Transient hyperphosphatemia: a benign laboratory disorder in a boy with Gitelman syndrome

Hiperfosfatemia transitória: uma alteração laboratorial benigna em um menino com síndrome de Gitelman

Authors
Sylva Skalova [1]
Stepan Kutilek [2]

[1] Medical Faculty Hradec Kralove, Hradec Kralove, Czech Republic.
[2] Hospital Klatovy, Klatovy, Czech Republic.

Abstract

Transient hyperphosphatasemia of infancy and early childhood (THI) is characterized by transiently increased activity of serum 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. THI is benign disorder, rather laboratory than clinical disorder, which is usually accidentally detected in both healthy and sick children. When encountered in a child with either chronic bone, liver or kidney disease, it might concern the physician. We present a three year old boy with genetically confirmed Gitelman syndrome where THI was detected accidentally during periodic check-up. S-ALP peaked to 41.8 µkat/L, there were neither laboratory or clinical signs of liver or bone disease; the S-ALP dropped to normal value of 4 µkat/L 60 days later. Therefore, the patient fulfilled the criteria for THI. There were no further increases in S-ALP.

Keywords: alkaline phosphatase; bone diseases, metabolic; Gitelman syndrome.

Resumo

A hiperfosfatasemia transitória benigna da infância (HTBI) é caracterizada por elevação transitória da atividade da fosfatase alcalina sérica (S-ALP), predominantemente em sua isoforma óssea ou hepática, em crianças com menos de cinco anos de idade. Não há sinais de patologia óssea metabólica ou hepatopatia correspondentes ao aumento da S-ALP. A HTBI é um distúrbio benigno, mais laboratorial que clínico, normalmente detectado acidentalmente em crianças saudáveis e acometidas por alguma patologia. Quando encontrada em crianças com doença crônica óssea, hepática ou renal, maiores preocupações são justificadas. O presente relato descreve o caso de um menino de três anos de idade com síndrome de Gitelman geneticamente confirmada, em que a HTBI foi detectada acidentalmente durante um exame periódico. A S-ALP atingiu o pico de 41,8 µkat/L, sem sinais laboratoriais ou clínicos de doença hepática ou óssea. O valor de S-ALP caiu para o nível normal de 4 µkat/L 60 dias mais tarde. Portanto, o paciente satisfazia os critérios para **HTBI. Não houve outros aumentos na S-ALP.**

Palavras-chave: doenças ósseas metabólicas; fosfatase alcalina; síndrome de Gitelman.

Introduction

Transient hyperphosphatasemia of infancy and early childhood (THI) is characterized by transiently increased activity of serum 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 there is a disease common to all children with THI.

THI is benign, rather laboratory than clinical disorder, which is usually accidentally detected in both healthy and sick children.[1-3] When encountered in a child with either chronic bone, liver or kidney disease, THI might concern the physician.[2,3]

Case report

Three year old boy with genetically confirmed Gitelman syndrome (three

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Correspondence to:
Sylva Skalova.
Faculty of Medicine in Hradec Kralove, Charles University in Prague, Czech Republic.
Hradec Kralove, 500 05, Czech Republic.
E-mail: skalovasylva@seznam.cz

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different mutations in SLC12A3 gene; c.2576T > C and c.2929C > T mutations considered as causal ones; mother: heterozygous carrier of mutation c.2567T > C; father: heterozygous carrier of mutation c.2929C > T), reported earlier,[4] presented for a periodic check-up in our out-patient clinic. He was receiving potassium supplementation (KCl tablets 3x1000 mg/day) and ACE inhibitor (enalapril; 1.25 mg/day).

He was doing well, without any clinical signs of psychomotor retardation or tendency to failure to thrive. The serum values of blood urea nitrogen (BUN), creatinine, potassium(S-K), sodium (S-Na), calcium (S-Ca), phosphate (S-P), magnesium (S-Mg), alanin-aminotransferase (S-AST), apartate-aminotransferase (S-ALT) were within normal reference range, same as urinary concentrations of Ca, P, Mg and urinary calcium/creatinine ratio (U-Ca/U-cr).

However S-ALP was 41.8 μkat/L and this value was confirmed by the biochemical lab (normal age-related value 1.8 - 6.7 μkat/L). Wrist X-ray was normal without any signs of rickets. As there were neither laboratory or clinical signs of liver or bone disease, THI was considered as the most likely diagnosis. The boy was checked two months later, and at that time the S-ALP dropped to normal value of 4 μkat/L. Therefore the patient fulfilled the criteria for THI. There were no further increases in S-ALP and the patient, who is currently 10 years old, remains stable on the current medication of KCl and enalapril.

Discussion

Gitelman syndrome (GS) is a rare autosomal recessive salt-wasting nephropathy, characterized by hypokalemia, hypomagnesemia, hypocalciuria, metabolic alkalosis and low blood pressure. Typical clinical signs include fatigue, muscle weakness and muscle paralysis.[4,5] Transient hyperphosphatasemia of infancy and early childhood (THI) has been reported in more than 800 subjects, both sick and healthy children.[1-3] The definition of THI was delineated by Kraut in 1985 using the following criteria:

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

These criteria are not strict, as THI has been occassionaly observed even in adult individuals, and the duration of THI has repeatedly exceeded the time limit of 4 months.[2,3,7] Furthermore, the electrophoretic evaluation of the ALP isoenzymes in THI is characterized by an atypical transient pattern of cathodal and anodal migrating fractions, bearing some similarities to the isoforms of bone and liver origin.[8] The incidence of THI has been estimated at 2.8%.[9]

The etiology of THI was presumed to be an infectious one, as some of the children with THI experienced signs of viral disease 2-3 weeks prior to the S-ALP elevation and THI was also observed either in siblings or in children who were hospitalised together.[10-12] The exact mechanism of THI is unclear, however, the impaired clearance of ALP from circulation is still considered as the most likely one.[1,2]

THI is generally considered a benign disorder. Furthemore, THI has to be differentiated from skeletal or liver diseases and can cause concern in patients with metabolic bone disorders.[13] However, normal bone turnover has been observed in children with THI.[14,15] In the presence of high S-ALP where basic biochemical markers (S-Ca, P, creatinine, ALT, AST) and radiograph of the wrist are normal, THI is the most likely diagnosis. Therefore, the children with THI should be spared from further diagnostic procedures (such as ^{99}Tc bone scans, repeated radiographs and blood draws) and the S-ALP can be re-assessed after 2-3 months.[2,16]

Our patient with genetically confirmed GS presented with high S-ALP, thus drawing some concern about disturbed bone metabolism due to possible mineral dysbalance that may occur in GS.[5,17] However, the normal values of S-Ca, P, Mg, U-Ca/U-cr and normal wrist X-ray ruled out this possibility and pointed to the diagnosis of THI, which was further confirmed by normalisation of S-ALP within two months.

In conclusion, we presented a case of THI in a boy with GS. This case met the criteria for THI, which is a benign condition with good prognosis. Extremely high values of S-ALP can draw some concern, especially in children with chronic disorders of kidney, bone or liver.[2,3,13,16-18] Children with THI should be spared from unnecessary early diagnostic procedures and therapeutic interventions. The monitoring of S-ALP on a monthly or two-monthly basis is recommended before any further diagnostic steps are undertaken.

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