Transient Hyperphosphatasemia Following Gastroenteritis: Avoid Over-Investigation in Otherwise Healthy Children

Gastroenterit Sonrası Geçici Hiperfosfatazemi: Sağlıklı Çocuklarda Aşırı Tetkikten Kaçınılmalı

Gizem YILDIZ [1] Erkam YILDIRIM [1] Meral TORUN BAYRAM [1]
Salih KAVUKÇU [1] Alper SOYLU [1]

[1]Dokuz Eylül University Faculty of Medicine, Department of Pediatrics, Izmir, Türkiye.

Abstract: Benign transient hyperphosphatasemia (BTH) is a self-limiting condition characterized by markedly elevated serum alkaline phosphatase (AP) levels in the absence of liver or bone disease, most commonly seen in children under 2 years of age. It often follows infectious episodes, particularly gastroenteritis. This study aims to raise awareness of BTH and emphasize the importance of avoiding unnecessary investigations in otherwise healthy children.

We present three male patients aged 13 months, 42 months, and 6 years, all of whom exhibited significantly elevated AP levels following gastroenteritis episodes. None showed clinical or laboratory evidence of liver or bone pathology. AP levels returned to normal within 1–2 months without intervention, confirming the diagnosis of BTH.

BTH is a benign, temporary condition with excellent prognosis. Recognizing its clinical features can help clinicians adopt a “wait and see” approach, reduce parental anxiety, and avoid unnecessary referrals and testing, even in children outside the typical age range.

Keywords: Transient hyperphosphatasemia, gastroenteritis, children

Özet: Benign geçici hiperfosfatazemi (BGH), karaciğer veya kemik hastalığı olmaksızın serum alkalen fosfataz (AF) düzeylerinin belirgin şekilde yükselmesiyle karakterize, kendiliğinden düzelen bir durumdur ve en sık 2 yaş altı çocuklarda görülür. Genellikle enfeksiyon ataklarını, özellikle de gastroenteriti takiben gelişir. Bu çalışma, BGH’ye dikkat çekmeyi ve sağlıklı çocuklarda gereksiz tetkiklerden kaçınmanın önemini vurgulamayı amaçlamaktadır.

Gastroenterit sonrası belirgin AF yüksekliği gösteren, yaşları 13 ay, 42 ay ve 6 yıl olan üç erkek hasta sunulmuştur. Hiçbirinde karaciğer veya kemik hastalığına dair klinik ya da laboratuvar bulgusu yoktu. Müdahale olmaksızın, AF düzeyleri 1–2 ay içinde normale dönmüş ve BGH tanısı doğrulanmıştır.

BGH, tamamen iyi huylu ve geçici bir durumdur. Klinik özelliklerinin tanınması, hekimin “bekle-gör” yaklaşımını benimsemesini sağlayarak aile kaygısını azaltır ve gereksiz tetkik ve yönlendirmelerin önüne geçer. Bu yaklaşım, tipik yaş aralığı dışında kalan çocuklarda da uygulanabilir.

Anahtar Kelimeler: Geçici hiperfosfatazemi, gastroenterit, çocuk

Corresponding Author: Alper Soylu **E-mail:** alper.soylu@deu.edu.tr
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INTRODUCTION

Alkaline phosphatase (AP) is an enzyme found in different body tissues such as liver, bone, kidney and intestine, and has different isoenzymes depending on its location (Corathers, 2006). Serum AP concentration rises in some conditions related to the tissue of origin. Additionally, there is a condition called benign transient hyperphosphatasemia (BTH), which is most commonly recognized in infants and children younger than 2 years of age. It has also been described in adults. BTH is a self-limiting condition characterized by an evident elevation in AP that returns to baseline within a few months without additional systemic manifestations and any treatment (Gualco et al., 2013). It is usually accompanied by some infectious and allergic disorders. Therefore it is important to keep this entity in mind and to avoid unnecessary investigations. Here, we report two children who were diagnosed with BTH following gastroenteritis.

CASE REPORTS

Case1: A 42-month-old boy was admitted to the pediatric nephrology outpatient clinic for routine follow-up due to antenatal hydronephrosis. It was reported that the patient had viral gastroenteritis one week prior to the hospital admission, with symptoms resolving within three days. His physical examination including anthropometric development was normal. Laboratory tests were shown in Table 1. Complete blood count and biochemical tests were normal except AP level that was elevated to 16 times the upper limit of normal. 25-OH-vitamin-D level was mildly depressed, but parathyroid hormone level was normal. He had no dysmorphic features, skeletal abnormalities, bony tenderness, conjunctival icterus, hepatosplenomegaly or any other stigmata of chronic liver or bone disease. Although AP level rose up to 7030 U/L two days after the first detection, it started to decrease on the 22nd day (703 U/L) reaching to normal ranges on the 30th day. Thus, the diagnosis of BTH was made and further investigations were not required.

