Doi: 10.32677/IJCH.2016.v03.i04.018

Case Report

Transient hyperphosphatasemia: A case report

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Received – 09 September 2016 Initial Review – 16 September 2016 Published Online – 01 October 2016

ABSTRACT

Transient hyperphosphatasemia (THP) is characterized by temporary elevation of serum alkaline phosphatase (AP). We report a case of a 26-month-old girl referred for slow growth and found to have THP as AP levels returned to normal without active treatment. THP is a benign condition in healthy children, which resolves spontaneously without any intervention. In the absence of signs and symptoms of any underlying liver, bone or gastrointestinal disease, isolated elevation of AP levels should alert the clinician to a diagnosis of THP to avoid expensive, extensive, and unnecessary investigations.

Key words: *Hyperphosphatasemia, Transient, Benign, Children*

Transient hyperphosphatasemia (THP) is a condition characterized by a temporary elevation of serum alkaline phosphatase (AP) most commonly seen in infants and children younger than 5 years of age, in the absence of bone, gastrointestinal, or liver disease [1]. AP is mainly derived from bone, liver, gastrointestinal tract, and kidneys [1]. The structure of AP differs depending on where that particular enzyme originated. These organs specific APs are called isozymes. The isoenzymes hydrolyze organic phosphate esters at alkaline pH, generating inorganic phosphate, and an organic radical [2].

Investigations in a child with raised serum AP can be quite extensive and expensive. In the absence of any underlying liver, bone and gastrointestinal disease, a raised serum AP level usually points toward THP. We report a case of THP in a 26-month-old girl, the serum AP levels returned to normal in 4 weeks without any intervention.

CASE REPORT

A 26-month-old Chinese girl was referred to pediatric outpatient for slow growth for nearly 1 year when she started refusing milk. Her birth weight was 3 kg and parents were average sized for race. Her dietary history revealed refusal to drink milk; her total calorie intake was assessed by a dietician and felt to be inadequate for age. There was no history suggestive of malabsorption. She did not have any gastrointestinal or allergic symptoms on consuming milk, and hence, refusal to drink milk was attributed to be behavioral. No recent history of viral or febrile illness. There was no significant past medical history or family history of note.

Clinical examination revealed a well child with weight on the 10th centile and height between the 3rd and 10th centile. She did not show any signs of clinical rickets (no rachitic rosary, thickening of wrists and ankles, bowlegs, and knock-knees). She was not jaundiced and had no hepatomegaly. Systemic examination was otherwise unremarkable.

Baseline blood investigations done in view of slow weight gain revealed a normal renal panel, thyroid function, C-reactive protein, and slightly low hemoglobin of 11.3 g/dl (12.5-15.0 g/dl) with normal red cell indices. Serum calcium and phosphate were normal. Liver function test (LFT) (Abbott ARCHITECT c8000 analyzer) revealed elevated AP of 959 U/L (range 156-369 U/L) with mildly raised aspartate aminotransferase (AST) (50 U/L) and a normal gamma-glutamyl transpeptidase. Her vitamin D levels were normal. Viral studies (antihepatitis A virus [HAV], hepatitis B surface antigen, and antihepatitis C virus [HCV]) done by referring doctor were nonreactive.

In view of her being systemically well with isolated elevation of AP on laboratory tests and no other sign of bone or liver disease, a diagnosis of THP was considered. She was referred to dietician and a follow-up was arranged in 4 weeks with a view to repeat LFT and plan further investigations if AP levels were still markedly raised. Repeat test 4 weeks later showed return of AP to normal (222 U/L) with normal AST which confirmed the diagnosis of THP.

DISCUSSION

Characteristic features of THP as defined by Kraut et al. [3] include an age of presentation less than 5 years, no other evidence of bone or liver disease on physical examination or laboratory findings except for the spectacular isolated rise in serum AP activity, elevation in both bone and liver isoenzyme fractions, and a return to normal serum AP values within 4 months.

Table 1: Characteristics of transient benign hyperphosphatasemia (Gualco et al.) [5]

Marked increase (mostly ≥5 higher than the upper reference range*) in AP level
Affects both sexes equally
Affects especially healthy infants and toddlers (with prevalence between 1.1% and 3.5%). One-quarter of the published cases occur in older children, adolescents, or in adults
The condition sometimes also affects the subjects with a chronic underlying disease (the diagnosis can be tricky in this setting#)
History of a recent infection (typically from a virus) in >60% of the cases (but no clear-cut causal association with the preceding infection)
No clinical evidence of any bone disease (delayed closure of the fontanelles, soft skull bones, parietal and frontal bossing, enlargement of the costochondral junction, Harrison groove at the lower margin of the thorax, widening of the wrists, double malleoli sign, progressive lateral bowing of femur and tibia) or liver disease (jaundice, itching, spider naevi, bruises, prominent abdominal vessels, and hepatosplenomegaly)
No laboratory evidence of bone or liver disease; AP level mostly resolves spontaneously within 16 weeks without intervention (but persists for ≥17 weeks in one-fifth of the cases)

***Adjusted for age, sex, and laboratory's own normal values, #And in adults. AP: Alkaline phosphatase**

The exact cause for the transient rise in AP levels is unknown. This condition appears to have no long-term adverse consequences [1]. Huh et al. also found THP to be a relatively common condition among healthy infants and toddlers. In their prospective cohort, the prevalence of THP was not associated with seasonal clustering, anthropometric measures, or biochemical markers of calcium and vitamin D metabolism [4]. Gualco et al. [5] in a systematic review of the literature found that the elevation in AP persists for >4 months in ≈20% of the cases. In childhood, THP often follows a benign, mostly viral infection. They concluded that THP is likely the most common cause of hyperphosphatasemia among healthy infants and toddlers (Table 1).

Teitelbaum et al. [6] in a prospective cohort of 20 children with benign THP with an average age of children of 2.5 years (range: 1 year 2 months-5 years) and an average serum AP of 2383 IU/L (range: 1013-5700 IU/L) with no additional investigations except repeat serologic evaluation in 2-3 months found AP levels returned to normal within several months.

Our child had raised serum AP and mildly raised AST. The reason for mild elevation of AST is not known but may suggest a recent viral infection. Tests for hepatotropic viruses - such as HAV, hepatitis, B, and HCV - were negative. We did not extend our screening to include other viruses as the repeat tests showed normalization of the AST.

CONCLUSION

THP is a benign condition in healthy children and serum AP returns to normal within few months without any intervention. Awareness of THP among clinicians shall help avoid unnecessary, extensive and expensive investigations in children presenting with isolated raised AP levels, in the absence of any underlying liver, bone, and gastrointestinal disease.

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Funding: None; Conflict of Interest: None Stated.

How to cite this article: Sahu VK. Transient hyperphosphatasemia: A case report. Indian J Child Health. 2016; 3(4):344-345.