BENIGN TRANSIENT HYPERPHOSPHATASEMIA OF CHILDHOOD

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ABSTRACT

Objective: To report a case series of benign transient hyperphosphatasemia of infancy (BTHI). Description (Case report): A series of four girls with BTHI is described. The age range was 11-45 months (median: 13 months). At diagnosis, the serum alkaline phosphatase was 1.1- 6.1 times (median: 1.36) above the reference values. Return to normal values occurred between 7-11 months (median: 9 months). There was no evidence of bone, liver, or endocrine disease, and none of the patients were using medications that could lead to serum alkaline phosphatase level rise. One of the patients presented with upper airway infection before the hyperphosphatasemia was diagnosed. Aspartate-aminotransferase, alanine-aminotransferase, calcium, phosphorus and magnesium levels were normal in all children. Parathyroid hormone was normal in the three patients tested. In two patients, the investigation for hepatitis A, B and C was negative. Alkaline phosphatase was normal in three of four parent couples tested. Comments: BTHI is a self-limited and benign disease with spontaneous resolution affecting children younger than five years old, without clinical or laboratorial evidence of osseous, hepatic and endocrine disorders. The etiology remains unclear. BTHI potential should be considered in the diagnostic evaluation of hyperphosphatasemia in order to avoid unnecessary tests.

Keywords: *Hypophosphatasia. Alkaline phosphatase. Child.*

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INTRODUCTION

Benign transient hyperphosphatasemia of childhood (BTHC) affects children younger than five years, with no evidence of bone, liver or endocrine disease, being characterized by a sudden and transient rise of serum alkaline phosphatase in an otherwise healthy child.[1-3] Alkaline phosphatase rise may reach serum levels 2-50 times higher than reference values for the age group.[1,3] The return to normality occurs in an average period of four months.[1,3] Its etiology is still unknown, but the reduced enzyme clearance on blood stream has been regarded as the most likely mechanism.[2-3] There are reports in literature correlating alkaline phosphatase transient rise to upper respiratory tract infections or fever accompanied by diarrhea.[4]

Diagnosis is usually provided accidentally when laboratory tests are required for assessing other conditions.

In view of the benign nature of this condition and its various differential diagnoses, which can be very expensive and invasive, this article was designed to describe a series of BTHC cases.

CASES REPORT

Between June 2005 and June 2007, four children were identified by medical files review with confirmed diagnosis of BTHC who have received care at the Pediatric Endocrinology Outpatient Facility of Hospital São Rafael, Salvador – Bahia. The initial alkaline phosphatase rise was detected by children's pediatricians in routine evaluations, therefore, they have been referred to us for etiological investigation. The clinical-laboratorial assessment performed on these children followed the protocol used in our service for investigating persistent hyperphosphatasemia. All children were females. Age group ranged from 11 to 45 months (median: 13 months). Alkaline phosphatase was high in 1.1-6.1 times (median: 1.36 times) and the return to normal levels occurred between 7 and 11 months (median: 9 months) after initial diagnosis. Clinical history was negative for bone, liver and endocrine diseases, as well as for use of drugs associated to alkaline phosphatase rises. One patient presented with upper respiratory tract infection preceding hyperphosphatasemia diagnosis. Alanine-aminotransferase (ALT), aspartate-aminotransferase (AST), calcium, phosphorus, and magnesium levels were normal in all patients. (Table 1). Parathyroid hormone (PTH) levels were normal in 3 patients (75%) tested. In two patients, the investigation for hepatitis A, B and C was negative. Alkaline phosphatase was normal in three of four parents tested. (Table 2)

Clinical and laboratorial data were collected by respecting the secrecy and confidentiality of data, according to the premises governing ethics in research.

DISCUSSION

Alkaline phosphatase is produced on several tissues, such as: bones, liver, kidneys, bowel, lungs, placenta, vascular bed, neu-

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trophils and activated T-lymphocytes.[2,3,5] In pediatric populations, under physiological conditions, alkaline phosphatase is composed by 85% of bone fraction and 15% of hepatic fraction.[2]

It represents a group of four isoenzymes (bone, liver, bowel and placenta) taking part of key metabolic processes, such as: bone formation, fat transportation, renal and intestinal phosphate transportation, IgG transportation during pregnancy and pancreatic chlorine channels regulation.[2-3]

Serum levels vary according to age, gender and pregnancy status. In infants in their first three months of life, and in adolescents, serum levels can be 3-6 times as high as adult values.[2,3,5] Therefore, laboratory description of reference values according to these parameters is critical.

The most common causes for a pathological rise of alkaline phosphatase in pediatrics are osteoblastic diseases, rachitis, hyperparathyroidism, congenital defects, blood diseases, Crohn's disease, immunodeficiency, use of antibiotic, chemotherapeutic and anticonvulsant agents of hepatic metabolism (*e.g.*, phenobarbital, sodium valproate, sulfametoxazol-trimethopim), chemotherapy, lymphoma, and, less frequently, Crohn's disease, pulmonary and kidney infarct.[6] None of the patients reported here showed any of these conditions.

