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TRANSIENT BENIGN HYPERPHOSPHATASEMIA DUE TO ROTAVIRUS GASTROENTERITIS

ROTAVİRÜS GASTROENTERİTİNE BAĞLI GEÇİCİ BENİGN HİPERFOSFATAZEMİ

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ABSTRACT

Transient benign hyperphosphatasemia (TBH) is a benign condition characterized by transiently elevated serum alkaline phosphatase (ALP) levels by 3-50 times normal values. It can sometimes be seen in connection with different clinical disorders such as respiratory tract infections, gastrointestinal diseases, congenital metabolic disorders, malignancies, congenital anomalies, anemia, and neurological disorders. In this report, we describe three children who had TBH after rotavirus-associated gastroenteritis and in whom there was no evidence of liver or bone disease. We aim to raise awareness and draw attention to TBH in this case report.

Keywords: Transient hyperphosphatasemia, alkaline phosphatase, rotavirus, gastroenteritis, children

ÖZET

Geçici benign hiperfosfatazemi (TBH), serum alkalen fosfataz (ALP) düzeylerinin normalin 3-50 katı kadar geçici olarak yükselmesi ile karakterize ve bazen de gastrointestinal hastalıklar, solunum yolu enfeksiyonları, doğumsal anomaliler, doğumsal metabolik bozukluklar, anemi, maligniteler, nörolojik bozukluklar gibi farklı klinik bozukluklarla birlikte görülebilmektedir. Bu çalışmada, karaciğer veya kemik hastalığı olmayan, rotavirüs ile ilişkili gastroenterit sonrası TBH'li üç çocuk sunuldu. Bu olguların sunulması ile TBH konusuna dikkat çekilmesi ve farkındalık yaratılması amaçlandı.

Anahtar Kelimeler: Geçici hiperfosfatazemi, alkalin fosfataz, rotavirüs, gastroenterit, çocukluk evresi

INTRODUCTION

Alkaline phosphatase (ALP) is present in different concentrations in many tissues such as the placenta, ileal mucosa, kidney, bone, and liver. In healthy individuals, more than 80% of ALP in serum is released from the liver and bone. Levels of serum ALP are high during childhood and adolescence, mainly due to bone growth and development (1, 2). Transient benign hyperphosphatasemia (TBH) is a benign condition characterized by above normal levels of serum alkaline phosphatase (ALP), transiently elevated by 3-50 times the normal value. This disease can be seen in connection with different clinical disorders such as respiratory tract infections, gastrointestinal diseases, congenital metabolic disorders, malignancies, congenital anomalies, anemia, and neurological disorders (3).

The characteristic features of TBH have previously been described in the literature: a) no signs of liver or bone disease on laboratory findings or physical examination, b) serum ALP elevation, c) return to normal levels of serum ALP within four months, d) age of presentation less than five years (4).

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In this report, we describe three children who had TBH after rotavirus-associated gastroenteritis. This study aims to raise awareness and draw attention to TBH.

CASE PRESENTATIONS

A two and half-year-old female, a three-year-old boy and a four and a half-year-old boy were admitted to our pediatric emergency department with the complaint of acute diarrhea. All three cases had been born full term, and their neuromotor developments were compatible with their peers. They had no history of illness and were not on any medication. Their physical examinations were normal except for increased bowel sounds. Their growth parameters were normal for their age. When rotavirus antigen was tested in fresh stool specimens of the patients, all samples were positive. The initial blood test results of the patients are shown in Table 1. Their laboratory examinations also revealed high ALP activity.

Levels of 25-hydroxy vitamin D, parathormone, phosphorus, and calcium were all within normal values. Skeletal radiographs were checked, and they were all normal as well. Liver function tests, albumin, total and direct bilirubin and prothrombin time were all within normal values. Abdominal ultrasonography for possible hepatic disorders were normal. The results of examinations carried out on the parents were within normal levels. After excluding bone and liver diseases in the differential diagnosis, we thought that the high ALP levels might be due to rotavirus gastroenteritis. Serial levels of ALP were checked during follow-up of the patients (Table 2). Alkaline phosphatase levels decreased and returned to normal levels at 3 months. As a result of all these findings, the patients were diagnosed with TBH due to acute rotavirus infection.

Informed consent was obtained from the families of the patients for the publication of the case report.

