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Transient Hyperphosphatasemia of Infancy: A Report of 4 Cases And A Review of The Literatüre

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Abstract

Benign transient hyperphosphatasemia (BTH), determined during infancy and early childhood that is characterized by a transiently increased serum activity of alkaline phosphatase (ALP) predominantly of its bone or liver isoforms, with no identifiable liver or bone diseases, which return to normal levels within 4 months. Benign transient hyperphosphatasemia is discovered incidentally with a routine blood analysis, or various illnesses when laboratory studies are obtained for another purpose. Therefore BTH is considered a benign biochemical disorder with no clinical consequences.

We report four infants with highly elevated ALP activity detected incidentally who were diagnosed as having BTH based on clinical and biochemical findings. Of the patients 3 infants presented with failure to thrive accompanying BTH. We emphasize that BTH should be kept in mind in case of very high serum ALP levels without underlying significant pathology in order to avoid misdiagnosis and unnecessary investigations.

Keywords: benign; hyperphosphatasemia; infancy

Introduction

ALP is a phosphohydrolase enzyme produced primarily in the liver, bone, and placenta with normally high concentrations in growing bone and in bile [1]. The serum levels of ALP depend on age, and normal ranges typically are higher in children than adults, due to physiologically higher osteoblastic activity. This elevation is seen during the rapid growth period in the first three months of life, then again with a twofold to threefold rise during puberty which coincides with adolescent growth spurt [1]. Serum ALP is a sensitive indicator of liver and bone disease in adults and children. Sometimes, a markedly elevated serum ALP is found in children during routine blood chemistry analysis or in patients with various childhood diseases. The condition has been termed transient hyperphosphatasemia of infancy and childhood. Transient hyperphosphataemia has not been found to be life-threatening and is classified as a benign phenomenon. The definition of BTH was delineated by Kraut et al [2] in 1985 using the following criteria: i) age of presentation <5 years ii) variable, unrelated symptoms iii) no other evidence for bone or liver disease on physical examination or laboratory findings iv) elevation of both bone and liver ALP isoenzymes v) a return to normal serum ALP levels within 4 months.

In this paper, we report four infants with transient increases in serum ALP, whose clinical and biochemical findings suggested the diagnosis of transient hyperphosphatasemia of infancy. In three of these infants, BTH was preceded by a a history of prematurity or a failure to thrive.

Case 1:

A 9- month-old female infant was found to have a high elevated ALP level at her routine health check-up at 7 months of age and was referred to the pediatric oncology outpatient clinic of our hospital by his physician. She was then transferred to our pediatric endocrinology unit for further evaluation of elevated ALP levels. Her past medical history was uneventful and her family history was unremarkable. She was

taking 400 IU/d vitamin D supplementation since birth. On physical examination, her growth parameters were normal for her age. She was in good general condition. She had no dysmorphic features, bone deformities or tenderness, and no hepatosplenomegaly. Laboratory examination revealed high ALP activity [2612 U/L (normal range:80-340 U/L)] with normal results of a serum creatinine (0,2mg/dl), aspartate aminotransferase (AST) (33 U/L), alanine aminotransferase(ALT) (15 U/L), gamma-glutamyl transferase (GGT) (26 U/L), electrolytes, calcium (Ca) (9,9 mg/dl), phosphorus(P) (5,5mg/dl), magnesium (Mg) (2,1mg/dl), 25-hydroxyvitamin D (25 OHD) (53,5ng/dl) and intact parathyroid hormone (iPTH) (21,6 pg/ml) levels. Left wrist X-ray revealed normal findings. The abdominal ultrasound was normal. Serological screening for Ebstein- Bar virus (EBV) and cytomegalovirus (CMV) were all negative. As there were neither laboratory nor clinical signs of liver and bone disease, TH was considered as the most likely diagnosis. The infant was checked 9 weeks later and at that time the serum ALP dropped to the normal value of 215U/L, confirming the diagnosis of HT (Table 1).

Patient No	1	2	3	4
Age (months)	9	12	3	10
Sex (F/M)	F	M	F	F
Clinical features	-	failure to thrive	failure to thrive	failure to thrive
Highest Serum ALP	2612	1248	1208	1084
Isoenzyme study	liver fraction of 63% bone fraction of 37% 0% other isoenzymes	liver fraction of 26%, bone fraction of 74% 0% other isoenzymes	-	-
Time (weeks) until normal value recorded	9	6	16	12

Table I: Clinical data of the infants with BTH

Case2:

A 12-month old male infant was referred to our pediatric endocrinology unit by his pediatrician for evaluation of increased ALP levels.

