

Transient Hyperphosphatasemia: A Case Report

Krittha Jeerawongpanich, MD



Krittha Jeerawongpanich, MD

Department of Pediatrics, Faculty of Medicine, Burapha University, Chonburi, Thailand.

* Address Correspondence to author:
Krittha Jeerawongpanich, MD
169 Long-Hard Bangsaen Road,
Saen Sook Sub-district, Mueang District,
Chonburi 20131, Thailand.
email: kathy22_3@hotmail.com

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Abstract

We report a case of a 2-year-3-month-old boy who had poor weight gain since 1 year of age. He had a history of difficulty eating since he was 6 months old. Vaccinations were up to date and his developmental assessment was normal. Physical examination revealed no dysmorphic features. His weight was 9.4 kilograms (< P3) and he was 82 centimeters in length (< P3). He had no rachitic rosary nor swelling of wrists or knees, no bowed legs or genu varus. He was referred to Burapha University Hospital for evaluation of failure to thrive. The laboratory investigations showed serum calcium of 10.2, phosphorus 4.5, magnesium 2.3 mg/dL and alkaline phosphatase 1,603 U/L. The x-ray on both knees and wrists showed no fraying and no flaring of the metaphyses. Serum 25-OH vitamin D and parathyroid hormone levels were 27.4 ng/mL and 24.7 pg/mL, respectively. The serum alkaline phosphatase decreased to 494 U/L. After 2 weeks of follow-up it further decreased to 185 U/L in 3 months with normal levels of calcium 9.8, phosphorus 5.3 mg/dL. The diagnosis of transient hyperphosphatasemia is crucial to avoid excessive investigations.

Keywords: alkaline phosphatase, bone disease, rickets, transient hyperphosphatasemia

Transient hyperphosphatasemia (TH) in infancy and childhood is a condition of elevated serum alkaline phosphatase (ALP) level without evidence of bone or liver disease. The common age at presentation is younger than 5 years old. However, investigations are needed to exclude other serious conditions such as liver disease or bone disease.¹ Transient hyperphosphatasemia is not associated with any anthropometric measurement or biochemical markers of calcium and vitamin D metabolism.² This condition is postulated to be from the immaturity of the mechanism responsible for ALP clearance resulting in an increasing level of plasma ALP. The associations between transient hyperphosphatasemia and viral, protozoal or other infections have been reported, such as gastrointestinal disease, respiratory infections,³ and the duration of the elevation of serum alkaline phosphatase was less than 4 months in 80% of cases.⁴ This condition resolves without intervention.⁵ Most TH cases were found to be associated with upper airway diseases, suggesting that TH might be caused by enterovirus infection.⁶ This report describes a case of TH which might be associated with viral infection, TH resolved without intervention.

Case Report

A 2-year-3-month-old boy had a history of poor weight gain for one year. He was the second child of non-consanguineous parents. Pregnancy and delivery were uncomplicated. He was born at term by vaginal delivery with birthweight of 2,800 grams. He had history of difficulty eating since he was 6 months old. He was breastfed until 1 year and 6 months old. He had no history of chronic diarrhea. During the past year, he only gained 1.4 kilograms in weight. At the time of this admission, his daily food intake included three meals and 125cc of milk per day. He had no history of drug or food allergy. His vaccinations were up to date. Developmental milestones were assessed to be normal for his age. He was admitted twice in the past year for viral gastroenteritis and his last admission was 4 months ago from upper respiratory tract infection.

Physical examination revealed a thin boy with a weight of 9.4 kilograms (< P3) and 82 centimeters in height (< P3). He had no dysmorphic feature, no rachitic rosary nor swelling of wrists and knees, no bowed legs or genu varus. The rest of the physical examination was normal.