DISCUSSION

Alkaline phosphatase is a widely used biochemical marker to screen for hepatic or skeletal disorders. Therefore, patients with high ALP levels are potentially referred to tertiary care centers for further evaluation. Transient benign hyperphosphatasemia is a benign condition typically caused by viral infections such as Epstein-Barr virus, enterovirus, and rotavirus. However, it is certainly difficult to diagnose TBH in children (5-8). Behulova et al. reported a wide variety of clinical disorders associated with TBH (9). The most common diseases associated with TBH are gastrointestinal diseases (24%), respiratory infections (21%), congenital anomalies and metabolic diseases (15%) (9). Zemer et al. reported that the three leading diagnoses noted with hyperphosphatasemia included fever (28%), gastroenteritis or diarrhea (25%) and acute otitis media (11%) (10). Suzuki et al. reported that the four most common infectious diag-

Table 1: Initial blood test results of patients

	Case-1	Case-2	Case-3	Reference range
ALT (IU/L)	10	24	31	5-45 IU/L
AST (IU/L)	10	23	39	15-55 IU/L
GGT (U/L)	16	28	24	5-32 U/L
D bil (mg/dl)	0.21	0.40	0.35	0-0.5 mg/dl
ALP (IU/L)	1846	2423	1958	145-420 IU/L
LDH (U/L)	348	284	326	180-345 U/L
Ca (mg/dl)	9.2	9.6	10.2	8.8-10.8 mg/dl
P (mg/dl)	4.0	4.3	4.8	3.7-5.6 mg/dl
PTH (pg/dl)	38	41	31	9-65 pg/dl
25 (OH) Vit. D (ng/ml)	36	28	34	7.4-53.3 ng/m

ALP: Alkaline Phosphatase, Ca: Calcium, P: Phosphorus, PTH: Parathormone, LDH: Lactate dehydrogenase, 25 (OH) vit. D: 25-Hydroxy Vitamin D, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma glutamyl transferase, D bil: Direct bilirubin

Table 2: Serial ALP (IU/L) measurements

	1st day	3rd day	7th day	1st month	2nd month	3rd month	4th month
Case 1	1846	2284	2784	1946	454	401	345
Case 2	2423	2372	2057	1155	427	354	320
Case 3	1958	1848	1764	978	357	368	290

noses observed in TBH cases were bronchitis, pneumonia, diarrhea, and fever (11). The pathogenesis of TBH is not fully understood. The presence of diarrhea may lead either to impaired clearance of ALP from the circulation or to increased production of ALP secondary to hyperactivated osteoblasts (6). In our cases, TBH was associated with diarrhea or rotavirus infection.

The prevalence of TBH is difficult to estimate because it is usually discovered incidentally in laboratory tests requested for other reasons (12). Its prevalence in patients whose age falls between 6 months and 5 years ranges between 2-6% depending on the ALP values used for the diagnosis (13-17). In one study, 2.8% of patients had a transient and unexplained elevation of the ALP level among 321 healthy infants and toddlers aged 8-24 months (13). A study in Israel reported that 87% of patients with TBH between the ages of one day and 18 years consisted of children under the age of 2 years (10). This condition is not common in older children or adults (15). All three patients in our case report were under 5 years old, which is consistent with the literature.

An evaluation of the patient with a detailed history, basic laboratory tests, and accurate physical examination are usually sufficient to exclude possible bone or liver disease. We found 25-hydroxy vitamin D, parathormone, phosphorus and calcium levels within normal values, therefore we excluded increased bone turnover. High levels of serum ALP (3-50 times above the normal value of serum ALP levels) return to normal levels within an average of four months in TBH. It is recommended that the diagnosis of TBH according to age criteria should be considered in children younger than five years old (4). Although there is no clear information on the timing to check the ALP levels in the follow-up of patients with TBH, a conservative approach recommending testing again in 2-3 months has been reported to be safe and cost-effective (17). In our patients, the time it took for ALP levels to normalize again was within four months, and all children with TBH were under five years of age, consistent with both Kraut's criteria and previous reports (4, 5, 17). In the follow-up of our patients, their growth and development were normal, and no additional pathology was observed. According to these findings, our patients met all the diagnostic criteria of TBH.

Transient benign hyperphosphatasemia is associated with a marked but transient benign elevation of ALP without any other abnormality and it does not have any specific treatment (7). No special treatment was applied to our patients except symptomatic treatment. The clinical course of our patients showed an event-free improvement in the expected time, consistent with previously reported cases.

CONCLUSION

Transient benign hyperphosphatasemia is a self-limited clinical condition, and no treatment is required. For patients with elevated ALP for any reason, if there is no known chronic disease nor evidence of bone or liver diseases, outpatient follow-up will be sufficient until their ALP values decrease. Awareness of this condition among pediatricians will reduce expensive and unnecessary investigations.

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