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Transient Hyperphosphatasemia in an Infant with Bronchiolitis and Pneumonia

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Abstract
We present a case of benign transient hyperphosphatasemia in a 4-month-old infant with acute bronchiolitis and pneumonia. During hospitalization the infant had an increased catalytic activity of alkaline phosphatase (ALP): day 2, 5074 U/L; day 3, 5622-U/L; and day 8, 3129 U/L. The x-ray, leukocytosis, and C-reactive protein findings pointed to bacterial etiology of the respiratory disorder. Electrophoretic separation revealed an atypical isoenzyme profile: fast anodal, near-cathodal and bone fractions. ALP levels normalized within 54 days, and control electrophoresis indicated normal liver, placental/placental-like, intestinal and bone isoenzymes. The appearance of atypical fast anodal and near-cathodal fractions of ALP in this infant during the course of acute lower respiratory tract infection and rapid return to the reference intervals pointed to benign transient hyperphosphatasemia.

Key words: transient hyperphosphatasemia, bronchiolitis, pneumonia

Introduction

Transient hyperphosphatasemia (TH) in children under the age of 5 years is a benign increase in the catalytic activity of alkaline phosphatase (ALP) in serum, which may persist for several weeks [1]. Since it is not part of some metabolic bone or liver disease, it is randomly recognized on routine laboratory work-up. The diagnosis is established upon the ALP catalytic activity returns to the reference interval within 3-4 months [2, 3].

Case Report

S.J., a 4-month-old girl, was admitted to the Intensive Care Unit due to acute bronchiolitis, with x-ray and C-reactive protein (CRP) findings consistent with acute bacterial pneumonia. The infant was healthy until the current disease. The changes in laboratory findings recorded during hospital stay and at follow-up (up to day 54) are shown in Table 1. The infant received ceftriaxone, oxygen and i.v. fluids. Catalytic ALP activity was determined on day 2 (5074 U/L), day 3 (5622 U/L) and day 8 (3129 U/L) of hospital stay, and at follow up (day 54 of admission, 349 U/L). The infant was discharged on day 9 with normal physical and routine laboratory findings. During hospitalization serum ALP was electrophoretically separated (both diluted serum and lectin-treated-serum) into three isoenzymes: an atypical fast anodal fraction (faster than usual liver ALP), a near-cathodal (placental/placental-like) fraction, and a bone fraction (Fig. 1: bands 2 and 3). Bands 1-7 in Figure 1 refer to diluted sera and bands 1'-7' to the same samples after pretreatment with lectin. Normal isoenzymes in diluted serum were masked by bone isoenzyme. However, control electrophoresis revealed the appearance of liver, placental-like, intestinal and bone isoenzymes (Fig. 1: band 6).

As a band appeared at the site of placental and placental-like ALP, serum samples from TH patient (day 54 of admission to the hospital; ALP = 349 U/L) and a pregnant woman (25th week of gestation, ALP=74 U/L) were incubated at 65 °C for 15, 30 and 60 minutes. After 15-min incubation, the level of ALP was 4 U/L in TH patient and 8 U/L in pregnant woman. After longer serum heating up, ALP catalytic activity could neither be measured nor demonstrated by electrophoretic separation in either of the serum samples tested.

Discussion

Benign TH occurred in a female infant during severe bacterial lower respiratory tract infection. Electrophoretic separation revealed an atypical isoenzyme profile: fast anodal (faster than usual liver ALP), near-cathodal (placental or placental-like, or both) and bone fractions. In the first three days, the activity was on an increase, to be almost halved by day 8, and returned to the normal values within 8 weeks.

The criteria for diagnosing benign TH include age less than 5 years; increase in ALP 3 to 50 times above the upper reference limit for age; clinical framework of diverse disorders like respiratory or gastrointestinal infections but no clinical or biochemical signs of bone or liver disease; increase in isoenzymes derived from bone and/or liver; and return to the normal level within 4 months [4].

TH is usually observed during infections, acute viral respiratory and gastrointestinal infections in particular [4, 5]. Our patient presented a serious acute respiratory disease which, on the basis of leukocytosis and in-

Table 1. The levels of various analytes in the infant with TH during hospital stay and at follow up.

