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Benign transient hyperphosphatemia; is awareness enough to reduce unnecessary dispatch and costs?

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Abstract

Aim: This study aims to examine the etiology of benign transient hyperphosphatemia (BTH) and the necessity of further investigations in patients with elevated alkaline phosphatase (ALP).

Materials and Methods: This study was carried out by retrospectively scanning the files of pediatric cases fewer than five diagnosed with isolated ALP elevation and BTH. They were admitted to our tertiary-care hospital for various reasons in January 2017 and March 2021.

Results: A total of 47 cases were included in the study. Twenty-five (53.2%) cases were female, and 22 (46.8%) were male. The cases mainly applied in the summer and autumn seasons (72.4%). The most common age groups were 1 to 2 years (44.7%) and 0 to 1 years old (29.8%). When the laboratory values of the patients were examined, no abnormal values were observed except for ALP elevation. The median ALP value was 2211 (1019-4555) (IU/mL). The median time for ALP to return to normal was 43.5 (15-120) days. When the patients were examined according to the age group, it was observed that the elevation in the ALP level increased as the age decreased, but there was no difference between the median recovery times.

Conclusion: Transient ALP elevation is a benign and temporary condition. ALP levels usually return to normal before four months, and ALP levels may persist in sporadic patients. Transient ALP elevation has been associated with many diseases, and it is difficult to attribute its etiology to a precise mechanism. ALP elevation is usually multifactorial.

Introduction

Benign Transient Hyperphosphatemia (BTH) is a benign condition seen in early childhood, manifested by increased alkaline phosphatase (ALP) levels without hepatic or bone metabolism disorder, and usually resolves within weeks or months. It is defined as a temporary high level of ALP, which usually peaks in childhood between 6 and 24 months [1]. BTH is associated with many conditions, such as infections, low birth weight, chronic diseases, and organ transplantation [2-4]. Our aim in this study is to examine the etiology of BTH and the necessity of further research in patients with elevated ALP.

Materials and Methods

This study was carried out by retrospectively scanning the files of pediatric cases under five diagnosed with isolated ALP elevation and BTH. Before the study, approval was obtained from Adıyaman University Non-Invasive Clinical Research Ethics Committee (Decision Date: 23/06/2020. Number of decision: 2020/6-33). They were admitted to our tertiary care hospital for various reasons between January 2017 and March 2021. BTH was diagnosed according to the definition of Kraut et al., who did not have bone disease, liver, and metabolic disease, infectins and ALP levels returned to normal within four months [5]. The sample size was calculated as 45 using G*Power (3.1 Version, Dusseldorf, Germany) (The power of test: 0.8, alpha significance level: 0.05, Cohen's d effect size: 0.71). ALP values, calcium, phosphorus, 25-OH-D3, and parathormone values were recorded at the time of admission. ALP levels and recovery times during follow-up were recorded. The study did not include cases with chronic diseases (chronic liver diseases, bone diseases, chronic kidney disease, chronic diarrhea, celiac disease, etc.).

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Statistical analysis

Analyzes were run in the IBM SPSS Statistics version 22.0 (Armonk, NY: IBM Corp.). Descriptive data were exhibited with n, % values in categorical data. Continuous data were shown as median (minimum-maximum). The conformity of the quantitative data to the normal distribution was evaluated with the Shapiro-Wilk test. The Kruskal Wallis H test were used to evaluate difference the parameters between the groups. For statistical significance, a p-value of <0.05 was considered significant.

Results

A total of 47 cases were included in the study. Twenty-five (53.2%) cases were female, and 22 (46.8%) were male. The cases mainly applied in Summer and Autumn seasons (72.4%). The most common age groups were 1 to 2 years (44.7%) and 0 to 1 years old (29.8%). The descriptive and clinical features of the cases included in the study are given in Table 1.

When the laboratory values of the patients were examined, no abnormal values were observed except for ALP elevation. The laboratory values of the patients are shown in Table 2. The median ALP value was 2211.2 (1019-4555) (IU/mL).

