REVISTA CHILENA DE PEDIATRÍA
Sociedad Chilena de Pediatría
www.scielo.cl

Rev Chil Pediatr. 2017;88(1):176-181
DOI: 10.1016/j.rchipe.2016.04.011

CLINICAL CASE

Benign transient hyperphosphatasemia in infants, clinical series

Hiperfosfatasemia transitoria benigna de la infancia. Serie clínica

Luisa Schonhaut B., Ana Rocha R.

Department of pediatrics, Clínica Alemana de Santiago, School of Medicine, Universidad del Desarrollo, Santiago, Chile

Received: 30-12-2015; Accepted: 28-4-2016

Abstract

Introduction: Alkaline Phosphatase (ALP) is a group of 4 isoenzymes produced in different tissues. Elevated levels of ALP can be developed under physiological conditions, and can indicate the presence of bone or hepatobiliary diseases. In children, one of its most common harmless causes is benign transient hyperphosphatasemia (BTH), a little known condition. The objective is to report BTH cases and propose a monitoring plan. **Case reports:** The cases of 5 children aged between 11 and 50 months are presented, 4 of them female, with the incidental finding of a sudden and severe ALP elevation (> 1,000 U/l), in tests ordered due to either abnormal growth and development, or intercurrent infections. Bone and liver disease were ruled out using the patient history, physical examination and basic laboratory results. Isoenzymes levels were determined in 2 patients. A return to normal ALP levels was observed over a period of 1-6 months, with no evidence of further complications. **Conclusion:** BTH is a benign self-limiting biochemical disorder, which should be considered in children under 5 years old with severe ALP elevation in the absence of clinical or laboratory abnormalities suggestive of bone or liver disease.

Keywords:
Alkaline phosphatase;
Isoenzymes;
Benign transient hyperphosphatasaemia.

Introduction

Alkaline Phosphatase (ALP) is a group of 4 isoenzymes produced in different tissues such as bones, liver, kidney, placenta and bowel; in children approximately 85% of these are produced in the bones and the rest are primarily hepatic. Serum ALP activity varies throughout life, greater in children than in adults, especially during puberty, with an increment of 3 to 4 times above the reference value due to an elevated osteoblastic activity in the bone during pubertal growth[1].

Hyperphosphatasemia is characterized by elevated serum levels of ALP and can be developed under physiological conditions, during pregnancy or puberty, under clearly pathological circumstances, in response to bone or hepatobiliary diseases, due to benign family history, Paget's disease and under idiopathic conditions; one of the most frequent and harmless causes in infants and preschoolers is benign transient hyperphosphatemia in infancy (BTH).

In 1985 Kraut defined the diagnostic criteria for BTH that are still valid nowadays. Based on these re-

Correspondence:
Ana Rocha R.
arocharuiz@hotmail.com

ferences, BTH is presented in children under 5 years of age with a severe (greater than 1,000 IU/ l), isolated and transient elevation of ALP levels in the absence of signs and symptoms of bone or liver disease, returning to normal values over a period of 4 months (table 1).

The prevalence of BTH is difficult to estimate because it is usually an incidental finding in laboratory tests requested by different causes[3,4]. In healthy children, between 6 months and 5 years old, rates of severe ALP elevation from 2% to 6% have been reported[5–7], condition not common in older children or adults[8].

The aim of this paper is to report a case series of BTH, a differential diagnosis to be considered in the event of elevated ALP, and to propose management guidelines to avoid costly tests and unnecessary distress among parents and pediatricians.

Clinical Cases

A retrospective series on 5 children diagnosed with BTH between 2011 and 2015 is presented.

Patient 1

8 month-old infant, female, with a history of recurrent respiratory distress associated with abnormal growth and development since 6 months of age, progressive decrease in growth rate (H/A: 0.5 to -0.4 Standard deviation [SD]) and drop in weight/height ratio (W/H: -0.8 to -2DS), with normal physical examination. Blood count, VHS, biochemical profile, sweat test, liver profile and urine test were requested, all of which were normal. Blood count, VHS, biochemical profile, sweat test, liver profile and urine test were requested, all of which were normal. One finding that attracted attention was a plasma ALP elevation (1512 IU/l) (tables 2 and 3); to complete the study, after a month, repeated examinations were carried out to rule out bone and liver disease, with return of plasma ALP to normal levels of 343 IU/l. During the first year of follow-up, the patient presented a favorable clinical course with recovery of the development curve and decrease of the respiratory episodes.