Case2: The second case was a 6-year-old male referred for suspected nephrolithiasis detected on ultrasound during the workup for growth retardation at a local hospital. He had a history of diarrhea 1.5 months ago. Although the acute symptoms resolved within a week, mildly soft stools persisted for an additional 2-3 weeks. Physical examination was normal and his weight and height were at 6th percentile. All laboratory tests were within normal limits except for markedly elevated AP levels (Table 1). Urinary system ultrasonography was normal. As the patient had no sign of bone or liver disease associated with increased AP level, laboratory tests were repeated 10 days later demonstrating only sharply increased AP level (2000 U/L). Thus, we considered the patient as having BTH. The diagnosis was confirmed by the return of AP levels to normal range (339 U/L) one month later.

Case 3: 13-month-old boy with known horseshoe kidney was presented for routine nephrology outpatient visit. His physical examination was normal. Laboratory tests was normal except significantly increased AP level (Table 1).

On detailed questioning, it was learned that the patient had diarrhea two weeks prior, with non-bloody and non-mucoid stools lasting for about a week. Since there were no findings of liver or bone disease to explain the patient's elevated AP levels, laboratory tests were repeated two weeks later demonstrating further increased AP level (3810 U/L). He was considered to have BTH and the diagnosis was confirmed by normalization of AP level (301 U/L) two months later. Informed consents were received from the families.

Table 1: Anthropometric data and laboratory analyses of case 1 and 2 at the first visit.

	Case 1	Case 2	Case 3
Anthropometric data			
Height percentile (SDS)	33 (-0.45)	6 (-1.53)	33 (-0.44)
Weight percentile (SDS)	46 (-0.10)	6 (-1.49)	24 (-0.68)
Complete blood count			
White blood cells (10^9 cells per liter)	8.6	8.8	9.7
Hemoglobin (g/dl)	11.7	13.0	11.0
Platelet count (10^9 per liter)	321	401	465
Neutrophil count (%)	54.0	52.8	44.4
Lymphocytes (%)	32.0	39.7	44.9
Monocytes (%)	9.3	5.8	8.3
Eosinophils (%)	2.7	1.3	2.1
Basophils (%)	0.7	0.4	0.3
Biochemistry			
Sodium (mmol/L)	140	141	137
Potassium (mmol/L)	4.2	4.3	4.5
Chloride (mmol/L)	100	106	104
Bicarbonate (mmol/L)	25	-	-
Phosphate (mg/dl)	4.5	5.4	5.4
Calcium (mg/dl)	9.7	9.7	9.7
Alkaline phosphatase (U/L; range 104-345)	5383	842	2376
Parathyroid hormone (pg/mL; range 14-72)	26	22	24
25-OH-vitamin D (ng/ml; range 30-100)	18	38	31
Creatinine (mg/dl)	0.31	0.41	0.34
Total protein (g/dl)	6.5	6.7	6.4
Albumin (g/dl)	4.4	4.0	4.5
Aspartate transaminase (U/L; range 0–50)	49	45	45
Alanine transaminase (U/L; range 0–50)	27	35	14
Gamma-glutamyl transferase (U/L; range 3-22)	17	21	19

CONCLUSION

Benign transient hyperphosphatasemia in childhood was first reported in 1954. The incidence of BTH in childhood is reported to be 1.5% in healthy children. Although it has been reported that it is seen equally in boys and girls, there are publications showing that it is slightly more common in boys. All three children in our case series were male and all presented after an infectious gastroenteritis episode. The incidence of BTH was found to increase in autumn and winter, when infections are more common (Crofton, 1988). However, seasonality has not been consistently reported, and was not evident in our cases (Schonhaut and Rocha, 2017).

BTH is a clinical condition in which serum AP levels rise 3-50 times, mostly in children younger than five years of age. AP that were 2.5 times the upper limit of normal were found in 2.8% of 316 healthy children younger than two years of age in a cohort (Huh et al., 2009). In a systematic review 80 of 813 cases were older than 18 years (Gualco et al., 2013). Most of the patients are diagnosed incidentally during examination for another reason or routine laboratory investigation. There are no clinical, laboratory and radiological findings associated with liver or bone disease, except for elevated ALP. This clinical condition is often accompanied by acute gastroenteritis, respiratory tract infections, some viral infections (respiratory syncytial virus, rotavirus, COVID-19, enterovirus, HIV) and asthma. A similar picture can sometimes be encountered after liver and kidney transplantations or in malignant diseases such as lymphoma (Shkalim Zemer et al., 2023). In studies with large patient numbers, BTH after gastroenteritis were reported 25% and 17%, respectively (Gualco et al., 2013; Shkalim Zemer et al., 2023). All of our patients also had a history of previous gastroenteritis.

One of our patients also admitted with growth retardation. An association between BTH and poor weight gain/growth retardation has been reported in previous studies (Shkalim Zemer et al., 2023). Nevertheless, this link has not been definitively established (Huh et al., 2009). These correlations might result from selection bias, given that laboratory tests in otherwise healthy infants are typically conducted only when there are particular concerns, such as nutritional or infectious problems. A systematic review showed that 35% of BTH cases are identified during routine screenings (Gualco et al, 2013). In accordance with this data, two of our patients were detected during routine evaluation for underlying urological abnormalities.

