

Benign transient hyperphosphatasemia in juvenile idiopathic arthritis: a case report

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ABSTRACT

Benign transient hyperphosphatasemia of infancy and early childhood is a self-limiting condition characterized by transiently increased serum alkaline phosphatase in the absence of liver, kidney or metabolic bone diseases. It is often accidentally found in children under five years old and it might be associated with a variety of underlying clinical disorders. Its pathophysiology remains unclear.

Herein, we report a case of a 4-year-old girl with a 1-year history of persistent oligoarticular Juvenile Idiopathic Arthritis, who was found to have transient hyperphosphatasemia during a periodic check-up. This clinical case underlines the importance of promptly recognizing this benign condition, which avoids unnecessary extensive investigations.

Keywords: Hyperphosphatasemia; Juvenile idiopathic arthritis.

INTRODUCTION

Benign transient hyperphosphatasemia of infancy and early childhood (BTHI) is a self-limiting condition characterized by a sudden and temporary increase of serum alkaline phosphatase (ALP) in the absence of liver, kidney or metabolic bone diseases^{1,2}. It predominantly affects children, especially those aged less than 5 years, though it has also been reported in adults³⁻⁵.

BTHI is often accidentally detected when laboratory tests are required in healthy children or in children diagnosed with a variety of unrelated disorders. It can be found in 1.5% up to 5.1% of the infants, although

its real prevalence is difficult to estimate since ALP levels are not routinely measured in all children, especially in those who are asymptomatic^{6,7}. Studies addressing gender distribution are contradictory: some have shown that BTHI affects both sexes equally^{1,5,8}, while others have reported a male predominance².

The diagnosis is confirmed by the spontaneous return of ALP to normal levels within weeks or months of initial observation. It has no adverse long-term consequences.

BTHI was first described by Bach in 1954⁹, and since then, some case reports and few case series have been published in the literature. It remains a relatively unrecognized condition and it might be a potential, yet avoidable, concern for physicians when faced with a marked elevation of ALP levels.

CASE REPORT

A 4-year-old girl with a 1-year history of persistent oligoarticular Juvenile Idiopathic Arthritis (JIA) presented to our Pediatric Rheumatology department for a routine follow-up visit. She was in clinical remission for at least 6 months, following two single intra-articular corticosteroid injections of both knees. She was not taking any medication.

At the time of visit, she was asymptomatic and her physical examination was unremarkable. Laboratory tests showed a normal blood count, an erythrocyte sedimentation rate of 19 mm/h and a C-reactive protein of 0.1 mg/dL. However, alkaline phosphatase was markedly increased (1578 U/L; normal age-related value 150-380 U/L). Alanine-aminotransferase (ALT), aspartate-aminotransferase (AST), gamma-glutamyl transpeptidase (GGT) and total bilirubin were within normal reference ranges, as well as renal function, calcium and phosphorus levels.

Her parents were healthy and reported no complaints or abnormalities in their routine laboratory tests.

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Since there were no other findings suggestive of liver, kidney or metabolic bone disease either in physical examination or in the laboratory tests, BTHI was suspected and a “wait-and-see” strategy was adopted. After two months, there was a spontaneous reduction of ALP to normal levels (201 U/L), while all the other laboratory tests remained normal, supporting the diagnosis of BTHI.

DISCUSSION

ALP is a glycoprotein that can be synthesised throughout the body in a variety of isoenzymes, depending upon the site of origin. In humans, there are four isoenzymes: tissue-nonspecific (liver, bone, kidney), intestinal, placental and germ cell ALP^{3,10,11}. In the pediatric population, under physiological conditions, the bone and liver fractions contribute 85% and 15% to the total serum ALP pool, respectively¹¹.

Serum ALP level varies according to age. It is generally higher in children than in adults, particularly during the rapid growth phases of infancy and puberty, due to increased rates of osteoblastic activity¹¹.

In this report, we describe a transient increase in ALP levels in an asymptomatic 4-year-old child. The serum level of ALP was increased four to five times above the upper reference limit for age, which is typically seen in BTHI, although elevations up to 20 times the upper standard value have been described¹².

