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Benign transient hyperphosphatasemia in infants and children: a prospective cohort

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Abstract

A total of 20 children with benign transient hyperphosphatasemia were prospectively evaluated with no additional investigations recommended except repeat serologic evaluation in 2–3 months. The average age of our patients was 2.5 years (range: 1 year 2 months–5 years 10 months). The serum levels of alkaline phosphatase averaged 2383 IU/L (range: 1013–5700 IU/L). Levels returned to normal within several months. This condition should be recognized by the clinician in order not to put patients through lengthy, expensive and unnecessary investigations.

Keywords: alkaline phosphatase; benign transient hyperphosphatasemia; prospective cohort.

Introduction

Alkaline phosphatases (APs) are a group of isoenzymes that hydrolyze organic phosphate esters at alkaline pH, generating inorganic phosphate and an organic radical. Serum AP consists of isoenzymes which can originate from bone, liver, intestine, and/or placenta. Abnormally high serum values of bone isoenzyme can be seen with increased osteoclastic activity, whereas the liver isoenzyme is typically elevated in cholestatic conditions or biliary tract injury. Transient but marked elevation of AP has been observed in infants and children, without any clinical findings suggesting liver or bone disease, termed benign transient hyperphosphatasemia (BTH).

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Bach (1) published the first description of BTH in 1954. Kraut et al. (2) suggested that the criteria for diagnosing BTH should include: age younger than 5 years, absence of symptoms or presence of illnesses (i.e., seizures, diarrhea, vomiting, recurrent upper respiratory tract infection), absence of clinical or biochemical evidence of bone or liver disease, elevation of serum AP ranging 3–50 times the upper normal value for age, isoenzyme analysis showing an elevation in bone and/or liver fraction, return to normal serum AP values within 4 months. These parameters have not been universally accepted, and although many patients do fall within these parameters, some deviation has been seen with regard to patient age, and timing of resolution. Elevated AP are often observed during "routine serologic testing" of otherwise well children or as part of a "comprehensive metabolic panel" when assessing unrelated conditions. Thus, recognition of this entity is important so as to avoid unnecessary and costly testing such as bone X-rays, liver ultrasound, isoenzyme fractionization, vitamin D levels, and parathyroid hormone levels.

We prospectively followed a cohort of patients with suspected BTH and report their outcomes after intentional avoidance of unnecessary testing, and only suggesting repeat serology in 2–3 months.

Materials and methods

Patients who were referred to a community based academic Gastroenterology or Endocrinology office for evaluation and found to have elevated AP above 1000 IU/L were prospectively recorded. Patients needed to have normal history and physical examination without concerning features for cholestatic liver disease (i.e., no jaundice or pruritis) or bone diseases such as vitamin D deficiency. Accompanying laboratory data had to include normal liver transaminases, albumin, bilirubin, and calcium. Demographic data including gender, age, reason for measurement of AP, and month of initial measurement were recorded. Patients were then instructed to have a "metabolic panel" (i.e., electrolytes, calcium, AP, bilirubin, albumin, and transaminases) repeated in 2–3 months from the original abnormal value. A Health Insurance Portability and Accountability Act (HIPAA) waiver form was accepted by the institutional Institutional Review Board (IRB) so as to access the patients' data.

Results

Patients were prospectively recorded beginning in October 2003 and ending October 2009. A total of 20 patients were identified with BTH during this time period, whereby 11 of the patients were boys. The average age was 2.5 years (range: 1 year 2 months–5 years 10 months). Out of the 20 patients, 11 were referred to the specialist owing to abnormal AP level

discovered during routine screening of otherwise healthy children during their yearly well child examination. Other patients were found to have abnormal AP during serologic screening for poor weight gain (1 patient), screening for a chronic condition (2 patients, chronic hepatitis C virus and heart transplant patient), lethargy (1 patient), abdominal pain (1 patient), acute infection (2 patients, methacillin resistant *Staphylococcus aureus* skin infection, and pneumonia), and diarrhea (2 patients).

The serum levels of AP averaged 2383 IU/L (range: 1013–5700 IU/L). Repeat testing was performed at various time intervals despite our recommendation to repeat in 2–3 months. Owing to patient non-adherence with our recommendation, repeat testing was not performed in five patients; however, clinical follow-up 2–3 years later revealed them all to be clinically well. A total of 11 patients (55% of the total, 73.3% of those with repeat testing) had documented normal AP levels within 3 months. Of those, six were normal within 6 weeks. The shortest duration to resolution was observed at 2 weeks in a patient in whom the pediatrician ordered testing at that early interval. The remainder delayed testing beyond what was recommended and were recorded as normal at 4.5 months, 6 months, 2 years 7 months, and 4 years 2 months. None of the patients had abnormal repeat testing at a time greater than 2 months from the original laboratory abnormality.

The initial abnormal laboratory results were distributed among the various seasons such that three patients had elevated levels in January–March, four patients in April–June, seven patients in July–September, and six patients in October–December.

