

Transient hyperphosphatasemia: Possible association with pediatric acute respiratory infection

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ABSTRACT

Importance: Acute respiratory infections are quite prevalent in children. Transient hyperphosphatasemia (TH) is defined as the transient elevation of serum alkaline phosphatase (ALP) level, which occurs mainly in infants and children without liver or bone disorders. Although no apparent cause has been identified, a possible association of respiratory infections with TH has been reported in the literature.

Objective: In this study, we aimed to investigate the association between TH and respiratory infectious diseases.

Methods: We collected the results of biochemical investigations, including ALP level, for a period of 5 years in our hospital. We then examined the patients with transiently elevated ALP levels of > 2000 U/L.

Results: During the observation period, 1501 blood samples were collected from 1097 patients. Marked elevation of serum ALP level was observed in 12 patients. All patients with hyperphosphatasemia, except for one with Fanconi syndrome attributable to the underlying Wilson's disease, were aged < 5 years and were diagnosed with TH. Ten of these 11 patients with TH had acute respiratory infections. Marked ALP elevation was not found in any patients with non-inflammatory diseases. ALP isoenzyme profiles showed a characteristic pattern in all six patients in whom the ALP isoenzyme test was conducted.

Interpretation: Our results suggest an association between respiratory infections and TH. The consideration of TH in patients with acute respiratory infections may lead to earlier and accurate diagnosis of this condition, thereby avoiding unnecessary medical interventions.

KEYWORDS

Alkaline phosphatase, Respiratory infection, Transient hyperphosphatasemia, Isoenzyme

INTRODUCTION

Children often become infected with bacteria, viruses, parasites, or fungi, which may affect various organ systems. Acute respiratory infections are quite prevalent in children, which can lead to various complications. For upper respiratory infections, common complications include

secondary bacterial sinusitis, bronchitis or pneumonia after a viral infection, and worsening of underlying asthma.¹ For lower respiratory tract infections, common complications include congestive heart failure, sepsis, and lung abscess.² Furthermore, transient hyperphosphatasemia (TH) is a rare and generally unrecognized condition that may be associated with acute respiratory infections.

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Alkaline phosphatase (ALP; E.C.3.1.3.1) is a ubiquitous membrane-bound glycoprotein that catalyzes the hydrolysis of a broad range of phosphate monoester substrates at high pH. ALP is expressed in all tissues, with high levels in specific tissues. There are six ALP isoenzymes with distinct electrophoretic properties: high-molecular-weight ALP (ALP1), hepatic ALP (ALP2), bone ALP (ALP3), placental ALP (ALP4), intestinal ALP (ALP5), and IgG-bound ALP (ALP6).³ Serum ALP levels are well known to be elevated in patients with bone or hepatobiliary diseases. However, because ALP levels are altered in relation to variations in sex, blood type, and age, caution is needed when interpreting the results of ALP assessments in children. Notably, bone ALP (ALP3) activity is enhanced by bone growth during infancy and adolescence; thus, the total ALP level is several-fold greater in children than in adults. Nevertheless, we occasionally encounter pediatric patients in whom ALP levels are markedly elevated, despite adjustment for age.

Over four decades ago, Posen et al⁴ reported transient ALP elevation in infants without any bone or hepatobiliary diseases, supporting the concept of infant TH. In 1985, the diagnostic criteria were defined as follows: age of presentation < 5 years, presence of various unrelated symptoms, no evidence of bone or liver disease, elevation of both bone and liver ALP isoenzymes, and return to the normal ALP range within 4 months.⁵ Although the nomenclature of this condition was subsequently modified to benign TH⁶ or TH,⁷ because it also occurs in adults, TH was later reported to develop in children up to 5 years of age, especially those aged < 2 years.⁸ Thus far, the cut-off value of ALP in patients with TH have not yet been defined. (Thus far, the ages of patients with TH have not been fully defined.)

The cause of TH remains unknown. However, the involvement of acute respiratory infections, such as respiratory syncytial virus (RSV) infection, has been suspected.^{9,10} TH may represent a postinfectious disorder, otherwise, its apparent association with recent infections may simply reflect a detection bias.¹¹ Besides, the incidence of TH in healthy infants was found to reach a few percent; thus, TH might be a relatively common condition unrelated to any infection.^{12,13} To elucidate the relevance of TH in the presence of respiratory infections, we retrospectively reviewed patients with TH in our hospital and investigated the association between respiratory infections and TH.

