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ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2024;13(1):116-9

Retrospective evaluation of cases of benign transient hyperphosphatasemia

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Received 26 August 2023; Accepted 06 December 2023
Available online 15.02.2024 with doi: 10.5455/medscience.2023.08.172

Abstract

This study aimed to evaluate the demographic, clinical, and laboratory characteristics of children with benign transient hyperphosphatasemia (BTH) and to increase awareness of BTH. Children with BTH followed up in a tertiary pediatric endocrinology outpatient clinic were included in this retrospective study. Children who were aged under 5 years, who had no evidence of liver, kidney, or bone disease, who had serum total alkaline phosphatase (ALP) levels above 1000 IU/L, and whose ALP values resolved within 4 months, were included in the study. The study included 10 infants and children (4 females) with BTH who were referred to our clinic during 1 year for high ALP levels. The mean age was 2.4±0.5 years. The mean weight SDS was -0.24±1.27 and the mean height SDS was -0.51±0.67. The mean ALP level was 2.395±934 IU/L. The mean normalization time for serum ALP was 2.4±1.1 months. Benign transient hyperphosphatasemia is an entity that occurs in healthy infants and children without evidence of liver or bone disease and resolves without intervention.

Keywords: Alkaline phosphatase, isoenzyme, infection, benign transient hyperphosphatasemia

Introduction

Alkaline phosphatases (ALP) are transmembrane metalloenzymes attached to cell plasma membranes that generate inorganic phosphate from organic substrates. Serum total ALP consists of a group of isoenzymes that are expressed in the liver, bone, intestines, and placenta. The highest levels of ALP are detected during infancy and adolescence due to high osteoblastic activity. The bone fraction of ALP is between 77% and 89% in children and between 58% and 67% in adults. Serum ALP activity is used as a biochemical marker to evaluate high osteoblastic activity in bone disorders, primary hyperparathyroidism, fracture, rickets, osteomalacia, bone malignancies, and Paget's disease. Also, drugs and liver and kidney diseases can cause high ALP levels [1,2].

Benign transient hyperphosphatasemia (BTH) is characterized by transiently increased serum activity of ALP, which is most often seen in children under 5 years of age. Serum ALP levels that rise in BTH without any kidney, bone, or liver pathology returns to normal levels within weeks and months. There are no signs or symptoms of bone or liver diseases associated with increased ALP, predominantly the bone or liver isoform [3]. According to the criteria developed by Kraut et al., the diagnosis of BTH is based on elevations in the activity of bone and/or liver ALP isoenzymes in children under 5 years of age, in the presence of unrelated variable symptoms, no evidence of bone or liver disease on physical examination and/or laboratory investigations, and normalization within four months [4]. Since 80% of the cases return to normal within 4 months and do not cause clinical sequelae, they are defined as "transient" and "benign" [5].

This study aimed to evaluate the demographic, clinical, and laboratory characteristics of children found to be suffering from BTH to increase awareness of this completely benign entity and to prevent cases from undergoing unnecessary examinations and procedures.

Material and Methods

This retrospective study included 10 children with BTH who were followed up in the pediatric endocrinology outpatient clinic, at Ordu University, Training and Research Hospital between July 2022 to June 2023.

CITATION
Ozer Y. Retrospective evaluation of cases of benign transient hyperphosphatasemia. Med Science. 2024;13(1):116-9.

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DOI: 10.5455/medscience.2023.08.172

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ordu University, Faculty of Medicine, Clinical Research Ethics Committee (approval date: 04/08/2023, number:2023/204).

The inclusion criteria for our study were as follows: (1) being under 5 years of age, (2) elevated serum total ALP levels above 1000 IU/L, (3) no evidence of liver or bone disease, and (4) resolved ALP values within 4 months. The children, who had evidence of chronic disease (such as liver, bone, or renal disease), who used medications that might affect serum ALP levels, and whose ALP value did not resolve within 4 months, were excluded from the study.

Demographic, clinical, laboratory and radiologic findings of the subjects with BTH were obtained from medical records. The child metrics online calculator program (http://www.childmetrics.com) was used for the calculation of standard deviation scores (SDS) of anthropometrics according to the Turkish child growth reference data [6].

Statistical analyses were performed using the IBM SPSS 21.0 program (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to report the demographic and clinical variables of the subjects. The continuous variables were presented as mean±standard deviation. The categorical variables were presented in percentages.