It is speculated that the excessive synthesis of alkaline phosphatase in BTHC occurs as part of the inflammatory response at the acute phase or of the reduced hepatic clearance due to an increased sialination.[6-7] Viral (*e.g.*, cytomegalovirus, adenovirus, rotavirus, enetrovirus, mononucleosis), protozoal and intestinal bacterial infections, and upper respiratory tract infections have been suggested as potential triggering factors.[4,6,7] Carroll and Coackley[8] reported a stronger association with gastroenteritis (40-60%). No patient in this series presented with gastrointestinal infection. Upper respiratory tract infections preceding AP rise was reported in one case. Some authors report a higher number of cases during Fall and Winter.[8-10] However, the small number of patients in this series precludes a seasonal correlation. Studies addressing the prevalence of a given gender are contradictive, showing male prevalence in some cases, and absence of correlation in others, maybe because of the small number of reports.[8]

The traditional BTHC diagnosis uses the propositions by Kraut et al.[11], which require the presence of the following criteria: age < 5 years, absence of evident hepatic, bone or kidney disease; alkaline phosphatase rise in apparently healthy children about 2-50 times higher than the normal level and return to normal values within 4-6 months, and increased liver and bone fraction of alkaline phosphatase.[2,3,12] Except for the identification of alkaline phosphatase isoenzymes, which was not performed in this study, all the criteria for diagnosing BTHC have been met. However, the segregation of alkaline phosphatase fractions, as suggested by Kraut et al.[11], is not crucial for diagnosis, since several studies describing patients with typical picture of BTHC have not been able to show the typical enzymatic pattern of electrophoretic mobility rise of liver and bone fractions.[5,6,8] This could have occurred as a result of methodology failures or for having conducted the test when the enzyme was on its way back to normal levels.[6] Similarly, routine bone X-ray investigations are not required, unless there are clinical or laboratory evidences of bone disease.[2] Although BTHC predominantly occurs in children younger than 5 years, there are reports describing adults being affected by this condition.[1]

In individuals with clinical picture suggesting BTHC, laboratory investigations could be restricted to the determination of the levels of: alkaline phosphatase, AST, ALT, GGT, calcium, phosphorus and magnesium. Other tests can also be requested at baseline: bilirubins, total enzymes and fractions, urea, creatinin, hemogram, and urine summary.[2] When the age group is not typical, when the return to normal alkaline phosphatase levels takes longer than four months, or in the presence of bone, liver, bowel, endocrine or kidney disease symptoms, other causes should be investigated.[8] Parathyroid hormone levels (PTH), which were normal for three out

Table 2 – *Timetable of alkaline phosphatase serum levels normalization.*

Timetable	Alkaline phosphatase (U/L)			
	Patient 1	Patient 2	Patient 3	Patient 4
At diagnosis	319	376	1.655	1.108
1 month	-	-	406	-
3 months	355	-	-	-
5 months	342	-	-	-
7 months	324	-	272	597
8 months	-	422	-	-
9 months	-	247	-	-
10 months	356	-	-	-
11 months	264	-	-	-
Normal value	< 270 U/L	< 270 U/L	< 270 U/L	< 830 U/L

Table 1 – *Laboratory tests at baseline for investigating BTHC.*

N	Gender	Age at diag.	AP (U/L)	P (mg/dl)	Ca (mg/dl)	Mg (mg/dl)	PTH (pg/ml)	AST (U/L)	ALT (U/L)	GGT (U/L)
1	F	45 m	319	4,7	10,4	NP	39	18	36	13
2	F	11 m	376	1,8	2,46	0,9	10,8	32	16	17
3	F	11 m	1655	6,4	10,2	2,14	20	38	14	12
4	F	15 m	1108	2,0	2,64	0,9	NP	38	19	NP

* Legends: (BTHC): benign transitive hyperphosphatasemia of childhood; (F): female; (m): months; (AP): alkaline phosphatase; (P): phosphorus; (Ca): calcium; (Mg): magnesium; (PTH): parathyroid hormone; (AST): aspartate-aminotransferase; (ALT): alanine-aminotransferase; (GGT): gamaglutyl transpeptidase; (NP) not performed.
** Reference values: (AP): patients 1-3 = < 270 U/L, patient 4 = < 830 U/L; (F): 2,5-7 mg/dL; (Ca): 8,8-11 mg/dL; (Mg): 0,7- 1,15 mg/dl; (PTH): 10-65 pg/mL; (AST): < 55 U/L; (ALT): < 50 U/L; (GGT): < 55 U/L

of four tested patients, may be requested in selected cases. Vitamin-D, hydroxyproline and osteocalcin (bone remodeling markers) dosages have not been checked due to the absence of symptoms of endocrine or bone diseases that could justify its request. Only one study in literature showed a rise of the 25-hydroxyvitamin D in BTHC patients, speculating that the increased synthesis of alkaline phosphatase could be mediated by vitamin-D metabolites.[7]

The normal level of alkaline phosphatase in three of four pairs of parents tested rules out a potential familial hyperphosphatasemia in these cases.

In conclusion, it is important to consider the potential for BTHC when assessing hyperphosphatasemia without a clear reason, especially if the patient is younger than 5 years, in order to avoid unnecessary diagnostic evaluations.

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