He was born at 34th weeks gestation age with a birth weight of 2550 g. He was taking vitamin D supplementation with a daily dose of 400IU/d since birth. His history revealed a cow milk allergy.

On examination revealed his length (70.3 cm) and weight (7200g) was also below 3rd percentile for age, suggesting failure to thrive. There were no dysmorphic features, bone deformities, or hepatosplenomegaly. Laboratory workup revealed the serum values of BUN, Cr, potassium, sodium, Ca, P, Mg, ALT, ALT, GGT were all within normal reference range as well as serum PTH and 25OHD levels. However, serum ALP was markedly increased at the level of 1248U/L (normal 80-340U/L).

ALP isoenzymes were determined as an iso-liver fraction (26%), iso-bone fraction (74%), and 0% for other isoenzymes.

EBV and CMV-specific antibody testing were all negative. Wrist X-ray was normal without any signs of rickets. The abdominal ultrasound was normal.

In both parents, serum ALP levels were found to be normal values ruling out hereditary hyperphosphatasemia.

Case 3:

A 3 month (42 weeks gestational age)) old girl infant with a complicated perinatal history (severe prematurity- 29th week of gestation, birthweight 830g, respiratory distress, artificial ventilation, grade1 intraventricular hemorrhage, suspected necrotizing enterocolitis) was referred to our pediatric endocrinology unit for evaluation and management of elevated serum ALP level. She was taking 800IU /d vitamin D supplementation and iron prophylaxis (3mg/kg /day) since birth. On physical examination, she was a well-nourished infant with normal vital signs and both weight and height below the 3rd percentile for age. There were no dysmorphic features, skeletal abnormalities, bony tenderness, conjunctival icterus, hepatosplenomegaly or other signs of chronic liver or bone disease Laboratory findings revealed high ALP level (1208 IU/L normal age-related 80-340) with otherwise normal values serum creatinine, AST, and ALT ruling out hepatic pathology. Serum calcium, phosphate, PTH, and 25-OHD levels were within the normal range. There were no rachitic changes on the wrist X-ray. Blood count revealed mild anemia. Abdominal and portal Doppler ultrasonography was normal. There was no evidence of cholestasis and bone disease that can explain the very high ALP levels. The patient was diagnosed with BTH. ALP levels returned to normal levels within four months.

Case 4:

A 10 month- old female infant was referred to our hospital for failure to thrive and delay in tooth extraction. She was a full-term baby with a birth weight of 2600g. She was taking 400U/d vitamin D supplementation since birth. On admission, her body weight was 6500 gr (< 3 centiles), body length 67 cm (<3 centile) and head circumference was 43 cm (<3 centile). Her systemic examination was unremarkable except growth parameters were below the 3rd percentile. Initial laboratory investigations revealed the serum values of creatinine, potassium, sodium, calcium, phosphate, magnesium, PTH, 25-OHD, ALT and AST were within the normal reference range, as well as normal X-ray of the wrist. The abdominal ultrasonographic scan was normal.

Family history was unremarkable. Serum ALP levels determined by both parents were found within the normal range, so hereditary hyperphosphatasemia was ruled out.

Repeat ALP level was also remarkably high (1384 IU/L) (normal 80-340U/L) suggesting BTH when considered together with clinical and laboratory findings. We undertook careful monitoring and observation without therapy or further extensive

examinations. Three months later, serum ALP decreased (140 IU/L) supporting the diagnosis of BTH.