Results

We describe 10 infants and children diagnosed with BTH, who were referred to our clinic during a 1-year time period for elevated ALP levels. The mean age was 2.4±0.5 (range, 1.6-3.2) years. Forty percent (n=4) of the study participants were female. The mean weight SDS was -0.24±1.27 and the mean height SDS was -0.51±0.67. All participants had a serum ALP level of >1000 IU/L (range, 1,002-4,014 IU/L). The mean ALP level was 2.395±934 IU/L. None of the children with BTH had a physical examination finding suggesting evidence of bone or liver disease. All study participants had a normal range of alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, calcium, phosphate, parathyroid hormone, and 25-hydroxyvitamin D. The mean normalization period for serum ALP was 2.4±1.1 (range, 1.1-4) months. The demographic and clinical features of the study participants are summarised in Table 1.

Table 1. Descriptive characteristics of 10 patients with benign transient hyperphosphatasemia

Subject	Age (years)	Gender	Clinical features	Weight SDS	Height SDS	ALP (IU/L)	ALT (IU/L)	AST (IU/L)	GGT (IU/L)	Ca (mg/dL)	P (mg/dL)	PTH (pg/mL)	25(OH)D (ng/mL)	Left wrist graph	Normalization period (months)
Normal range						<350	0-41	0-40	3-36	8.8-10.8	4.5-6.5	15-61	>20		
1	1.6	F	Delay in closure of fontanelle	-0.3	-0.74	1002	8	41	6	10.7	5.3	28	29	Normal	1
2	2.7	M	Normal	-0.75	-0.53	2311	22	39	6	10.2	5.5	25	33	NA	2
3	2.7	M	Normal	-0.25	-0.27	1503	29	36	7	10.4	5.9	30	44	NA	2
4	2.8	F	Normal	2.8	-1.16	2500	13	36	7	9.5	5.6	25	29	NA	1.3
5	1.8	F	Normal	0.21	-0.04	1178	17	33	11	10.2	5.1	15	38	NA	2
6	2	M	Normal	-1.78	-1.78	4014	12	30	9	10.2	5.4	42	23	Normal	2
7	1.9	M	Upper respiratory tract infection	0.51	0.71	2968	16	30	9	10.2	5.3	35	28	NA	4
8	3.2	F	Normal	-0.91	-0.70	2916	13	25	10	10.3	5.5	27	32	NA	1.1
9	2.1	M	Normal	-1.33	-0.25	2562	23	62	9	9.8	5.2	32	31	NA	4
10	2.8	M	Normal	-0.57	-0.1	3000	17	35	8	10.1	5.6	29	35	NA	3

F: female, M: male, SDS: standard deviation score, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase, Ca: calcium, P: phosphate, PTH: parathyroid hormone, 25(OH)D: 25-hydroxyvitamin D, NP: normalization period, NA: Not available,

In the majority of the cases included in our study, elevated serum ALP was detected as an incidental finding during routine screening. One subject had a history of upper respiratory tract infection before referral. Subject 2 and Subject 3 were twins. ALP elevation was detected during evaluations before the elective operation for circumcision. They were diagnosed at the same time and their ALP levels normalized in the same period. While four subjects were diagnosed in the autumn and winter seasons, 6 subjects were diagnosed in the spring and summer seasons.

The bone isoenzyme of ALP of Subject 10 with a total ALP level of 3,000 IU/L was studied, and it was measured to be 91.3%. Three months later, serum ALP was decreased to 225 IU/L, and the ALP bone isoenzyme was measured to be 61.3%.

Discussion

Benign transient hyperphosphatasemia is an entity characterized by transient elevation of serum ALP levels in children younger than five years of age without evidence of bone or liver disease. In this retrospective study, we describe 10 otherwise healthy

DOI: 10.5455/medscience.2023.08.172

children with BTH. In our study, we found that BTH was seen at a mean age of 2.4±0.5 years and resolved in a mean time of 2.4±1.1 months. The mean age and normalization period of serum ALP levels of the subjects in our study were similar to other studies published in the literature [3]. In a recent study evaluating 382 infants and children diagnosed with BTH, the age range was between 2 months and 14 years, and 87% of the subjects were younger than 24 months. In the same study, the normalization period for serum ALP level was between 4 and 28 weeks. However, it mostly returned to the normal range within 4 to 12 weeks [2]. Calcium, phosphorus, parathyroid hormone, and 25-hydroxyvitamin D levels were normal in all subjects, similar to previous studies [7,8]. This non-gender predominance entity is mostly seen in infants and children under 5 years of age, but BTH has also been reported in older children and adults. In a meta-analysis review, elevation in ALP was reported to persist for more than 20 weeks in 17% of the cases. In addition, it was reported that BTH did not recur in childhood. When 733 cases with BTH were evaluated, the presence of chronic disease was reported in 13% (n=92) of the cases. While the majority of the subjects with chronic disease were solid organ transplant recipients, the others suffered from malignancy, immunodeficiency, and congenital diseases. Benign transient hyperphosphatasemia was associated with either incidental or acute infections (>60%) in those without chronic disease [9].

