The Turkish Journal of Pediatrics 1999; 41: 151-160 Review

TRANSIENT HYPERPHOSPHATASEMIA – WHERE DO WE STAND?*

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SUMMARY: Kutílek Š, Bayer M. (Department of Pediatrics, Charles University Faculty of Medicine, Prague, Czech Republic). Transient hyperphosphatasemia-where do we stand? Turk J Pediatr 1999; 41: 151-160.

Transient hyperphosphatasemia of infancy and early childhood (THI) is characterized by transiently increased serum activity of alkaline phosphatase (S-ALP), predominantly its bone or liver isoform, in children under five years of age. There are no signs of metabolic bone disease or hepatopathy corresponding with the increased S-ALP, nor is there a disease common to all children with THI. To date, THI has been reported in more than 400 children. Viral etiology of THI has been proposed; transiently increased bone turnover and impaired clearance of ALP from the serum were originally considered as its causes. The pathogenesis is most probably multifactorial. THI is a benign disorder, as prospective follow-up of children with a history of TH revealed normal growth and normal bone density. Children with TH should be spared from excessive diagnostic procedures. *Key words: alkaline phosphatase, hyperphosphatasemia.*

The serum activity of alkaline phosphatase (S-ALP) is a routine marker in the diagnosis of hepatic disorders and metabolic bone diseases. In healthy adults, the major activity of S-ALP is represented by liver and bone isoenzymes, while in healthy infants and children, as a result of growth, serum is rich in the bone isoenzyme of ALP[1,2]. Increased total S-ALP, termed as hyperphosphatasemia, is usually indicative of hepatopathy or is a marker of increased bone formation. Further determination of the ALP isoenzymes and isoforms is helpful in identifying the cause of hyperphosphatasemia.

Transient hyperphosphatasemia of infancy and early childhood (THI) is characterized by transiently increased S-ALP, predominantly its bone or liver isoform, in children under five years of age. There are no signs of metabolic bone disease or hepatopathy corresponding with the increased S-ALP, nor is there a disease common to all children with THI. To date, THI has been reported in more than 400 children. The etiology of the condition remains unclear, as does its mechanism. In this article, we focus on its clinical and biochemical features and management and the prognosis for children with TH.

History and Criteria of THI

Transient hyperphosphatasemia of infancy and early childhood (THI) was first observed by Bach et al.[3] in 1954. In 1969, Geudeke[4] performed an analysis of ALP isoenzymes and found that the hepatic isoform was responsible for the

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high ALP activity. In 1977, Posen et al.[5] observed increased activity of the bone isoform of ALP in children without metabolic bone disease. They considered this a new and insufficiently recognized syndrome and used the term "transient hyperphosphatasemia of infancy" for the first time. Wieme[6] performed an electrophoretic evaluation of the ALP isoenzymes in 1983 and discovered a new atypical pattern which consisted of cathodal and anodal migrating fractions, bearing some similarities to those isoforms of bone and liver origin. This pattern was considered a characteristic biochemical feature of THI[6, 7]. In 1983, Weiber et al.[8] documented a return to normal isoenzyme pattern which occurred simultaneously with the return of total S-ALP to normal values. The definition of THI remained vague until Kraut et al.[9] delineated criteria for its diagnosis in 1985. These include:

1. an age of less than five years.
2. variable, unrelated symptoms,
3. no bone or liver disease noted on physical examination or
4. from laboratory investigations,
5. isoenzyme and isoform analysis showing elevations in both bone and liver activity, and
6. a return to normal S-ALP values within four months.

However, these criteria may need some corrections, as THI has occasionally been observed in adults, and since the duration of THI has repeatedly exceeded the time limit of four months[7, 10-13].

Clinical and Biochemical Features of Children with THI

Transient hyperphosphatasemia of infancy and early childhood has been observed in healthy children, as well as in children with various chronic and acute diseases, in particular in children with respiratory, urinary and gastrointestinal tract infections, viral infections, hematological disorders (anemia, lymphoblastic leukemia), neurological affections (breath-holding spells, epilepsy, cerebral palsy), malabsorption syndrome, allergic disorders, Crohn's disease, metabolic bone diseases (vitamin D-dependent rickets type I, vitamin D-deficient rickets), in patients after liver transplantation and in children with congenital abnormalities[7, 11, 14-22]. In the above-mentioned patients with metabolic bone diseases and those with liver transplantation, no relationship was found between the severity of their state and S-ALP[16, 18, 21]. Transient hyperphosphatasemia had earlier THI been related to treatment with co-trimoxazol[7, 23], but this is unlikely, as THI has occurred in children who were never treated with this drug. A seasonal clustering of THI has been described, with the highest incidence reported September through December[19]. However, such clustering has not been observed by other authors[12].