Discussion

ALP is a phosphohydrolase and a membrane-bound metalloenzyme, responsible for removing P groups from many types of molecules, including nucleotides, proteins, and alkaloids. There are three tissue-specific isoenzymes (intestinal, placental, and placental-like) and tissue nonspecific ubiquitous isoenzymes compromising hepatic, bone, and renal isoforms [3]. Differences in electrophoretic mobility are used to identify the various isoenzymes, and the clearance of bone and liver ALP from plasma is usually rapid with a half-life of only 2 days [4]. The serum level of ALP depends on age, and the normal range typically is higher in children than adults, due to physiologically higher osteoblastic activity. In healthy adults, the major activity of ALP is represented by liver and bone isoforms while in healthy infants and children, as a result of growth, the serum rich in the bone isoform of ALP [3]. The differential diagnosis of high ALP in childhood includes bone disorders (rickets, osteomalacia, healing fractures, juvenile Paget's disease, bone tumors), hepatopathy (cholestasis, malignancy), kidney disease (chronic renal failure, renal tubular acidosis, and other tubulopathies), drug ingestion (co-trimaxol, antiepileptics) or BTH. The peak value of ALP in BTH is usually very high (5-30 fold above upper reference ranges) in comparison with the other causes of ALP elevation [1]. In this report, all our patients fulfilled the criteria for BTH described by Kraut et al [2] They were in the infancy period, had no evidence of bone and liver disease, their elevated ALP levels had been detected incidentally and ALP levels were normalized within 4 months (table1). Even though the underlying cause of BTH still is unknown, there is often a history of recent infection in subjects with BTH without any underlying chronic disease. The possible link to infection has been supported by a seasonal clustering of BTH to fall and winter months [5]. BTH was observed in siblings and in children who were hospitalized together, further suggesting the infections, most probably viral origin [6]. Common viral infections including gastroenteritis or respiratory infections [5] and specific infections such as enterovirus and Epstein –Barr virus have been reported in literatüre [6]. BTH has also been described in children with failure to thrive, leukemia, and lymphoma [3], after organ transplantation in adults [5]. The patients had neither history of recent infection nor evidence of clinical and laboratory findings of any infectious disease at the time of diagnosis of BTH. While the BTH was accompanied by a failure to thrive in three patients (patient 2, 3, and 4), the other patient was free of symptoms. Additionally, two patients had a history of prematurity.

Although the etiology and pathophysiology of BTH remain unclear, three mechanisms have been proposed as responsible for BTH including excessive synthesis or release of the enzyme from its tissue origin, activation of a normal amount of circulating enzymes, and impaired clearance of the enzyme from the circulation [3]. Out of these hypotheses, the last one, namely impaired clearance of ALP from the circulation which seems to be the most probable mechanism, This could be due to viral infection or excessive sialylation of the liver isoenzyme. The cause of increased sialic acid is unknown, but it may impair hepatic clearance of serum ALP [1]. It has been speculated that BTH develops either during the period of catch-up growth after weight loss or as a consequence of subclinical vitamin D insufficiency [7]. In a case-control study, growth parameters and blood levels of circulating calcium, magnesium, inorganic phosphate, parathyroid hormone, and vitamin D were similar in the subjects with transient hyperphosphatasemia and healthy controls [8]. In all our cases, serum levels of calcium, magnesium, phosphorus were all within the normal range as well as serum vitamin D and PTH levels, although three infants had failure to thrive.

Transient hyperphosphatemia affects both sexes equally. In a 2013 review of 733 subjects, the mean age of presentation of BTH was 18 months with no gender predominance [5]. Recently Ridefelt et al [9] reported that the prevalence of highly elevated serum ALP levels was 6.2 % in healthy children under 2 years of age in a cohort study. These children had ALP levels > 16.7µkat/l (>1000U/l) including 4 females and 2 males. All our cases aged less than 2 years consistent with literature findings but the female gender (3 girls) was found to be predominant as similar to the recent study [8].

Transient hyperphosphatemia of infancy and early childhood is a benign disorder, a biochemical rather than clinical abnormality, of multifactorial pathogenesis and transient character, with a good prognosis [3]. Transient hyperphosphatasemia usually diagnosed by excluding other diseases, which, may require extensive biochemical and radiographic studies, all adding significant costs for the health care system.

To prevent unnecessary tests and costs Otero et al [9] have proposed a new diagnostic flow chart for clinical practice. This flow chart uses a simple step-by-step strategy and suggests a'' wait and see'' approach if a child is under five years of age, has no evident clinical and laboratory features of bone and liver disease. In addition, Chu and Rosthild [10] have also updated Kraut's original diagnostic criteria recently. Accordingly, a presumptive diagnosis of BTH can be made in children having features as follows:

1. Significantly elevated alkaline phosphatase level (median: 9 times the upper limit of normal)
2. Age <5 years (median: 18 months)
3. History and physical examination not suggestive of bone and liver disease
4. Normal liver tests (AST, ALT,bilirubin, GGT)
5. Normal electrolytes, calcium, blood urea nitrogen and creatinine
6. ALP isoenzymes show an absolute elevation of both bone and liver fractions, but the relative predominace may be of bone, liver or mixed origin
7. Normal iPTH and vitamin D levels
8. Confirm BTH with a normal ALP level repeated within 3-4 months (median: 10 weeks)

In conclusion, primary care physicians and pediatricians should keep in mind BTH of infancy and early childhood in the differential diagnosis of a markedly elevated serum ALP, especially it is an isolated finding to avoid unnecessary frequent diagnostic procedures and therapeutic intervention.

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