In a meta-analysis published in 2013, the prevalence of BHT in infants aged between 2 and 24 months was reported to be between 1.1% and 3.5% [9]. In a cohort of 321 healthy children, the prevalence of BTH was 2.8% [7]. However, BTH has often been associated with incidental laboratory results in otherwise healthy children who presented for other reasons, such as infection. Likewise, publications on BTH in the literature are case reports or retrospective studies defined by incidental laboratory findings [9]. Considering its asymptomatic nature, however, it can be assumed that the true prevalence of this entity is much higher. We were diagnosed 10 cases of BTH during a 1-year period at a reference hospital found in a region with a population 765,000 people.

Although various theories have been proposed on the etiology of BTH, the underlying mechanism has not been determined. Many cases with BTH have a history of recent viral infection, with a seasonal peak reported in autumn and winter [2]. Demonstration of this relationship in other studies supports its relationship with infectious diseases [8,10,11]. Mostly, a relationship between respiratory tract infections and BTH has been reported [12]. Suzuki et al. demonstrated the association of BTH with enteroviruses (Echo 22, Entero 71, and Coxsackie B4) [13]. Respiratory syncytial virus, rotavirus, human bocavirus, Epstein-Barr virus, and SARS-CoV-2 are other pathogens that have been shown to be associated with BTH [14-18]. Concurrent BTH was reported in twin or non-twin siblings [11,13]. Subject 2 and Subject 3 with BTH in our cohort were twins. The simultaneous elevation and resolution of ALP in our twin cases support the hypothesis that exposure to viral infection is involved in the etiology, although this has not been proven. On the other hand, Huh et al. reported that there was no seasonal trend in 9 children diagnosed with BHT [7]. Consistent with the study of Huh et al., the lack of seasonal clustering in our cohort may be due to the small number of subjects. Seasonal distribution and the presence of other affected individuals in the family strongly support its association with infections. Although BTH represents a postinfectious disease, a causal mechanism with prior infection could not be demonstrated [9]. It has also been argued that these findings may be due to a genetic predisposition related to the response against infections [11].

The serum ALP level is the sum of isoforms from the liver, bone, intestine, and placenta. In healthy individuals, separate bands are observed from the liver (16-84%) and bone (20-75%) sources of ALP. The bone isoform is often predominant in the pediatric population [19]. As a result of the isoenzyme evaluation of the cases diagnosed with BTH, it was reported that the increased ALP level may be of bone, liver, or mixed origin [9]. Dursun et al. reported elevated "bone-specific ALP isoenzyme" levels (>90%) in 11 of 15 cases [20]. When Suziki et al. analyzed the ALP isoenzymes by electrophoresis, they showed that the ALP isoenzyme had a distinctive isoform band at the fast K2 position, between K1 (biliary ALP) and K2 (liver ALP). Analysis of sialidase-treated samples showed that the specific ALP in BTH was liver-type ALP with excess sialic acid [13]. In addition, Gualco et al. claimed that ALP isoenzyme evaluation was not useful in clinical practice for the follow-up of cases of BTH [9].

Several hypotheses have been proposed to elucidate the underlying etiopathogenesis of BTH. Increased production, increased activation, or decreased clearance of ALP in tissues are the proposed mechanisms responsible for BTH [3]. It has been argued that circulating ALP may result from sialylation of the enzyme resulting in decreased hepatic clearance [7]. It has been claimed that the transient increase in bone resorption triggered by infections may be involved in the etiology since the increase in bone resorption is associated with bone formation. The presence of normal bone turnover was demonstrated by bone turnover biomarkers against hypotheses suggesting increased bone turnover as indicated by elevated urinary hydroxyproline levels in BTH [3].

The limitations of our study were that it was a retrospective study, the number of the subjects was small, and evidence related to infectious diseases could not be detected. Also, ALP isoenzymes were not studied in all subjects. Prospective studies involving larger populations will be necessary to determine the true incidence of BTH and to elucidate the mechanisms associated with viral infections.