The peak total S-ALP is typically five to 30 times the adult upper reference limit (URL), but it may exceed this limit up to 70 times[7]. The atypical isoenzyme pattern as revealed by the electrophoretic evaluation of ALP is a characteristic biochemical feature of THI. However, this is not reflected by inactivation-inhibition methods, where bone and hepatic isoforms prevail[7]. The serum concentrations of calcium and phosphate (S-Ca, S-P) and activity of transaminases (S-ALT, S-AST) in children with TH are within reference ranges and thus are not suggestive of either metabolic bone disease or hepatopathy[7]. However, there are reports of changes in markers of bone resorption during the course of THI, as increased serum activity of tartrate resistant acid phosphatase (S-TRAP) was observed in one child[24] and increased urinary excretion of hydroxyproline was observed in 15 children[25-21].

In a recent multicenter study by Griffiths et al.[28], electrofocusing technique was applied in the S-ALP analysis. S-ALP Serum activity of alkaline phosphatase was evaluated in 135 children aged three months to 12 years with hyperphosphatasemia, who were diagnosed as THI; numerous actively involved tissue sites were identified as the source of increased S-ALP[28]. Based on the results, the patients were sorted into three groups[28]:

1. Previously healthy patients, who showed additional laboratory evidence of viral and protozoal infection, in whom the ALP isoenzyme pattern reflected the primary target organ(s) of the infection;

2. Patients with clinical evidence of failure to thrive due to preexisting disease, along with a superimposed infection, where the ALP isoenzyme pattern reflected the specific infection and fractions associated with the primary disease; and

3. Patients exhibiting failure to thrive (nonorganic or caloric deficit) who did not show evidence of infection.

With adjustment of the children's caloric intakes, the S-ALP levels returned to reference ranges in the third group[28].

Transient hyperphoptasasemia is definitely not a rare condition, as its incidence varies between 0.3-1.5 percent[14, 19, 29]. There is no preponderance by sex[7].

Transient hyperphosphatasemia was initially termed as the "Ulysses syndrome", as the patients underwent an odyssey of investigations with no conclusive results[30].

Suggested Etiology and Mechanisms

The etiology of THI is currently believed to be an infectious one, as some of the children with THI experienced signs of viral disease, including fever and gastrointestinal irritation, two to three weeks prior to the diagnosis of THI[7, 28]. Furthermore, THI was observed in siblings and in children who were hospitalized together, further suggesting the infectious, most probably viral origin[31-34]. So

far, all attempts to find a common causative infectious agent have failed, as THI has been diagnosed in children with cytomegalovirus, rotavirus, adenovirus, herpes simplex virus, echovirus, rhinovirus, influenza A, B, C, respiratory syncytial virus and Epstein-Barr virus infections[7, 8, 28, 35-38]. The study using electrofocusing techniques further confirmed the viral origin of THI[28].

The question remains whether a small group of children will respond to infection with a high magnitude of S-ALP or, conversely, do all children respond, but only a small number undergo laboratory investigations that include evaluation of S-ALP[28].

To date, four mechanisms have been proposed as responsible for the elevated serum ALP activity:

1. Increased Production of ALP in its Tissue of Origin, Most Probably in Bone and Liver

Part of this hypothesis is based upon isolated findings of increased S-TRAP and urinary hydroxyproline excretion, which are markers of bone resorption, in patients with THI[24-27]. The temporary increase in bone resorption is known to be closely coupled to bone formation and followed by increased osteoblast activity[39]. Furthermore, the duration of THI (4 months) resembles the duration of the bone resorbing cycle. Therefore, it has been postulated that in THI, the increased ALP activity, reflecting high bone formation, is preceded by an increased bone resorption, as evidenced by the increased urinary hydroxyproline excretion and/or high S-TRAP[26, 38]. We have earlier speculated that putative transient increase in bone resorption might have been triggered by the viral infection[26, 38]. However, the heterogeneity of viral agents diagnosed in children with THI makes this hypothesis less likely. Furthermore, there has not been a similar increase observed in other markers of bone resorption in patients with THI, and there was no correlation between ALP activity and urinary hydroxyproline excretion[27].