Patient 2

11-month old female, with a history of allergy to cow's milk, diagnosed by a compatible medical history and positive counter-evidence, breastfed and use of a hypoallergenic formula. She presented a stable growth and development until 9 months (W/H -0.2 DS and H/A -0.5 DS), but evolved as steady weight and drop in weight/height curve (W/H 4 DS and H/A -0.8). Intercurrent high fever required general examinations and urine tests, compatible with urinary tract infection. Blood count showed leukocytosis with left shift and severe ALP elevation (4,552 IU / l), meanwhile calcium, phosphorus, and liver enzymes were within the normal range. Isoenzymes revealed predominance of bone over liver from 96.3% to 3.7% respectively (tables 2 and 3). It evolved with return of ALP to normal levels of 269 IU/l 3 months after follow-up and recovery of the development curve.

Table 1.

Edad menor de 5 años
Sintomatología variable
Ausencia de signos clínicos de enfermedad ósea y/o hepática[a]
Ausencia de signos bioquímicos de enfermedad ósea y/o hepática[b]
Análisis isoenzimático que muestra una elevación de las fracciones ósea y/o hepática
Normalización en un plazo igual o inferior a 4 meses

[a]Signos clínicos de enfermedad ósea: deformidades esqueléticas, mal incremento estatural, fracturas patológicas o dolores óseos; signos clínicos de enfermedad hepática: ictericia, coluria, acolia, visceromegalias. [b]Signos bioquímicos de enfermedad ósea: alteración de los niveles de calcio, fósforo, 25-OH vit. D_3 y hormona paratiroidea; signos bioquímicos de enfermedad hepática: elevación de enzimas hepáticas. Fuente: Kraut et al.[2].

Table 2.

N° de caso	Edad (meses)	Sexo	Razón del examen	Nivel máximo de FA (UI/l)[a]	Mes año	Periodo normalización (meses)	Peso/talla (DS)	Talla/edad (DS)
1	20	F	Mal incremento de peso	1.512	Febrero	1	–2	–0,4
2	11	F	Mal incremento de peso y cuadro infeccioso (infección urinaria)	4.552	Mayo	3	–0,4	–0,8
3	19	F	cuadro infeccioso (herpangina)	5.857	Marzo	6	–0,4	0,5
4	50	F	Diarrea y dolor abdominal	2.950	Junio	5	+2	–1,7
5	26	M	Mal incremento de peso	1.583	Julio	2	–0,3	–1,7

FA: fosfatasas alcalinas; DS: desviaciones estándar. [a]Peso/edad y talla/edad (tomando como referencia las curvas de la OMS 2006).

Table 3.

N° caso	Nivel de FA al diagnóstico (UI/l)	Isoenzimas hepáticas/óseas (%)	GOT/GPT (U/l)	Calcio (mg/dl)	Fósforo (mg/dl)	PTH (pg/ml)	25-OH D_3 (ng/ml)
1	1.512	-	39/18	10,3	4,7	13,9	40
2	4.552	3,7/96,3	44/25	10,5	5,2	-	-
3	5.553	24/75	28/15	9,7	5,3	21,3	38,5
4	2.950	-	36/16	9,2	5,2	24,1	17,7[a]
5	1.583	-	37/18	10,1	5,8	26,7	34,3
Valores de referencia	< 400		< 56/< 39	8,5-10,5	3,1-6,0		< 30

FA: fosfatasa alcalina; GOT/GPT: transaminasa glutámico oxalacética/transaminasa glutámico-pirúvica; 25-OH D_3: 25-OH vit. D_3; PTH: hormona paratiroidea. [a]Valores bajo el rango de referencia.