In 1985, Kraut *et al.* proposed the following diagnostic criteria for BTHI¹³: 1) age less than 5 years; 2) variable clinical picture, ranging from asymptomatic to variable unrelated symptoms; 3) no evidence of bone or liver disease on physical examination; 4) no biochemical or laboratory evidence of bone or liver disease, except for the severe isolated rise in serum ALP; 5) elevation in both bone and liver fractions of ALP; 6) return to normal ALP values within four months. In our clinical case, all these diagnostic criteria were met, except for the identification of ALP isoenzymes, whose analysis was not performed. However, some studies have shown that the characteristic isoenzyme pattern is not always observed in infants with otherwise typical features of BTHI^{1,2,14}. This could be explained by differences in laboratory methods, lack of experience in interpreting results or by a late performance of the test during the course of the condition when the isoenzyme pattern has returned to normality¹. Therefore, failure to meet the fifth criterion described by Kraut

should not preclude the establishment of the diagnosis.

Kraut's criteria have been further contested because, as previously stated, BTHI has been observed in older children and adults³⁻⁵ and its duration can exceed the time limit of four months in nearly 20% of cases^{5,15}. In our clinical case, ALP levels returned to normal after two months, portraying the classic natural history of BTHI.

The pathophysiology of BTHI remains poorly understood. The most plausible explanation for the rise in ALP levels is a delayed clearance of ALP from circulation due to excessive sialylation^{13,16}. Still, the cause of this abnormal sialylation is also unclear. Viral infections (cytomegalovirus, herpes virus, adenovirus, Epstein-Barr virus, rotavirus, enterovirus, among others) have been suggested as potential triggering factors^{1,2,14}. In fact, several studies have found a temporal association between the development of BTHI and a previous or concomitant viral infection, especially in the upper respiratory or gastrointestinal tracts. In our patient, no history of any recent infection was described.

Although most children are healthy, BTHI has been linked with a variety of underlying clinical conditions, such as gastrointestinal diseases (Celiac disease, Crohn's disease^{1,2}, multiple congenital anomalies¹, phenylketonuria¹, hemophilia¹, congenital HIV infection¹⁷, malignancies (leukemia, lymphoma, rhabdomyosarcoma)¹⁸, post liver and kidney transplant^{19,20} or seizure disorders¹³. Our patient had a history of oligoarticular JIA, with 1-year evolution. In the literature, this association with JIA is rare but has already been described. In 1985, Jerry Jacobs reported the occurrence of BTHI in two girls with polyarticular JIA²¹. In these cases, the elevation of ALP occurred 2 and 16 months after the onset of JIA. Nonetheless, we hypothesize that this apparent association may be a temporal coincidence rather than a causal relationship, reflecting more frequent monitoring of JIA patients.

The differential diagnosis of increased ALP in childhood should include bone disorders (such as rickets, healing fractures, juvenile Paget's disease, fibrous dysplasia of bone, bone tumors), hepatic disorders (cholestasis, malignancy) and kidney disorders (chronic renal failure, tubulopathies)^{22,23}. However, these diseases are usually accompanied by other clinical elements or laboratory abnormalities. Our patient was totally asymptomatic and there was no other evidence of hepatic or bone disease in the physical examination or in the laboratory tests.

Drugs such as cotrimoxazole, cyclosporin A, anti-convulsants and chemotherapy can also cause an increase in ALP^{13,14,16} but, as mentioned, our patient was on no medication.

Benign familial hyperphosphatasemia (BFH) also needs to be considered in the differential diagnosis. BFH is an inherited disease characterized by the presence of persistently elevated levels of serum ALP in the absence of other cause of hyperphosphatasemia^{24,25}. BFH was excluded in our clinical case by the spontaneous reduction of ALP to normal levels and by the fact that the child's parents are healthy, with no history of hyperphosphatasemia.

In conclusion, the incidental finding of isolated hyperphosphatasemia in children should raise the possibility of BTHI. A careful clinical history, physical examination and routine laboratory tests are usually sufficient to rule out other possible causative illnesses. Given the benign nature and self-limiting evolution of this condition, monitoring of ALP levels is recommended before any further diagnostic steps are undertaken. The occurrence of BTHI in JIA patients is rare and it may be found by chance.

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