METHODS

Ethical approval

The institutional Ethics Committee Review Board of the Matsubara Tokushukai Hospital approved this retrospective study (approval no.1904-028), and informed consent was obtained using the opt-out method.

Patients

The incidence of hyperphosphatasemia was evaluated in electronic medical records of pediatric patients aged < 16 years who visited our outpatient clinic and underwent biochemical investigations (including ALP level measurement) during the period from May 1, 2013 to April 30, 2018. When ALP levels were measured multiple times in the same patient for the same condition within a span of 4 weeks, the highest ALP level was considered. In such instances, the number of multiple blood sample collections was regarded as one. In accordance to a previous report by Goto,¹⁰ we regarded serum ALP levels of > 2000 U/L as abnormally high (i.e., hyperphosphatasemia). The normal reference range of ALP, according to age and sex, was used to establish the ratio of ALP level to the upper limit of the normal range, in accordance with a previously published method.¹⁴ The ALP isoenzyme assay was performed by BML, Inc. (Tokyo, Japan). For patients who fulfilled these criteria, the following clinical information were recorded: medical history, chief complaints, physical examination, laboratory results other than ALP level, imaging findings, and diagnosis by attending physicians. Medical records were comprehensively reviewed to confirm the correctness of the clinical diagnosis in each patient with suspected TH.

RESULTS

During the 5-year observation period, 1501 blood samples were collected from 1097 patients for blood biochemical measurements, including ALP level. We plotted the ALP levels of all 1501 samples against age (Figure 1). A total of 983 samples were collected from patients with suspected/confirmed inflammatory diseases, including 51 from patients with autoinflammatory diseases such as familial Mediterranean fever. The remaining 518 samples were collected from patients with non-inflammatory diseases. Among patients with infectious diseases, most had acute respiratory infections (533 samples) followed by acute gastrointestinal infections (183 samples). These two conditions were present in nearly half of patients from whom blood samples were collected.

Serum biochemical analysis showed an elevated ALP level (> 2000 U/L) in 22 blood samples from 12 patients. The patients were all aged < 5 years, except a 12-year-old girl whose ALP level was elevated (approximately 2000 U/L) at each blood investigation throughout the evaluation period. This patient had Fanconi syndrome attributable to underlying Wilson's disease. Because her hyperphosphatasemia was not transient, this patient was excluded from the study.

Table 1 shows the characteristics of 11 patients who were diagnosed with TH. These patients were aged < 5 years (range, 7–54 months; median, 14 months) with a male to female ratio of 5:6. The age of female patients tended to be higher than that of male patients, but did not significantly

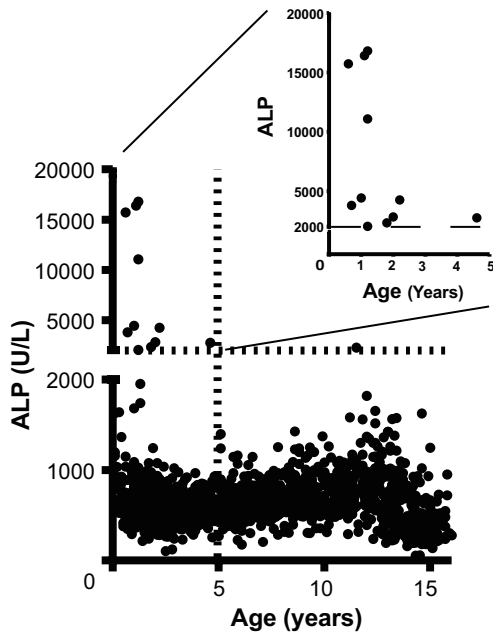


FIGURE 1 Alkaline phosphatase (ALP) levels in all samples. For 12 patients with elevated ALP levels (> 2000 U/L), the highest value in each patient was plotted. Elevations in ALP levels are evident in early infancy and puberty. In the upper right corner, the scatterplot of ALP levels of > 2000 U/L in patients aged < 5 years is enlarged. All 11 cases of transient hyperphosphatasemia are seen in this plot. Although a 12-year-old girl among the 11 patients had hyperphosphatasemia, her ALP level was constantly elevated due to Fanconi syndrome associated with Wilson disease.

