Türk Pediatri Arşivi
Turkish Archives of Pediatrics

Case Report

Benign transient hyperphosphatasemia in an infant during zinc supplementation

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Cite this article as: Sönmez AB, Arifoğlu İ, Yıldırım A, Tütüncüler F. Benign transient hyperphosphatasemia in an infant during zinc supplementation. Turk Pediatri Ars 2018; 53: 120-3.

Abstract

Benign transient hyperphosphatasemia is characterized by a significant increase in alkaline phosphatase levels, which is detected incidentally in infancy and children without underlying bone and liver disease. This condition is a biochemical disorder rather than a clinical disorder and resolves within a short duration. Recognition of this entity by pediatricians is important to avoid unnecessary investigations. Here, we report an infant who was diagnosed as having benign transient hyperphosphatasemia based on clinical and laboratory findings who had increased alkaline phosphatase levels during zinc supplementation, with the aim of highlighting benign transient hyperphosphatasemia in infancy and childhood.

Keywords: Alkaline phosphatase, benign transient hyperphosphatasemia, infant, zinc

Introduction

Alkaline phosphatase (ALP) is a zinc-containing glycoprotein consisting of four isoenzymes, which are produced mainly in the bone, liver, intestines, and placenta. The serum ALP levels vary by age. ALP levels, which are slightly increased in the first three months of life, increase 2-3-fold in adolescence, during which a growth spurt occurs and remains higher compared with adulthood (1). Although serum ALP levels are a sensitive marker for bone and liver diseases in children and adults, a more than five-fold increase and even 20-70-fold increases may be found incidentally in the absence of specific clinical and laboratory findings of bone and liver diseases in children. This condition with unclear etiology, which is called benign transient hyperphosphatasemia (BTH) and is mostly observed following a viral diarrhea or respiratory tract infection, is a biochemical problem rather than being an illness (2). Physicians' awareness of BTH will prevent excessive and unnecessary tests from being performed because of concerns in the presence of increased ALP levels in infants or children. Here, we present an infant who was incidentally found to have excessively increased ALP levels in the one-month period during which she used zinc.

Case

A 10-month-old female patient was referred to Trakya University Faculty of Medicine, Pediatrics Outpatient Clinic, with the objective of investigation and treatment when increased ALP levels were found in laboratory tests ordered by her pediatrician, who was following the patient because of closed fontanelle and eruption of six teeth in one month. In the history, it was learned that she was born by spontaneous vaginal delivery at the 40th gestational week with a birth weight of 3900 g, received prophylactic vitamin D at a dose of 400 IU/day from birth, her neuromotor development was compatible with her peers, her vaccinations were administered appropriately, she had no history of illness or long-term

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Received: 29.12.2015 **Accepted:** 27.12.2016

DOI: 10.5152/TurkPediatriArs.2017.3158

Table 1. Laboratory findings at the time of diagnosis and in the follow-up

Laboratory findings	Ca (mg/dL)	p (mg/dL)	ALP (IU/L)	PTH (pg/mL)	
Patient	At the time of diagnosis	11	5.6	9842	32.7
	At the first week	9.7	5.1	8398	
	At the third week	9.4	5.4	7002	
	At the seventh week	9.8	5.4	538	31
Treatment			Follow-up		
Mother		9.6	5.4	242	
Father		8.9	5.9	242	
Normal values		8.8-10.8	3.8-6.5	142-500	15-68.3

ALP: alkaline phosphatase; Ca: calcium; P: phosphorus; PTH: parathyroid hormone

use of any medication. Zinc (Zn) treatment was initiated about one month previously by the pediatrician who followed her up and she was currently receiving oral Zn at a dose of 40 mg/day. In the familial history, consanguineous marriage was not present and there was no family member with metabolic bone disease. The physical examination was as follows: weight: 9500 g (75-90p), height:75 cm (75-90 p), head circumference: 44 cm (10-25p), the anterior fontanelle was open and she had nine teeth. No hepatomegaly or splenomegaly was found in the abdominal examination. The findings of the musculoskeletal system and other systems were found to be normal. The laboratory tests were as follows: complete blood count and complete urinalysis: normal, serum aspartate aminotransferase (AST) and alanine transaminase (ALT) levels were normal (32 IU/L and 15 IU/L, respectively), ALP level was 9842 IU/L (excessively increased). The serum calcium (Ca), phosphorus (P) and parathyroid hormone (PTH) levels were found as normal (Table 1). The serum 25-hydroxyvitamin D3 (25-OHD) level (61 ng/mL) was normal. The serologic tests in terms of cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections were negative. Abdominal ultrasonography was normal. On wrist radiography, the bone age was compatible with one year and six months and the metaphyses had normal appearance. The serum Zn level was 540 (normal: 75-120) mg/dL. The parents' Ca, P and ALP levels, which were measured to exclude familial hyperphosphatasemia were found as normal (Table 1). The alkaline phosphatase isoenzyme test revealed that the increased ALP originated from the bone by 100% (Figure 1). Benign transient hyperphosphatasemia was considered because the patient was in infancy, the increased ALP level was incidentally found and there were no findings suggestive of hepatic or metabolic bone disease either in the physical examination or in the laboratory tests. It was thought that Zn intake might have caused ALP elevation because zinc was a cofactor for ALP and the patient had an increased serum Zn level. Zn supplement was discontinued. Monitoring in terms of ALP levels was initiated. In the follow-up, the ALP levels in the first, second, and third weeks were found to be increased, whereas the ALP level in the seventh week was normal (Table 1). The fact that the increased ALP level returned to normal within four months supported the diagnosis of BTH.