Patient 3

One year and 7 month-old female infant, previously healthy with good development and growth (W/H -0.4 DS and H/A 0.5 DS), whose tests showed a severe ALP elevation (5,553 IU / l) after prolonged fever with loss of appetite and vomiting (table 2). Isoenzyme measurements showed a predominance of the 75% bone over 24% hepatic. The rest of the study did not show hepatic or bone alteration through blood count, VHS, transaminases, calcium, phosphorus, parathyroid hormone (PTH); normal 25-OH vit D_3 and bone scintigraphy levels (table 3). The follow-up of ALP levels after a month showed a slight increase over the previous value (5,857 IU / l), with good clinical recovery of intercurrent fever. At 3 months, values decreased to 631 IU/l, returning to normal levels at 6 months, to a value of 297 U/l.

Patient 4

4 years 2 month-old female infant with Down syndrome and without a relevant medical history, with W/H > +2 DS; normal blood count, biochemical profile, transaminases, transglutaminase and urine antibodies after episodes of diarrhea and abdominal pain, but with an increase in ALP plasma values, 2,950 IU/l; a new ALP measurement was requested confirming high values (2,212 Ul/l), and with normal calcium, phosphorus and PTH levels, but low levels of 25-OH vit D3 (17.5 mg / ml), initiating an intake of 800 IU/day of 25-OH vit D3 (tables 2 and 3). At 5 months of follow-up, the ALP levels were normalized to 373 IU/l, but with low levels of 25-OH vit D3, 22.3 mg/ml, increasing the intake of 25-OH vit D3 to 1,000 UI daily. The clinical evolution of the patient was favorable.

Patient 5

2 years 2 month-old premature male patient, 31 weeks of gestational age, birth weight of 1,400 g (25th percentile), birth size 39 cm (25th percentile), with a history of osteopenia, which recovered at 3 months of age after treatment with calcium and phosphorus. No other complications related to prematurity. Repeated studies of ALP, calcium and phosphorus were within a normal range. Due to a history of regular weight gain (W/H-0.3 DS and H/A -1.7 DS), at 2 years of age a complete new study was requested, which was normal (blood count, VHS, biochemical profile, liver profile , urine test, serology for celiac disease, 25-OH vit. D3 and thyroid study), except for a severe ALP elevation (1,583 IU/l) (tables 2 and 3). Monthly follow-up showed decreasing values, reaching normal levels after 3 months (222 IU/l).

Discussion

A retrospective series of 5 children with incidentally detected severe (> 1,000 IU/l) and transient increase in ALP levels during 2011 and 2015 are presented. This finding was performed in laboratory tests requested by short height or intercurrent infectious disease. Four of the 5 patients were female, all younger than 5 years, coincident with what is reported[5,7], as this condition has been described in children older than this age and/or in adults[8], with a similar incidence in both genders[9].

The etiology of BTH is still unknown, but the finding of respiratory and gastrointestinal viral infections, and the temporal coincidence with antibodies against different enteroviruses, leads to a probable infectious etiology [10]; seasonality, another cause that would support this hypothesis, has not been consistent in all case reports, and it was not found in our series either [9,11]. Other authors associate the transient ALP increase to an abnormal growth and development, which has not been demonstrated yet [5]. These associations can be due to an individual selection bias, since in healthy infants, laboratory parameters are usually evaluated in relation to specific nutritional or infectious conditions. Accor-

Table 4.