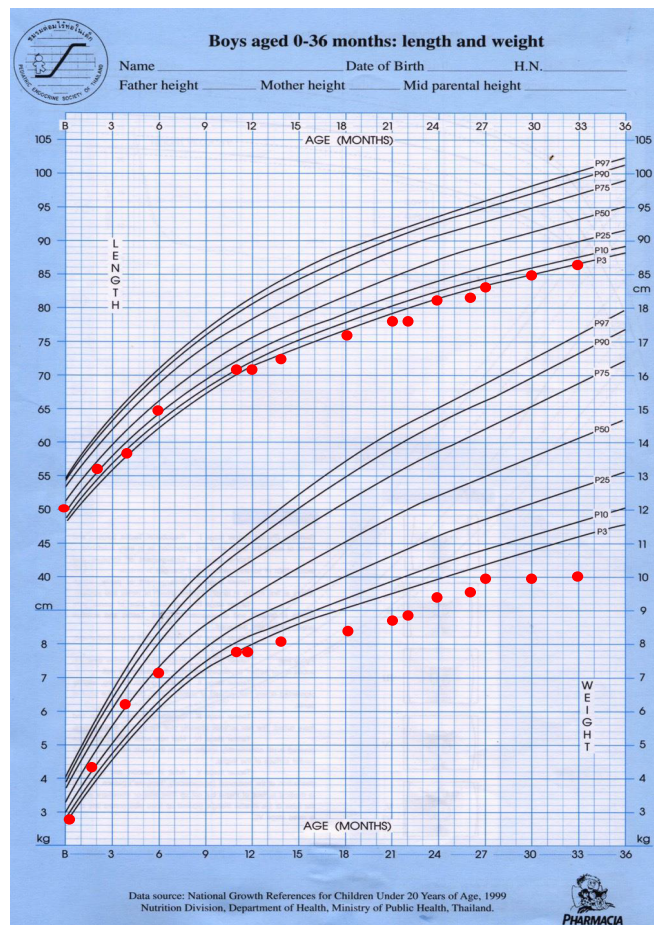


Figure 1: Growth chart showed weight below the 3rd percentile for age since 12 months of age

The patient was referred to Burapha Hospital University for further investigation of failure to thrive.

Laboratory investigations

- CBC: Hemoglobin 11.6 g/dL, Hematocrit 34.3%, WBC 8,500 cell/mm³ (Neutrophil 41, Lymphocyte 56, Monocyte 1, Eosinophil 2%, Platelet 243,000 cell/mm³, MCV 75.8 fL, MCH 25.6 pg, MCHC 33.8 g/dL, RDW 13.4%, Erythrocyte sediment rate 6 mm/hour
- Blood Chemistries: Blood Urea Nitrogen 12, Creatinine 0.49 mg/dL, Sodium 140, Potassium 4.1, Chloride 108,

Bicarbonate 20 mmol/L, Calcium 10.2, Phosphorus 4.5, Magnesium 2.3 mg/dL

- Liver function test: Direct Bilirubin 0.27, Total Bilirubin 0.55 mg/dL, aspartate transaminase 32, alanine transaminase 14, alkaline phosphatase 1603 U/L, Albumin 4.7, Globulin 2.0, Total protein 6.7 g/dL
- Urine analysis: pH 6.0, specific gravity 1.027, protein: negative, sugar: negative, ketone: negative, white blood cell 0-1/HPF, red blood cell 0-1/HPF
- Free T4 1.16 ng/dL, TSH 0.89 uIU/mL

Radiologic Findings:



Figure 2: Knees AP: no fraying and flaring of femur and tibial metaphyses

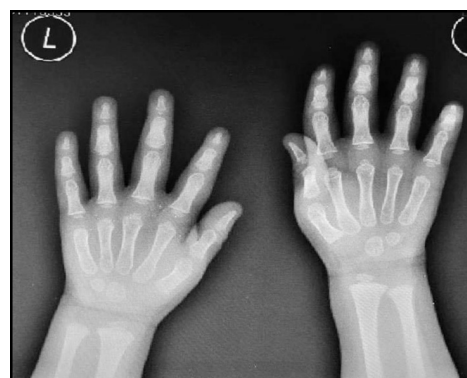


Figure 3: Wrists AP: no fraying and flaring of radial metaphyses



Figure 4: No genu valgus and genu varus of both legs



Figure 5: No rachitic rosary



Figure 6: No widening of wrists

The differential diagnosis of elevated alkaline phosphatase level are:

- Bone disorders: rickets, bone tumor, Paget's disease
- Liver disease: cholestasis, malignancy
- Renal disease: chronic renal failure, renal tubular acidosis
- Drug ingestion: bactrim, antiepileptic drugs
- Transient hyperphosphatasemia

Physical examination revealed no dysmorphic features. He had no rachitic rosary nor swelling of wrists or knees, no bowed legs or genu varus. The laboratory investigations were

unremarkable except alkaline phosphatase (1,603 U/L). Radiologic findings of both knees and both wrists showed no fraying and no flaring of the metaphyses.

Our patient had no clinical signs of rickets or bone disease, and all laboratory tests were normal except the markedly elevated ALP level. Therefore, liver disease and renal diseases were excluded. The laboratory tests at the time of follow-up at 2 weeks and 3 months later revealed declined levels of ALP as shown in Table 1. The patient was diagnosed with transient hyperphosphatasemia.

Table 1: Renal profile and fluid intake/output during admission

	Initial presentation	2-weeks follow-up	3-months follow-up
Calcium (mg/dL)	10.2	10.3	9.8
Phosphorus (mg/dL)	4.1	6.2	5.3
Magnesium (mg/dL)	2.3	2.4	-
25-OH Vitamin D (ng/mL)	-	27.4	-
PTH (pg/mL)	-	24.7	-
Alkaline phosphatase (U/L)	1,603	494	185
Creatinine (mg/dL)	0.49	0.29	-

Discussion

This patient has transient hyperphosphatasemia (TH), a condition that can be found in young children. The laboratory and radiographic studies were unremarkable except markedly elevated level of alkaline phosphatase. The follow-ups laboratory tests showed no evidence of bone or liver disease and the serum alkaline phosphatase level gradually declined to normal values within 3 months without intervention.