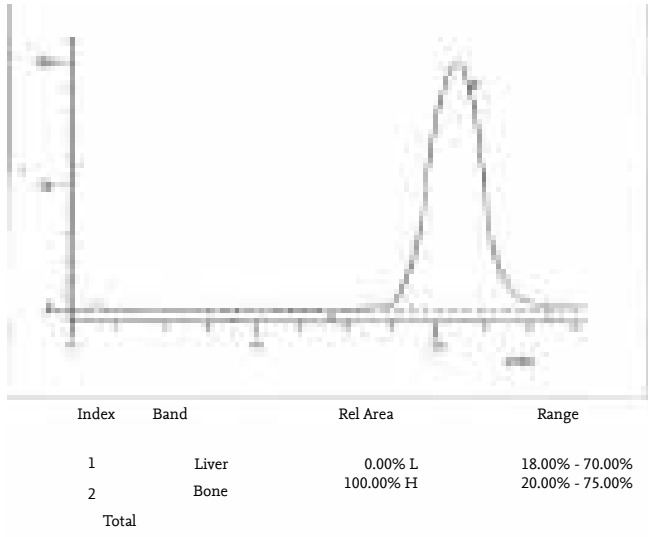

Figure 1. Alkaline phosphatase isoenzyme electrophoresis shows bone-derived increase in alkaline phosphatase

Discussion

In healthy adults, the greatest part of serum ALP levels is constituted from liver and bone isoenzymes, whereas the majority of serum ALP is bone-derived in children as a result of growth. In children, the differential diagnosis of increased ALP should include bone diseases (such as rickets, osteomalacia, recovery period in fractures, juvenile Paget disease, and bone tumors), hepatic

diseases (e.g., cholestasis, malignancy), renal diseases (e.g., chronic renal failure, renal tubular acidosis and tubulopathies), drug use (e.g., cotrimoxazole and antiepileptics) or BTH (3). BTH, which manifests with a transient excessive increase in serum ALP levels in the absence of hepatic or bone disease was first reported in adults and subsequently in children (1, 2). The diagnostic criteria of the picture defined as BTH of infancy or childhood are as follows: age younger than five years in patients with increased ALP level, absence of findings belonging to hepatic or bone disease on physical examination or in laboratory tests, confirmation that ALP is bone or liver-derived by isoenzyme test, and return to normal ALP levels in four months (1-3, 6). When our patient was evaluated in terms of the BTH diagnostic criteria, it was found that she was an infant aged 10 months and increased ALP was found incidentally. There were no findings suggestive of hepatic or metabolic bone disease either in the physical examination or in the laboratory tests. Isoenzyme typing revealed that the increased ALP was 100% bone-derived and the serum ALP level returned to normal in the second month of follow-up. With these findings, our patient met all diagnostic criteria of BTH.

BTH has been defined as a biochemical problem rather than a clinical illness because it is mostly found in infants with viral infection or incidentally during routine biochemical investigations (3). The absence of findings suggestive of metabolic bone disease in the history and in a physical examination and normal laboratory results except for increased ALP (>1000 IU/L) supported that BTH was a biochemical problem. BTH is observed with a similar frequency in boys and girls (1-3,8). Its prevalence ranges between 2.8% and 5.1% depending on the ALP values used for the diagnosis (9). Most patients diagnosed as having BTH are below the age of two years (1-9). Our patient was a girl and younger 2 years, which is below the age range in which BTH is observed most frequently.

Although the underlying cause of BTH is not clearly known, many factors have been proposed to be involved in the etiology. The most important causes are past viral respiratory infections and gastrointestinal infections. In addition, BTH may be observed in the presence of inadequate weight gain, with the use of some drugs, and following hepatic or renal transplantation (3). BTH is observed more commonly in autumn and winter months during which viral infections occur frequently (1,2, 4-7). Antibodies against many different types of enteroviruses (Echo 22, 12, Enterovirus 71, Coxsackie B4 and B5) were found in the serum in patients with BTH occurring after lower respiratory tract infections including bronchiolitis and pneumonia (5). In our patient, no recent gastrointestinal or upper respiratory tract infection was described. The serologic tests for CMV and EBV, which are the agents of the main viral infections, were negative. Although a history of recent drug use was not found, the patient had received Zn supplementation at a dose of 40 mg/day for the last one month and the serum Zn level was higher than normal. Alkaline phosphatase is a glycoprotein enzyme that contains four Zn ions (1). A recent study showed that oral Zn supplementation at a dose of 10 mg/day in school-age children caused a significant increase in serum ALP levels (10). It was thought the increased ALP might have been arisen from Zn intake because the increase in ALP was found during the period when Zn supplementation was used, the serum Zn level was increased, and Zn was a cofactor for ALP. However, it cannot be definitively stated that Zn supplementation caused the increase in ALP because the serum Zn level could not be measured after Zn supplementation was discontinued, especially in the period when the ALP level returned to normal. In the literature, no case of BTH associated with the use of Zn has been reported up to the present time.