Diagnóstico	Edad	Antecedentes familiares/personales	Curva crecimiento	Examen Físico	Ca	P	PTH	$25OHD_3$	Pruebas hepáticas	Otras exámenes de laboratorio
Procesos benignos y fisiológicos										
HFTBI	< 5 años	No	Variable	N	N	N	N	N	N	No se recomiendan
Hiperfosfatasemia benigna familiar	Variable	Uno de los padres con FA elevadas	N	N	N	N	N	N	N	N
Enfermedades óseas										
Osteopenia del prematuro	< 1 año	Prematuridad extrema	Variable	N	N	N o bajo	Elevado	N o baja	N	No se recomiendan
Raquitismo	< 2 años	Variables	Talla baja	Engrosamiento metafisiario Surco de Harrison, craneotabes, rosario costal, Genu-valgo/varo	No o bajo	N o bajo	N o elevado	No o baja	N	Signos radiológicos de raquitismo*
Neoplasias	Variable	Variables Dolores óseos	Variable	Variable	N	N	N	N	N	Hemograma alterado LDH elevada
Hiperfosfatemia idiopática/ enfermedad de Paget	Infancia	Variables	Talla baja	Deformidades óseas progresivas Fracturas, aplastamiento vertebral Macrocefalia Sordera	N o elevado	N	N o elevado	N	N	Variable
Enfermedades hepatobiliares										
Hepatitis, colestasis, enfermedades infiltrativas hepáticas	Variable	No	Variable	Variable Signos específicos	N	N	N	N	Enzimas hepáticas, bilirrubina, protrombina alteradas	Imágenes hepáticas

Ca: Calcio; P: fósforo; PTH: Hormona Paratiroidea; 25OHD3: 25 OH VitaminaD3; LDH: lactato deshidrogenasa; N: normal; HFTBI: Hiper Fosfatasemia Transitoria Benigna de la Infancia. *Principales signos radiológicos de raquitismo: ensanchamiento y deshilachamiento metafisiario, metáfisis en copa; aumento altura cartílago de crecimiento con ausencia de línea de calcificación previsoria; densidad ósea disminuida, con adelgazamiento de las corticales y líneas de Looser.

ding to the evidence gathered in Gualco review, 35% of BTH is diagnosed in a routine evaluation[9].

Liver or bone alterations were ruled out in all our patients by anamnesis, physical examination and basic laboratory tests, which measured levels of transaminases, calcium and phosphorus; in 4 children, 25-OH vit D3 and PTH levels, and in 2 others, isoenzymes levels were requested. The exception was patient number 4, whose levels of 25-OH vit D3 were in a low range, but in the absence of other signs suggesting rickets, it was concluded that this insufficiency would not explain the ALP increase. Patient 5 had a history of prematurity and osteopenia, he recovered during the first 3 months of corrected age, with normal ALP values prior to the finding of BTH. Authors have reported a non-association of BTH with other laboratory parameters, such as vit 25-OH D3, PTH, calcium, magnesium and phosphorus levels[5,7].