differ (Figure 2). The high ALP levels ranged from 2044 U/L to 16 814 U/L (mean \pm standard error of the mean, 7501 ± 1861 U/L). Of the 11 patients, 10 had respiratory disorders (four had upper respiratory inflammation [URI]

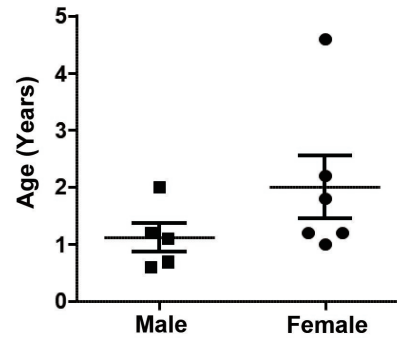


FIGURE 2 Age of diagnosis for transient hyperphosphatasemia. Each bar shows the mean \pm standard error of the mean.

and six had lower respiratory inflammation [LRI]); one of the patients with URI had a seasonal influenza A infection, but the causative pathogen(s) were not determined in the other patients. All patients with LRI were diagnosed on the basis of radiographic findings, as well as physical examination and laboratory findings. Two patients with LRI had RSV infection, one of whom had a co-existing adenovirus infection; a third patient with LRI had a mycoplasma infection. Clinical symptoms and signs of the remaining three patients with LRI and three with URI were suggestive of viral infections, consistent with laboratory findings. One of these three patients had periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome as underlying conditions. This patient was presumed to have URI because she exhibited cough and nasal discharge, which are not regarded as the major symptoms of PFAPA syndrome, and her elder brother, without any underlying diseases, also had similar symptoms at the same time. The remaining one patient without any respiratory disorders had cellulitis of the

TABLE 1 Profiles of the 11 patients with transient hyperphosphatasemia

No.	Sex	Age (years)	ALP level (U/L)	Disease	Causative agent	ALP ratio [†]	Time to return to normal limits (weeks)
1	F	1.2	16 814	URI	Influenza A	13.0	17
2	M	1.1	16 413	LRI	Unknown	12.3	6
3	M	0.6	15 729	LRI	RSV	10.0	5
4	M	1.2	11 081	LRI	Unknown	8.3	nd
5	F	1.0	4433	Cellulitis	<i>Staphylococcus aureus</i>	3.4	nd [§]
6	F	2.2	4266	LRI	Mycoplasma	3.7	nd
7	M	0.7	3800	URI	Unknown	2.4	17
8	M	2.0	2834	URI	Unknown	2.3	nd
9	F	4.6	2759	LRI	RSV/adenovirus	2.4	7
10	F	1.8	2339	LRI	Unknown	1.8	3
11 [‡]	F	1.2	2044	URI	Unknown	1.6	26

ALP, alkaline phosphatase; M, male; F, female; URI, upper respiratory infection; LRI, lower respiratory infection; RSV, respiratory syncytial virus; nd, not determined. [†]Measured level divided by the corresponding normal upper limit. [‡]Underlying condition: periodic fever, aphthous stomatitis, pharyngitis, adenopathy syndrome. [§]Normalization of the elevated ALP level was confirmed by chance blood test after 2 years.

lower limb due to *Staphylococcus aureus* infection.

Of the 11 patients with TH, 10 revisited our outpatient clinic and their conditions improved. The remaining patient did not return to our clinic, but improvement was confirmed in a reply to our medical referral letter from the hospital where the patient had been transferred. A reduction in ALP level to the normal range for age was confirmed over the next 3 weeks to 6 months in seven patients. In one of the remaining four patients, normalization of the elevated ALP level was confirmed after 2 years. For the final three patients, the ALP results were unavailable because no blood samples had been collected. ALP isoenzyme electrophoresis was performed in six patients. The isoenzyme pattern showed a bimodal appearance composed of ALP2 and ALP3, or a single peak with a shoulder in which ALP2 and ALP3 were merged.

