

The total alkaline phosphatase level in blood is a mixture of isoforms from the liver, bone, intestine, and placenta. In transient benign hyperphosphatasemia, the tissue source of increased alkaline phosphatase level was specifically addressed in 516 subjects by means of either electrophoretic (N = 207), selective inactivation (N = 60), or both electrophoretic and inactivation (N = 70) techniques. In the remaining 179 cases, no information on the applied technique was given. In the majority of the cases (N = 279; 54%), the interpretation of the results was impossible or unavailable. In the remaining 237 cases (46%), the assessment of the isoenzymes was consistent with a bone origin in 118 cases, a mixed origin in 81 cases, a hepatic origin in 34 cases, an intestinal origin in 3 cases, and a placental origin in 1 case.

Because there is often a prevalent elevation in the bone isoform, some authors determined the blood concentration of osteocalcin, a marker of the cellular activity of osteoblasts, and that of bone-related degradation products derived from C-terminal telopeptides of type I collagen, which, in turn, reflect bone resorption, during and after the temporary elevation of the alkaline phosphatase level. No relation was found between the dynamics of the alkaline phosphatase level and that of the mentioned biochemical markers of bone metabolism (45,51). Urinary hydroxyproline and circulating tartrate-resistant acid phosphatase, which have been in use as a marker of bone resorption but unfortunately lack in accuracy, were normal or at most marginally elevated in

subjects affected with transient benign hyperphosphatasemia (45,78,83). Finally, in most reported cases, normal levels of calcium, magnesium, phosphorus, and parathyroid hormone did not support increased bone resorption among subjects with transient benign hyperphosphatasemia.

Metabolism of Vitamin D

By definition, transient benign hyperphosphatasemia is not linked with altered levels of circulating calcium and inorganic phosphate or with vitamin D deficiency (3,4). Nonetheless, it has been speculated that the condition develops either during the period of catch-up growth after weight loss or as a consequence of subclinical vitamin D insufficiency (39). In a case-control study, growth parameters and blood levels of circulating calcium, magnesium, inorganic phosphate, vitamin D, and parathyroid hormone were similar in subjects with transient benign hyperphosphatasemia and healthy controls (39).

DISCUSSION

Transient benign hyperphosphatasemia is considered a relatively common, nonrecurring condition that affects healthy infants and toddlers of both sexes and resolves within 16 weeks without intervention (3,4). This extensive analysis of the literature demonstrates that ≈25% of the published cases occur either in children ages 37 months or older or in adults and therefore suggests that the term transient benign hyperphosphatasemia of infancy and early childhood may not be correct (3,4). It is tempting to assume, however, a possible publication bias, with rather extraordinary cases occurring in older children and adults that are more likely to be published than rather ordinary cases occurring in infants and toddlers. Furthermore, our analysis indicates that the laboratory abnormality persists for ≥17 weeks in ≈20% of the published cases. Finally, 13% of the published pediatric cases were noticed in patients with a preexisting chronic disease.

In childhood, transient benign hyperphosphatasemia often follows a benign, mostly viral infection. Furthermore, it occurs occasionally in ≥2 members of the same family. It has been therefore suggested that transient benign hyperphophatasemia represents a postinfectious disorder. Available data, however, fail to demonstrate a causal link with the preceding infection. In fact, the apparent association with a recent infection may simply reflect a detection bias that results from the tendency to perform laboratory testing to rule out a possible underlying medical condition in this setting.

In transient benign hyperphosphatasemia, the mechanisms of elevation in alkaline phosphatase remain elusive. Available data indicate that in 50% of the cases, there is a prevalent elevation in the bone isoform. This tendency, however, is coupled with normal blood biochemical markers of both bone formation and resorption. Hence, the still unproven but most plausible explanation for the alkaline phosphatase elevation is a reduced clearance from the circulation rather than a temporarily increased release of the enzyme. More important, our analysis indicates that alkaline phosphatase isoenzyme studies are not useful in clinical practice to evaluate subjects with isolated elevation of the alkaline phosphatase level. Furthermore, interpretation of isoenzyme studies is difficult because the relative activity of the bone and liver isoenzymes strongly varies with age, with a prevalence of the bone isoform in infants, children, and adolescents as opposed to a prevalence of the liver isoform in adults (9).

The most important limitation of this review results from the rather small number of reported subjects affected by transient benign hyperphophatasemia. A second limitation is that, because of the scant literature, the analysis incorporated almost exclusive information from single case reports or small case series that were mostly retrospective. Third, little data have hitherto been collected to explain the mechanisms underlying the condition. Finally, the largely accepted tenet that transient benign hyperphophatasemia is triggered by an infection could not be confirmed in a prospective study (3,4). Thus, this hypothesis still deserves further proof.

In conclusion, transient benign hyperphosphatasemia, likely the most common cause of hyperphosphatasemia among healthy infants and toddlers, not rarely also occurs in older children and adults (Table 2). Contrary to what is usually believed, the elevation in alkaline phosphatase persists for ≥17 weeks in ≈20% of the published cases. Recognition of this self-limited condition is crucial to avoid unnecessary further investigations. The evaluation should include a history and an accurate physical examination to assess for evidence of liver or bone disease. Because vitamin D deficiency is again a major public health challenge, the suspicion of vitamin D deficiency should be raised in exclusively breast-fed infants without vitamin D supplementation or poor adherence to the supplementation, in dark-skinned subjects, in subjects with vegetarian diets, in subjects taking anticonvulsant or antiretroviral drugs, and in subjects affected by malabsorptive conditions (10). Ideally, laboratory testing should include the assessment of aminotransferases, bilirubin, γ-glutamyl transferase, leucine aminopeptidase, calcium, inorganic phosphate, urea, creatinine, and repeat determination of alkaline phosphatase at intervals. It is true, however, that many experienced clinicians waive some, if not the great majority, of the laboratory testing and make the diagnosis of transient

TABLE 2. Characteristics of transient benign hyperphosphatasemia

Marked increase (mostly ≥5 higher than the upper reference range*) in alkaline phosphatase level
Affects both sexes equally
Affects especially healthy infants and toddlers (with a prevalence between 1.1% and 3.5%). One-quarter of the published cases occur in older children, in adolescents, or in adults
The condition sometimes affects also subjects with a chronic underlying disease (the diagnosis can be tricky in this setting†)
History of a recent infection (typically from a virus) in >60% of the cases (but no clear-cut causal association with the preceding infection)
No clinical evidence of any bone disease (delayed closure of the fontanelles, soft skull bones, parietal and frontal bossing, enlargement of the costochondral junction, Harrison groove at the lower margin of the thorax, widening of the wrists, double malleoli sign, progressive lateral bowing of femur and tibia) or liver disease (jaundice, itching, spider naevi, bruises, prominent abdominal vessels, hepatosplenomegaly)
No laboratory evidence of bone or liver disease; alkaline phosphatase level mostly resolves spontaneously within 16 weeks without intervention (but persists for ≥17 weeks in one-fifth of the cases).

* Adjusted for age, sex, and laboratory's own normal values.
† And in adults.

hyperphosphatasemia essentially based upon history taking and physical examination.

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