The release of ALP into the circulation from the liver as a result of cell destruction is unlikely, as S-ALT, S-AST and hepatic biopsy samples did not indicate evidence of hepatic disease[7, 28].

2. Increased Production of ALP Triggered by the Increased Conversion of Vitamin 25-OH-D to 1,25 $(OH)_2$ Vitamin D in Children with Previous Failure to Thrive

This hypothesis is based upon seasonal clustering of THI described by some authors, and upon an observed relationship between changes in body weight and serum concentrations of vitamin D metabolites[19]. Weight loss in adults has been reported to be associated with decreases in concentrations of 1,25 $(OH)_2$ vitamin D (calcitriol) and conversely, weight gain is associated with increases

in serum calcitriol levels[40]. In addition, 1,25 $(OH)_2$ vitamin D stimulates the synthesis of ALP in bone and possibly also in the liver[19, 41]. Therefore, it has been speculated that a period of weight loss (for various reasons) during the summer, when 25-OH vitamin D levels are relatively high, might block conversion to 1,25 $(OH)_2$ vitamin D, leading to further accumulation of 25-OH vitamin D. Then, as catch-up growth occurs, the block may be lifted. The accumulated 25-OH vitamin D is converted to 1,25 $(OH)_2$ vitamin D, causing a surge in this metabolite that stimulates synthesis of ALP[19]. However, seasonal clustering of THI, which is one of the fundamental points of this hypothesis, has not been universally confirmed[12].

3. Increased Activation of Circulating ALP

The activation of circulating enzymes is quite improbable in view of the unusual isoenzyme pattern[7].

4. Impaired Clearence of ALP from the Circulation

This hypothesis is based upon experimental findings in mice infected with Riley virus, resulting in impaired clearance of certain enzymes from the circulation by the reticuloendothelial system[42]. Alkaline phosphatase, like other glycoproteins, is cleared from the circulation by hepatocyte uptake, and removal of the sialic acid residues is probably required prior to the clearance[19, 43]. Virus-induced sialylation of the liver and bone isoenzymes with a consequent decrease in uptake and clearance might lead to high concentrations of the ALP molecules in serum[7, 19]. The findings of atypical anodal-migrating ALP isoenzyme and signs of viral infection preceding the THI support this hypothesis. The impaired clearance of ALP from the circulation is still considered as the most likely mechanism of THI, which may be in combination with the mechanisms mentioned above in items 1 and 2[7, 19]. The pathogenesis of THI is thus most probably a multifactorial one.

Differential Diagnosis of THI

Once the grossly increased S-ALP is encountered, it is necessary to rule out other, more serious reasons of hyperphosphatasemia, in particular metabolic bone diseases, bone tumors or hepatopathy. It is important for the clinician to consider THI in the differential diagnosis and to avoid unnecessary investigation[44].

1. Metabolic Bone Disease

In either vitamin D-deficient rickets or vitamin D-dependent rickets type I or II, the increased S-ALP is accompanied by low-to-normal calcemia, hypophosphatemia, hyperphosphaturia and secondary hyperparathyroidism. In X-linked hypophosphatemia (vitamin D-resistant rickets), there is hypophosphatemia and

hyperphosphaturia, while serum concentrations of calcium and parathyroid hormone (S-PTH) are within reference ranges. In all types of rickets, rachitic changes are apparent on the radiograph of wrist.

Familial benign hyperphosphatasemia of autosomal dominant inheritance is characterized by increased S-ALP, predominantly of intestinal, bone and liver origin, with no biochemical nor skeletal abnormalities[45, 46].

Persistent non-familial asymptomatic hyperphosphatasemia occurs in both children and adults. The increased S-ALP is of skeletal origin and persists for six to 10 years. No other abnormalities are reported[47].

Primary idiopathic hyperphosphatasemia (juvenile Paget's disease) is an autosomal recessive disorder characterized by severe skeletal deformities, dwarfism, premature loss of teeth, high S-ALP and increased urinary hydroxyproline excretion[48, 49].