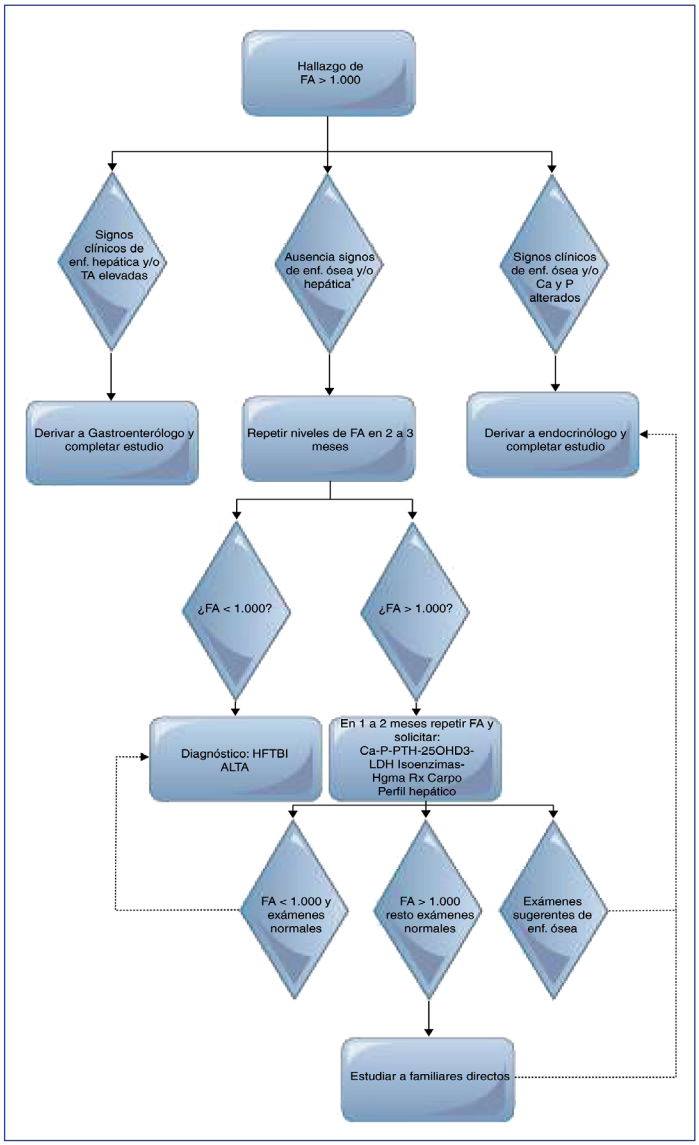

Figure 1.

It is important to mention that because children were referred to the specialist by different pediatricians, there was no common criteria for the study or follow-up. This is why the isoenzymes test was only performed in 2 of 5 patients, in which, according to expectations, bone predominated over liver elevation. Although this is another criteria defined by Kraut, recent articles argue its value to confirm the diagnosis [11]; Teitelbaum et al., in a prospective cohort study of 20 children with severe ALP increase and without evident disease, performed clinical follow-up and retest of ALP within 2 to 3 months without additional tests, demonstrating that the increase and subsequent regression of ALP (meeting Kraut's other criteria) are enough elements[12].

Kraut described that the return of ALP to normal levels occur within a period not exceeding 4 months, however, only in 81% of the published cases this criterion is met[9]. In the follow-up of our patients, we observed a return of ALP to normal levels in a slightly higher than expected period in 2 of the 5 patients.

It is important to keep in mind that when ALP increases as a response to skeletal diseases, as rickets, bone predominates (hyperphosphatase) and it is usually associated with abnormalities in calcium, 25-OH vit D3 and phosphorus levels, plus evident skeletal alterations. Polyostotic fibrous dysplasia, osteogenesis imperfecta, hereditary osteolysis and cystic fibrosis, as well as bone neoplasias and metastases may also produce an increase in ALP levels, but in these cases, elevation is accompanied by other clinical elements such as deafness, premature loss of teeth, hyperostosis enlargement of the long bones and pain in the phalanges of the hands, with accelerated bone remodeling and hypercalcemias.

Idiopathic hyperphosphatasia is a rare bone disorder and corresponds to the autosomal recessive form of Paget's disease, which is characterized by bone turnover. The affected children are normal at birth and then have progressive diffuse bone malformations, such as collapse of the spinal bone, lengthening of the skull and deafness. Benign familial hyperphosphatemia is another type of non-pathological hyperphosphatemia with autosomal dominant inheritance, with ALP increase in the bone, liver and bowel, and values generally range from 500 to 700 IU/l, plus one of the parents must be affected; bone scintigraphy is normal and bone or hepatobiliary diseases should be ruled out[13]. Table 4 shows the differential diagnosis of hyperphosphatasia.

Based on published evidence, we recommend that, in the absence of other altered clinical and biochemical

parameters, in those patients younger than 5 years of age who present an incidental elevation of ALP above 1000 IU/l, BTH should be suspected and ALP measurement should be repeated within 2 to 3 months[12,14,15]. If ALP persists elevated, the quantification should be repeated at 4 months of follow-up and complemented with: calcium, phosphorus, PTH, 25-OH vit. D3, quantification of isoenzymes, carpal radiography and liver profile measurements. If the complementary examinations were normal and ALP levels remained high, a family group study is also recommended to rule out benign familial hyperphosphatemia. However, if there are no affected relatives, a larger study and a subsequent follow-up should be carried out to establish the differential diagnosis between sporadic benign persistent hyperphosphatemia and secondary hyperphosphatasemia. Clinical follow-up should continue until the return of ALP to normal levels (figure 1)[3].

Conclusion

Nowadays BTH is accepted as a benign biochemical disorder rather than a clinical problem, with a self-limiting evolution and no following consequences, something important to keep in mind when confronting a case of a child with severe ALP increase in the absence of other clinical or laboratory disorders, so that unnecessary concerns and further examinations can be avoided.