Huh SY et al.² enrolled 316 healthy infants and toddlers at well-child visits aged 8 to 24 months during 2005-2007 and found that 9 children (2.8%) had an alkaline phosphatase level >1,000 U/L with serum calcium and serum vitamin D levels in the normal ranges. 6 of the 9 TH children had a history of upper respiratory tract symptoms (3 cases), rashes (2 cases) and diarrhea (1 case) about 1-2 months before the diagnosis of TH. The high ALP level declined to normal within 35 days.²

Behúlová D et al.³ studied 194 TH cases, aged 4-126 months (median 15 months) who had alkaline phosphatase level 2-20 folds higher than the pediatric upper reference limit (51-408 U/L) and found that TH were associated with viral, protozoal or other infections; gastrointestinal disease (24%), respiratory infections (21%), congenital anomalies and inborn errors of metabolism (15%), anemia (10%), malignancies (7%), neurological disorder (5%), and others (18%).³

A systematic review of TH by Gualco G et al.⁴ from 142 reports in English, French, German, Italian, Portuguese and Spanish found that 733 of 813 TH patients (90%) were younger than 18 years with the estimated prevalence of TH 1.1-3.5% in infants 2 to 24 months of age and the duration of the elevation of serum alkaline phosphatase was less than 4 months in 80% of cases.⁴

Kutilek S et al.⁵ reported two TH cases in Czech Republic. The first one was a 12-month-old girl who presented with

failure to thrive and had a history of gastrointestinal symptoms before the diagnosis of TH was made. The laboratory findings revealed high alkaline phosphatase level of 31.3 μ kat/L (normal range 2.5-9.5 μ kat/L) and other laboratory results were normal. The second case was a 12-month-old boy with underlying disease of congenital rubella syndrome. The laboratory investigations showed very high levels of serum alkaline phosphatase up to 109 μ kat/L with normal other laboratory findings. In both cases, serum alkaline phosphatase returned to normal level after six weeks of follow-up.

Suzuki M et al.⁶ collected 19,230 serum samples requested for ALP measurement from 1998-2001 and found 50 cases (0.26%) with elevated alkaline phosphatase from 3-42 folds of the upper normal limit. All 50 TH cases were children aged younger than 8 with the highest prevalence in an infant 1 year of age. Furthermore, most TH cases had high antibody titers for viruses causing upper airway infectious diseases, suggestive that TH might be caused by an infection particularly of the enterovirus group.⁶

Otero JL et al.⁷ reported a 27-month old previously healthy female was found to have isolated elevation of alkaline phosphatase (1,510 U/L) following acute gastroenteritis last month. On physical examination, she had no dysmorphic features and her weight and height were between the 25-50th percentile. The alkaline phosphate level declined to normal within 4 months (243 U/L).⁷ They postulated that the TH mechanism consist of excessive synthesis or release of enzyme from its tissue of origin⁸ and acute gastroenteritis has been suggested to be a risk factor for TH.⁷ They recommended a clinical algorithm for children who had an isolation elevation of alkaline phosphatase, and who otherwise are normal, which would avoid extensive work up or referrals to a specialist.⁷

Dursun F et al.⁹ reported 15 patients (mean age was 2.45 \pm 1.09 years) who were referred to the pediatric endocrinology clinic for elevated ALP levels. Mean serum ALP levels in this

study were 2315 \pm 1028 IU/L (1102-4662). Only one patient had a history of acute gastroenteritis one week prior to referral, while others did not have any evidence of additional illness. None of them had a physical examination finding suggesting rickets, other metabolic bone disease, liver or biliary system disease. They were diagnosed with Benign transient hyperphosphatasemia, and all saw the normalization of alkaline phosphatase at the end of 4 months without any treatment.

Eymann A et al.¹⁰ reported 4 cases of healthy children (mean age 33 months) with an elevated serum alkaline phosphatase (11900, 6500, 9700 and 7600 UI/L, respectively). All children had a normal physical exam and anthropometric measures. The alkaline phosphatase value was normalized over the course of 4 months in all of the patients, with exception of one that normalized at 8 months without any intervention. Benign transient hyperphosphatasemia of infancy was diagnosed in all patients.

Our patient had a history of runny nose, cough, low grade of fever and viral gastroenteritis 1 month before the diagnosis of TH was made. He was not given antibiotics. The ALP declined to normal level within 3 months of follow-up. These findings are consistent with previous published case studies in which patients achieved normalization of alkaline phosphatase within 4 months. We postulated that TH in our patient is most likely related to a viral infection.

Conclusion

Transient hyperphosphatasemia is a benign condition in young children. Follow-up of serum calcium, phosphate and alkaline phosphatase levels is necessary to exclude serious conditions such as bone and liver diseases. The marked elevation of serum alkaline phosphatase level gradually declines to normal within four months without any treatment or intervention.

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