The pathogenesis of BTH in childhood has not been fully explained. Electrophoretic techniques showed increased fractions of liver and bone isoenzymes with high sialic acid content. Thus, it has been hypothesized that clearance of AP isoenzymes decreases as a result of excessive sialization and accordingly, the serum AP level increases. While liver and bone isoenzymes increase together in most of the cases, intestinal isoenzymes may also increase rarely. BTH develops due to increased AP production during the catch-up period after weight loss or recovery from vitamin D deficiency. It has been suggested that the reason for this is the increased production of AP mediated by vitamin D

metabolites and decreased hepatic clearance due to high sialic acid content (Crofton, 1988).

The half-life of the serum AP is on average 5-25 days, and serum AP level usually returns to normal within 2-3 months in BTH. However it has been reported to be prolonged up to 80 weeks (Kraut et al., 1985l. The AP levels in our series decreased to normal range within 1 month in cases 1 and 2, and in 2 months in case 3.

The differential diagnosis of elevated serum AP includes a variety of liver and bone diseases that could be easily excluded by history, physical examination and routine laboratory tests including aminotransferases, bilirubin, *g*-glutamyl transferase, calcium, inorganic phosphate, parathyroid hormone (PTH), urea, creatinine, and repeat determination of alkaline phosphatase at intervals (Gualco et al., 2013). Hepatocellular and cholestatic liver diseases are associated with increased liver enzymes and/or serum bile acids. Rickets is characterized by low calcium, low phosphorus and high PTH levels along with radiographic findings. Vitamin D deficiency should be suspected in exclusively breast-fed infants without vitamin D supplementation. Renal osteodystrophy is also associated with increased PTH and creatinine. Presence of bone pain requires radiographic evaluation for trauma, tumors, infections and rheumatologic disorders. Determination of liver or bone isoenzyme of AP may help the differential diagnosis. A simple approach for primary care physicians has been recommended as shown in figure 1 (Otero et al., 2011).

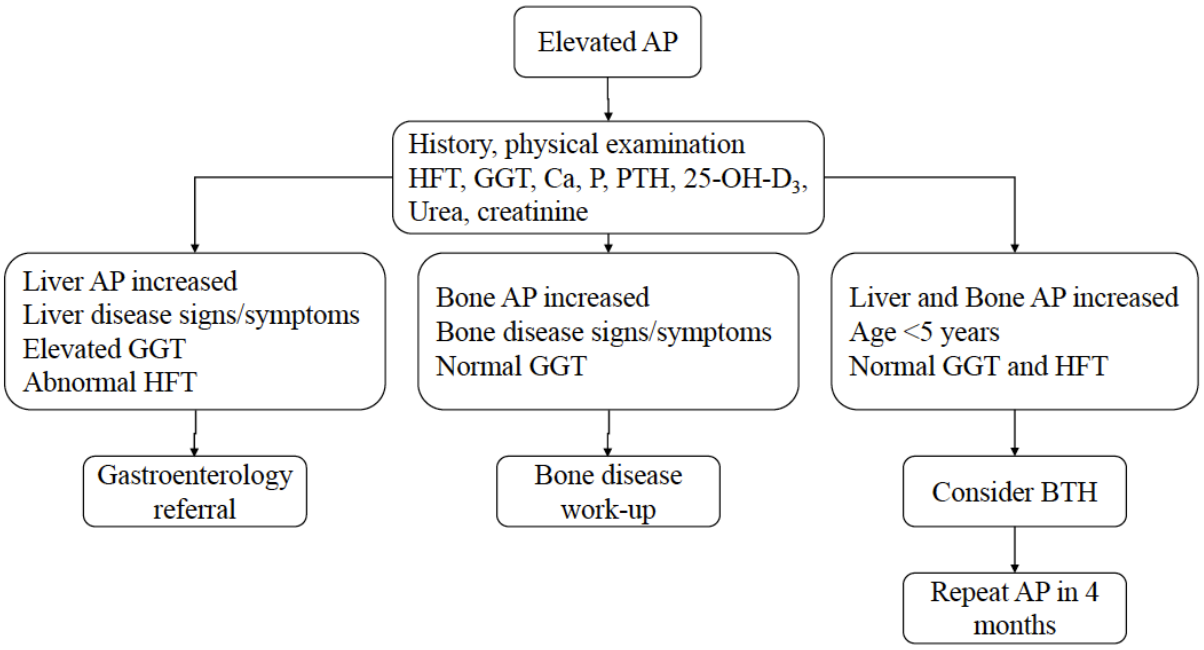

Figure 1: Approach to elevated alkaline phosphatase in children (adapted from reference 9). AP alkaline phosphatase, BTH benign transient hyperphosphatasia, GGT gamma glutamyl transferase, HFT hepatic function tests, PTH parathyroid hormone.

In conclusion, benign transient hyperphosphatasemia in childhood is a completely harmless and temporary condition that is unrelated to the clinical findings of the patient and may cause concern to physicians and families due to the excessive elevation of AP. Knowing that this condition is benign will not only save clinicians and families from serious psychological stress, but also prevent many unnecessary and expensive investigations.

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