Ethical Responsabilities

Protection of people and animals: The authors state that the procedures followed ethical standards of the responsible human experimentation committee and in agreement with the World Medical Association and the declaration of Helsinki.

Confidentiality of data: The authors state that they have followed the protocols of their work center on the publication of patient data.

Privacy rights and informed consent: The authors state that they have obtained the informed consent from patients and subjects included in the study. These documents are in the possession of the corresponding author.

Conflict of interests

This work complies with the requirements of informed consent, ethics committee, funding, studies on animals and the absence of conflict of interest as required.

Referencias

1. Cho SM, Lee SG, Kim HS, Kim JH. Establishing pediatric reference intervals for 13 biochemical analytes derived from normal subjects in a pediatric endocrinology clinic in Korea. Clin Biochem. 2014;47(18):268-71.
2. Kraut JR, Metrick M, Maxwell NR, Kaplan M. Isoenzyme studies in transient hyperphosphatasemia of infancy. Ten new cases and a review of the literature. Am J Dis Child. 1985;139: 736-40.
3. Eymann A, Cacchiarelli N, Alonso G, Llera J. Benign transient hyperphosphatasemia of infancy. A common benign scenario, a big concern for a pediatrician. J Pediatr Endocrinol Metab. 2010;23:927-30.
4. Behúlová D, Bzduch V, Holesova D, Vasilenkova A, Ponec J. Transient hyperphosphatasemia of infancy and childhood: Study of 194 cases. Clin Chem. 2000;46:1868-9.
5. Huh SY, Feldman HA, Cox JE, Gordon CM. Prevalence of transient hyperphosphatasemia among healthy infants and toddlers. Pediatrics. 2009;124:703-9.
6. Gallo S, Comeau K, Sharma A, et al. Redefining normal bone and mineral clinical biochemistry reference intervals for healthy infants in Canada. Clin Biochem. 2014;47:27-32.
7. Ridefelt P, Gustafsson J, Aldrimer M, Hellberg D. Alkaline phosphatase in healthy children: Reference intervals and prevalence of elevated levels. Horm Res Paediatr. 2014;82:399-404.
8. Jassam NJ, Horner J, Marzo-Ortega H, Sinclair M, Barth JH. Transient rise in alkaline phosphatase activity in adults. BMJ Case Reports. 2009.
9. Gualco G, Lava SAG, Garzoni L, et al. Transient benign hyperphophatasemia. J Pediatr Gastroenterol Nutr. 2013;57:167-71, http://dx.doi.org/10.1097/MPG.0b013e3182922807
10. Suzuki M, Okazaki T, Nagai T, Toro K, Sétonyi P. Viral infection of infants and children with benign transient hyperphosphatasemia. FEMS Immunol Med Microbiol. 2002;33:215-8.
11. Dori N, Levi L, Stam T, Sukhotnik I, Shaoul R. Transient hyperphosphatasemia in children revisited. Pediatr Int. 2010;52:866-71.
12. Teitelbaum JE, Laskowski A, Barrows FP. Benign transient hyperphosphatasemia in infants and children: A prospective cohort. J Pediatr Endocrinol Metab. 2011;24:351-3.
13. Navarro Despaigne D, Moro Álvarez MJ, Díaz Curiel M. Hiperfosfatasemia familiar: reporte de un caso y consideraciones diagnósticas. An Med Inter. 2007;24:387-9.
14. Luzardo M, Calcines N, Gil E. Hiperfosfatasemia benigna transitoria de la infancia: una entidad a tener en cuenta. Rev Pediatr Aten Primaria. 2011;13:107-11.
15. Otero JL, González-Peralta RP, Andres JM, Jolley CD, Novak DA, Haafiz A. Elevated alkaline phosphatase in children: An algorithm to determine when a "wait and see" approach is optimal. Clin Med Insights Pediatr. 2011;5:15-8.
16. Kutilek S, Cervickova B, Bebova P, Kmonickova M, Nemec V. Case report hyperphosphatasemia. J Clin Res Pediatr En docrinol. 2012;4:154-6.