Analyte [Reference value]	**Day 1**	**Day 2**	**Day 3**	**Day 8**	**Day 54**
ESR (mm/h)	11			26	
[1 - 20]					
Leukocytes (Nx10^9/L)					
[6.0 – 16.0]	17.3		8.7	17.1	15.9
Platelets (Nx10^9/L)					
[150 - 450]	363		402	575	534
CRP (mg/L)					
[< 5.0]	111.3		21.3	1.0	1.7
Serum iron (μmol/L)					
[4.0 – 25.0]		2.1		10,5	12.4
ALP (U/L)					
[25 - 500]		5074	5622	3129	349
Anodal		2020	1821	726	-
		[40%]	[32%]	[23%]	
Near cathode		1106	1642	1080	
		[22%]	[29%]	[35%]	-
Liver					5
[1 – 31%]		-	-	-	[2%]
Placental/placental-like					151
		-	-	-	[43%]
Intestinal					36
[0 – 14%]		-	-	-	[10%]
Bone		1948	2159	1323	157
[62 – 100%]		[38%]	[39%]	[42%]	[45%]

ESR - Erythrocyte Sedimentation Rate

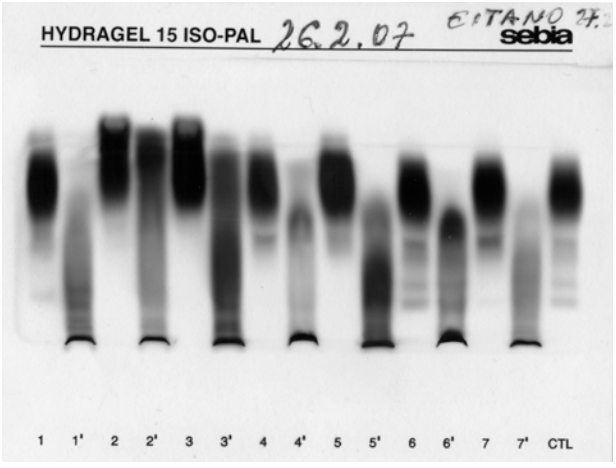

Fig. 1. Electrophoretic separation of ALP isoenzymes. Bands 1-7: diluted sera; bands 1' to 7': the same samples after pretreatment with lectin: control sample 1 (1); infant S.J., fast anodal (top), near-cathodal (middle) and bone (bottom) ALP (band 2 - day 3, band 3 - day 8); infant with bone and placental/placental-like (near-cathodal) ALP (4,7), infant with bone ALP (5); S.J. - normal finding, day 54 (6); CTL: control sample 2. Fast anodal isoenzymes (bands 2 and 3) are faster than usual liver ALP.

creased CRP, was bacterial in nature. Parisi et al. have described TH in four children with mild viral infections, one of them with febrile exanthematous disease following measles vaccination (probably postvaccinal measles) [6]. The incidence of TH in children with liver or kidney transplant is estimated to 2.8% [7]. It is more common in girls (female:male ratio, 1.29 : 1) [5].

The reasons for elevated catalytic activity of ALP are not fully understood. Several mechanisms have been proposed: (a) increased synthesis of ALP induced by vitamin D metabolites; (b) various pathologic conditions (e.g., viral infection) that influence the degree of sialization of the enzyme which reduces the enzyme clearance; and (c) the effect of drugs on enzyme synthesis [8]. Placental ALP is synthesized in placenta from the 12th week of gestation, and trace amounts are synthesized in lung tissue [9]. Placental-like ALP is synthesized in non-malignant testis, cervix and thymus, and trace amounts are synthesized in placenta and lung [10]. Both isoenzymes are heat stable (at 65 °C) and present 98% homology [11]. Placental ALP could be detected in normal plasma membrane of pneumocytes and in the unciliated epithelial cells of respiratory bronchioli [12]. Its activity could be observed in patients with adult respiratory distress syn-

drome, bacterial or viral pneumonia, and in patients on artificial ventilation [13].

There has as yet been no report of transient hyperphosphatasemia in children with bronchiolitis. Is it overlooked by simple explanation of physiologic bone growth? What is its incidence in children with acute infections? Or, is it that laboratory tests are not routinely run in numbers of children sufficient to detect such biochemical anomalies?

The detection of an unusually high catalytic activity of ALP in an infant during an acute lower respiratory tract infection indicates the presence of benign TH. The diagnosis can only be made retrospectively after the values have significantly dropped or returned within the normal range. It is important to timely recognize this biochemical anomaly as a benign and transient phenomenon, thus to obviate more extensive tests and inaccurate diagnoses [7]. If the activity is normalized within 4 months, no further investigations are warranted [1-3]. This is, in our knowledge, the first report of placental/placental-like isoenzyme in an infant with benign TH. In spite of some limitations of the study, such as the lack of differential inhibition by various amino acids, we believe that further evaluation of the presented isoenzyme(s) is worthwhile.

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