DISCUSSION

Our results showed that infants approximately 1 year of age are susceptible to TH. Of the 11 patients in this study, 10 (91%) were aged < 3 years. Sex differences in the incidence of TH were not evident. These observations are largely consistent with those of previous studies. A systematic review of TH in 733 patients aged < 18 years (range, 2 months to 17 years) in 2013¹¹ described that 82% of patients with TH were aged < 3 years; moreover TH developed frequently in children aged 13–18 months without differences in sex. In that systematic review,¹¹ ALP levels were elevated by two-fold to 71-fold above the upper normal limit; hyperphosphatasemia persisted for 2 weeks to 4 years. The ALP levels were normalized within 4 months in 81% of patients. Therefore, the overall prognosis of this condition is good. To the best of our knowledge, no recurrences have been reported in pediatric patients, although they have been reported in adults.¹⁵ Our results further support these previous observations. In our study, the ALP levels were elevated 1.6–13.0-fold times above the upper normal limit for age and sex. Although reductions below the upper normal limit for age and sex were confirmed in all eight patients in whom ALP levels were re-evaluated, follow-up of ALP levels was not performed in the remaining three patients.

Concerning the association between infections and TH, the abovementioned systematic review reported that infections were present in 60% of patients with TH and no underlying disease; half of these infections were respiratory infections while the remaining infections comprised enterocolitis. However, no causal relationship was demonstrated.¹¹ In our study, 10 of the 11 patients with TH had acute respiratory infections; the remaining patient had cellulitis due to *S. aureus* infection. Although the frequency of blood investigations in patients with gastrointestinal infections was one-third of that in patients with respiratory infections, no patient had an ALP level of > 2000 U/L. Furthermore, although one-third of the

total blood samples were collected from patients with non-inflammatory diseases, no abnormally elevated ALP level was recorded. This discrepancy is presumably because of the cut-off level that we established for the diagnosis of TH. We adopted an ALP level of > 2000 U/L as the cut-off, while the cut-off levels varied among previous studies (e.g., > 800 U/L,⁸ > 1000 U/L,¹³ or at least three-fold greater than the upper limit of the normal range^{9, 12}). Taken together, our findings support a relationship between infections, especially acute respiratory infections, and the onset of TH.

In patients with acute respiratory infections, we found no significant difference between URI and LRI in terms of TH incidence (data not shown). Furthermore, we did not identify specific causative agents in this study. However, rapid diagnostic tests for respiratory infections performed in our hospital were limited to infections caused by RSV, adenovirus, influenza viruses, pneumococcus, and streptococcus. Notably, our patients with TH did not undergo all these investigations. In addition, infants with acute respiratory infection may develop concurrent multiple infections due to other pathogens.^{16,17} Further respiratory pathogen panel testing in a larger number of patients is warranted.

The effectiveness of the ALP isozyme test is controversial. Some reports have indicated that the ALP isoenzyme test is useful for the accurate diagnosis of TH,^{5,6,18} while other findings have not supported this view.¹¹ In previous studies of the ALP isoenzyme test for TH, electrophoresis results showed a bimodal appearance (composed of a band on the anode side of ALP2 and an ALP3 band).^{6,19-21} These peaks are sometimes merged and form a single peak with a shoulder. The ALP isoenzyme patterns in our patients were consistent with previous observations, suggesting that the ALP isozyme test could be useful.

The mechanisms underlying abnormal elevation of ALP levels in patients with TH remain unknown. However, they might involve a temporary increase in ALP release from the liver and bones, or reduced clearance (i.e., reduced uptake of ALP into the hepatocytes due to excessive sialylation of ALP).¹³ Over all, the influence of respiratory infections on these mechanisms remains unclear. The relation between infections and elevation of the ALP level needs to be further studied.

Our study had some limitations. First it had a small sample size, presumably due to the selected ALP cut-off level. Although some patients with TH might have thus been omitted, we believe that this method prevented the inappropriate designation patients from being diagnosed with TH, thereby providing a clearer presentation of patients with TH. Second, the available pathogenic microbe tests were limited and did not allow a clear assessment of the associations of pathogens with TH. Furthermore, isoenzyme analyses were not performed for some patients. However, the analyses conducted for more

than half of the patients showed a common characteristic profile. Until this condition is ruled out, excessive laboratory workup and overmedication may be detrimental to patients because the differential diagnosis includes conditions such as hepatobiliary or bone diseases. When infants with acute respiratory infections exhibit elevated ALP levels, TH should be considered. The ALP isoenzyme test may be useful in this regard.

In conclusion, awareness of the existence of TH in association with acute respiratory infectious diseases may facilitate prompt diagnosis and reduce unnecessary laboratory investigations and imaging in pediatric patients.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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