Conclusion

In conclusion, BTH is an entity that occurs in healthy infants and children and resolves without any intervention. Benign transient hyperphosphatasemia is a diagnosis of exclusion and other

DOI: 10.5455/medscience.2023.08.172

causes, that may cause elevated ALP, should be excluded. Despite the concerns caused by high ALP, effective communication is important in these asymptomatic cases to increase awareness of physicians, avoid unnecessary additional research and reduce the anxiety of families when evaluated together with laboratory results that do not suggest liver or bone disease.

Conflict of Interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical Approval

This study has been approved by the Ordu University, Faculty of Medicine, Clinical Research Ethics Committee (approval date: 04/08/2023, number:2023/204).

References

1. Turan S, Topcu B, Gökçe İ, et al. Serum alkaline phosphatase levels in healthy children and evaluation of alkaline phosphatase z-scores in different types of rickets. J Clin Res Pediatr Endocrinol. 2011;3:7-11.
2. Shkalim Zemer V, Hoshen M, Levinsky Y, et al. Benign transient hyperphosphatasemia in infants and children: a retrospective database study. Eur J Pediatr. 2023;182:3211-6.
3. Kutilek S, Cervickova B, Bebova P, et al. Normal bone turnover in transient hyperphosphatasemia. J Clin Res Pediatr Endocrinol. 2012;4:154-6.
4. Kraut JR, Metrick M, Maxwell NR, Kaplan MM. Isoenzyme studies in transient hyperphosphatasemia of infancy. Ten new cases and a review of the literature. Am J Dis Child. 1985;139:736-40.
5. Chu AS, Rothschild JG. Update on benign transient hyperphosphatasemia: recognizing an underappreciated condition. Clin Pediatr (Phila). 2016;55:564-6.
6. Demir K, Özen S, Konakçı E, et al. A comprehensive online calculator for pediatric endocrinologists: ÇEDD Çözüm/TPEDS metrics. J Clin Res Pediatr Endocrinol. 2017;9:182-4.
7. Huh SY, Feldman HA, Cox JE, Gordon CM. Prevalence of transient hyperphosphatasemia among healthy infants and toddlers. Pediatrics. 2009;124:703-9.
8. Crofton PM. What is the cause of benign transient hyperphosphatasemia? A study of 35 cases. Clin Chem. 1988;34:335-40.
9. Gualco G, Lava SAG, Garzoni L, et al. Transient benign hyperphophatasemia. J Pediatr Gastroenterol Nutr. 2013;57:167-71.
10. Teitelbaum JE, Laskowski A, Barrows FP. Benign transient hyperphosphatasemia in infants and children: a prospective cohort. J Pediatr Endocrinol Metab. 2011;24:93-5.
11. Behúlová D, Bzdúch V, Holesová D, et al. Transient hyperphosphatasemia of infancy and childhood: study of 194 cases. Clin Chem. 2000;46:1868-9.
12. Sakurai Y, Higashiguchi T. Transient hyperphosphatasemia: possible association with pediatric acute respiratory infection. Pediatr Investig. 2021;5:94-8.
13. Suzuki M, Okazaki T, Nagai T, et al. Viral infection of infants and children with benign transient hyperphosphatasemia. FEMS Immunol Med Microbiol. 2002;33:215-8.
14. Erat T, Atar M, Kontbay T. Transient benign hyperphosphatasemia due to COVID-19: the first case report. J Pediatr Endocrinol Metab. 2021;34:385-7.
15. Goto M. Is respiratory syncytial virus one of the causative agents for transient hyperphosphatasemia?. Rinsho Byori. 2002;50:1146-9.
16. Koike Y, Aoki N. Benign transient hyperphosphatasemia associated with Epstein-Barr virus infection. Pediatr Int. 2013;55:667-8.
17. Akcaboy M, Zorlu P, Acoglu EA, et al. Human bocavirus infection associated transient benign hyperphosphatasemia in an infant. Indian J Pediatr. 2016;83:902-3.
18. Marrali V, Cutaia A, Zarbo C, et al. Transient idiopathic hyperphosphatasemia in a rotavirus infection. Minerva Pediatr. 1990;42:559-60.
19. Solé-Enrech G, Cano-Corres R, Nuez-Zaragoza E, et al. Benign transient hyperphosphatasemia: two case reports. Clin Biochem. 2021;91:67-9.
20. Dursun F, Kirmizibekmez H. A case series of benign transient hyperphosphatasemia from a pediatric endocrinology reference health facility in Turkey. Pan Afr Med J. 2018;30:206.