Although the etiology of BTH has not been defined, Crofton (4) reported that an increase in ALP production caused this condition. In the study conducted by Crofton, it was found that increased ALP was liver- and bone-derived and the level of 25-hydroxyvitamin D was also increased in 25 children who were diagnosed as having BTH (4). Both bone- and liver-derived ALP is encoded by the same gene located on the 1st chromosome. Therefore, it may also increase the production of 25-hydroxyvitamin D (2). However, other studies have not found an increase in markers directed to bone turnover (3,9). Therefore, it has been proposed that increased ALP arise from the lack of removal of ALP from the circulation as a result of inadequate destruction of the enzyme rather than increased production. The presence of fragmented parts of bone and liver isoenzymes of ALP and atypical ALP in serum supports the hypothesis of inadequate removal of ALP from the circulation during viral infections (9). In many studies (1,2-6,9), it has been reported that the time required for ALP levels to return to normal is approximately three months, and some studies suggested that this time period could extend up to six months (2,7,8). In our patient, ALP levels

returned to normal in the seventh week of follow-up, in accordance with the literature.

Two rare clinical conditions including benign familial hyperphosphatasemia (BFH) and chronic idiopathic hyperphosphatasemia (CIH) are included in the differential diagnosis of BTH. BFH is inherited in an autosomal dominant pattern and increased ALP in the absence of clinical findings is specific for this condition (3). CIH is a rare condition that manifests as an increase in serum ALP and urinary hydroxyproline levels in association with diffuse, symmetrical, progressive bone disorders. In our patient, the diagnosis of BFH was excluded with normal serum ALP levels found in the parents. In addition, CIH was not considered because the physical examination revealed no problems related to the skeletal system and the increased ALP level returned to normal in a short time.

In conclusion, BTH is a rare biochemical problem, but it should be considered in cases in which specific laboratory findings of bone and liver diseases do not accompany increased ALP levels that are found incidentally in the absence of clinical findings in infants and children. Awareness of BTH among pediatricians and family physicians will prevent unnecessary investigations from being performed because of excessive concerns.

Informed Consent: Written informed consent was obtained from the parents of the patient.
Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.T.; Design - A.B.S., F.T.; Supervision - F.T.; Funding A.B.S., F.T.; Materials - A.B.S., İ.A., A.Y.; Data Collection and/or Processing - A.B.S., F.T.; Analysis and/or Interpretation - A.B.S., F.T.; Literature Review - A.B.S., F.T.; Writing - A.B.S., F.T.; Critical Review - F.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Tolaymat N, de Melo MC. Benign transient hyperphosphatasemia of infancy and childhood. South Med J 2000; 93: 1162-4. [CrossRef]
2. Carroll AJ, Coakley JC. Transient hyperphosphatasaemia: an important condition to recognize. J Paediatr Child Health 2001; 37: 359-62. [CrossRef]
3. Kutilek S, Bayer M. Transient hyperphosphatasemia–where do we stand? Turk J Pediatr 1999; 41: 151-60.
4. Crofton PM. What is the cause of benign transient hyperphosphatasemia? A study of 35 cases. Clin Chem 1988; 34: 335-40.
5. Suzuki M, Okazaki T, Nagai T, Töro K, Setonyi P. Viral infection of infants and children with benign transient hyperphosphatasemia. FEMS Immunol Med Microbiol 2002; 33: 215-8. [CrossRef]
6. Teitelbaum JE, Laskowski A, Barrows FP. Benign transient hyperphosphatasemia in infants and children: a prospective cohort. J Pediatr Endocrinol Metab 2011; 24: 351-3. [CrossRef]
7. Dori N, Levi L, Stam T, Sukhotnik I, Shaoul R. Transient hyperphosphatasemia in children revisited. Pediatr Int 2010; 52: 866-71. [CrossRef]
8. Gualco G, Lava SA, Garzoni L, et al. Transient benign hyperphosphatasemia. J Pediatr Gastroenterol Nutr 2013; 57: 167-71. [CrossRef]
9. Huh SY, Feldman HA, CoxJE, Gordon CM. Prevalence of transient hyperphosphatasemia among healthy infants and toddlers. Pediatrics 2009; 124: 703-9. [CrossRef]
10. Rocha ED, de Brito NJ, Dantas MM, Silva Ade A, Almeida Md, Brandeo- Neto J. Effects of zinc supplementation on GH, IGF1, IGFBP3, OCN, and ALP in zinc-deficient children. J Am Coll Nutr 2015; 34: 290-9.