Jansen type of metaphysial dysplasia is caused by a constitutively active mutant receptor for parathyroid hormone (PTH), resulting in low-to-normal S-PTH, hypercalcemia, hypophosphatemia, hypercalciuria and high S-ALP. The children manifest with growth disturbance, short limbs and progressive metaphysial changes, initially reminiscent of rickets[50, 51].

Primary hyperparathyroidism is extremely rare in childhood, and is characterized by hypercalcemia, hypophosphatemia, hyperphosphatasemia, hyperphosphaturia, increased serum concentrations of PTH and subperiosteal lesions on the radiograph of the hand[52].

In renal osteodystrophy, hyperphosphatasemia is a result of secondary hyperparathyroidism and is present together with hypocalcemia, hyperphosphatemia and high serum creatinine levels[53].

Infantile cortical hyperostosis (Caffey's disease) occurs in infants under three months of age and is characterized by febrile course with marked swelling of soft tissues over the face and jaws together with progressive cortical thickening of long and flat bones. The S-ALP is midly elevated[54].

2. Bone Tumors

Increased S-ALP is a biochemical feature of osteosarcoma; however, this tumor occurs in patients over 10 years of age[55].

3. Hepatopathy

Increased total S-ALP with normal serum levels of bilirubin and normal transaminases (S-AST, ALT) activity is not indicative of hepatic disorders.

Management of Children with THI

Transient hyperphosphatasemia is generally considered a benign disorders. In children under five years of age with S-ALP exceeding five times the adult upper reference limit and no other apparent signs of bone or hepatic disease, the

diagnosis of THI should be taken into consideration. In 1988, Schonau et al.[56] proposed an algorithm for effective management of children with THI. One of the leading indices is electrophoretic evaluation of the ALP isoenzymes, as an unusual isoenzyme pattern is the most characteristic sign of THI. Unfortunately, electrophoretic evaluation of the ALP isoenzymes is not a universally available method. In such cases, the assessment of other relevant indices is necessary, together with the radiograph of the wrist. If basic biochemical markers (S-Ca, P, creatinine, ALT, AST) and radiograph of the wrist are normal, THI is the most likely diagnosis. Therefore, children with TH should be spared from further diagnostic procedures (such as ^{99}Tc bone scans, repeated radiographs and blood draws), and the S-ALP can be reassessed after two to three months.

On rare occassions THI might interfere with rickets. There is no causal relationship between those two conditions[18, 21]. Transient hyperphosphatasemia might occur or persist after the healing of rickets; it is the electrophoretic evaluation of S-ALP and the radiograph of the wrist which are helpful. A control x-ray of the wrist is required to confirm the healing of rickets. The abnormal isoform pattern obtained by the electrophoresis of ALP, or signs of healing or healed rickets in cases of THI following vitamin D-deficient rickets, can spare the children from unnecessary vitamin D overdosage[21].

Prognosis

As THI has been related to transiently increased bone resorption and formation[26, 27], questions have been raised about the further development and prognosis of children with a history of TH[7, 26]. Of particular concern was its postulated viral origin and thus a suggested parallel to Paget's disease[5, 7, 26]. Therefore, a follow-up of children with TH was recommended[7, 26]. It seems likely that any sharp increase in bone turnover during infancy and early childhood would influence bone density and somatic growth. However, in our recent work we did not observe any signs of stunted growth or failure to thrive during one to 102 months of follow-up of 40 children with a history of TH or with 29 children followed up for 12-102 months[57]. Neither was there a recurrence of THI: S-ALP was assessed in 12 of those children, six to 60 months after the last detection of THI, and was always found to be within reference ranges, together with normal S-AST and S-ALT values. Bone density, as reflected by velocity of ultrasound and broad band ultrasound attenuation of both heel bones, in seven children with a history of TH, was within reference ranges[57]. These data further suggest that THI is a benign state with good prognosis in a time horizon of at least eight years.

Conclusion

Transient hyperphosphatasemia of infancy and early childhood is a benign disorder, a biochemical rather than a clinical abnormality, of multifactorial

pathogenesis and transient character, with good prognosis. Children with TH should be spared from extensive investigations and unnecessary vitamin D applications.

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