Discussion

Serum AP is not stagnant during one's life span. It is mildly elevated during the first 3 months of life, increases during puberty, and falls in adulthood. Increased levels can be explained by the intensive bone growth in puberty. Pregnancy is another time when serum AP increases owing to fetal and placental production. The prevalence of BTH is 2.5%–5.1% depending on the AP value used (3). Despite the fact that this is a relatively common condition among healthy infants and toddlers, the exact etiology remains unknown.

In 1985, Kraut at al. (2) described 10 patients with a temporary pronounced elevation of AP in whom the source of elevation was both bone and liver fractions, with no contribution from small bowel isoenzyme. He suggested that a viral infection might play a role in a sudden, transient increase in AP activity in plasma. Several other reports of small numbers of children have been reported since the initial description by Bach (1), who described this entity in three normal infants, with resolution of AP elevation within 8 weeks.

Although the majority of our patients were found upon routine screening of well children, nine had other conditions, consistent with the findings of other studies. In a study by Steinherz et al. (4), five children aged 16–36 months were found to have serum AP levels 7–30 times the upper limit of the reference range. One of the patients (16 months old) had frequent otitis media and atopic dermatitis without evidence of rickets. Levels returned to normal in 1 month. Furthermore, three other reported children had leukemia and lymphoproliferative disorders and a fourth had rhabdomyosarcoma. These oncology patients were found to have high levels of AP while receiving chemotherapy. The hyperphosphatasemia was of short duration. No explanation for the sudden, transient elevation was discovered. In the Steinherz study, four of the five cases had neoplasia, a fact that might raise doubts about the benign nature of the hyperphosphatasemia in this cohort.

Transient hyperphosphatasemia was also observed in patients who underwent organ transplantation. In 2006, Arikan et al. (5) described this phenomenon in 2 out of 70 patients undergoing orthotopic liver transplantation between January 1998 and January 2005. Kidney transplantation patients and liver transplantation patients were described to have BTH by Ranchin et al. (6) in 2002.

In a study by Suzuki et al. (7) in 2002, two peaks were recognized in spring and autumn. Most of the cases had infectious diseases of upper airway accompanied by symptoms of fever and diarrhea. Antibody titers for viruses identified enteroviruses such as ECHO 22, Entero 71, Coxsackie B4. Similarly there has been seasonal clustering of BTH observed by Crofton (8) after summer months. In her study of 35 children she found that the etiology for this condition might represent increased synthesis of AP mediated by vitamin D metabolites. In this regard, a patient presented with weight loss and intensive growth. The high serum AP levels were attributed to decreased hepatic clearance by high sialic acid content. Our patients presented with a distribution among all seasons and a slight predominance in the summer and autumn months (65%).

The largest cohort to date was reported over 8 years (1992–1999) wherein 194 cases of transient hyperphosphatasemia of infancy and childhood were described by Behulova et al. (9) in a letter to the editor. They reported a wide variety of clinical disorders associated with this condition: gastrointestinal diseases (24%), respiratory infections (21%), congenital anomalies and inborn error of metabolism (15%), anemia (10%), malignancies (7%), and neurological disorders (5%). The authors observed a seasonal clustering of cases from September to November (43%) with the lowest incidence from January to March (13%). They also noted a simultaneous course of BTH in three sets of twins and two other sibling pairs.

Benign inherited hyperphosphatasemia of intestinal origin was postulated by Panteghini (10) in 1991. This Italian study of two families showed no evidence of clinical abnormalities or explanation for the unusual enzyme concentration. Agarose gel electrophoresis of AP isoenzymes in serum demonstrated markedly increased intestinal isoforms, which accounted for approximately 60% of total AP activity. The description of these families demonstrated patterns suggesting autosomal-dominant inheritance. Benign familial hyperphosphatasemia was reported in five families in which the increase of serum AP was of intestinal origin and resolved by 18 months (11).

Huh et al. (3) reported nine patients with AP levels over 1000 IU/L and 16 with intermediate serum AP levels (mean 544 IU/L). These were compared to 291 children without BTH and were found to have similar mean serum levels of 25

OH vitamin D, parathyroid hormone, calcium, magnesium, and phosphorus. This suggests that increased bone resorption does not account for the etiology of BTH.

Our cohort represents one of the largest to date on this entity and to our knowledge the first prospective cohort illustrating that a conservative approach of repeat testing in 2–3 months is safe and cost-effective. We therefore recommend this approach in the evaluation of isolated increases of AP levels over 1000 IU/L with normal transaminases, bilirubin, albumin, and calcium. More extensive investigations for hepatic or bone anomalies would seem warranted if the AP level remained elevated beyond 2–3 months.

Summary

BTH of infancy and childhood is a benign entity that typically resolves within several months. It is usually discovered on "routine blood testing" and could questionably be related to various viral illnesses, medications, or oncologic processes. Seasonal variation has been described but no clear pattern has emerged. Recognition of this diagnosis will help to avoid unnecessary investigations.

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