The median time for ALP to return to normal was 43.5 (15-120) days. The median values of laboratory parameters according to age groups are shown in Table 3. When the patients were examined according to the age group, it was observed that the elevation in the ALP level increased as the age decreased, but there was no difference between the median recovery times.

Table 1. Descriptive and clinical features of the cases.

Parameter	Number/n	Percentage/%
Gender		
Male	22	46.8
Female	25	53.2
Season		
Winter	5	10.6
Spring	8	17
Summer	17	36.2
Autumn	17	36.2
Age		
0-1 age	14	29.8
1-2 age	21	44.7
2-3 age	9	19.1
3-4 age	2	4.2
4-5 age	1	2.1
Complaint		
Diarrhea	11	23.4
Coughing	6	12.8
Nose flow	7	14.9
Lose of appetite	13	27.7
Lose of weight	3	6.4
Pale	1	2.1
Itching	1	2.1
Other	5	10.6

Table 2. Laboratory values of the patients.

Parameter	Minimum	Maximum	Median
Urea (mg/dl)	5	52	23.0
Creatine (mg/dl)	0.2	0.7	0.4
AST (IU/L)	19	46	35.4
ALT (IU/L)	9	38	17.4
Ca (mg/dL)	8.5	10.5	9.7
P (mg/dL)	3	6	5.0
PTH (pg/L)	10	42	28.9
25-OH-D3 (ng/dL)	16	70	28.5
ALP-1 (IU/mL)	1019	4555	2211.2
ALP-2 (IU/mL)	146	3380	630.3
ALP-3 (IU/mL)	188	816	308.3
ALP-4 (IU/mL)	208	333	265.7
ALP (correction interval)	15 days	120 days	43.5

*ALP-1: ALP value at first admission, ALP-2: ALP value at Month 1, ALP-3: ALP value on Day 75, ALP-4: ALP value on Day 120.

Table 3. Differences in clinical parameters by age group of the cases.

Parameter (mean)	Age			p value
	<1 age	2-3 age	>3 age	
Urea (mg/dl)	20.5	20	24.5	0.143
Creatine (mg/dl)	0.39	0.39	0.43	0.35
AST (IU/L)	39	35	33	0.34
ALT (IU/L)	16.5	15	16	0.893
ALP-1 (IU/mL)	2216	1636	1566	0.156
ALP-2 (IU/mL)	410	298	315.5	0.720
ALP-3 (IU/mL)	220	301	305	0.191
Ca (mg/dL)	9.95	9.7	9.8	0.272
P (mg/dL)	5.2	4.8	5	0.387
PTH (pg/L)	22	27	26	0.550
25-OH-D3 (ng/dL)	34	25	24.5	0.067
ALP (correction interval)	41 days	44 days	39 days	0.450

The Kruskal Wallis H test were used. p-value of <0.05 was considered significant.

Discussion

BTH is a temporary condition that usually affects those under age five, and its prevalence is 2.4% under the age of 5 years and 6.2% under the age of 2 years [6]. In the study of Gualco et al., transient elevated ALP was found to be the most common cause of BTH. This study showed that transient ALP elevation generally resolved before four months, and ALP elevation that lasted longer than four months was detected in 20% of the patients [7].

ALP levels were classified under five years and two years in many studies. Our study evaluated each age separately for the first five years. In our evaluation, we had a total of 47 patients, 14 years old, two years old, two years old, nine patients three years old, one-year-old, four years old, one-year-old, five years old, and 11 years old. Our study shows a severe decrease in the number of patients over three years

of age, which supports other studies. However, in addition to other studies, it has been shown that it is significantly under three years old for transient ALP elevation. In our study, ALP elevation that lasted longer than four months was not detected, and the time for ALP to normalize was between the second and third months. In our study, the seasonal increase in ALP was also examined, and ALP levels were found to be higher in autumn and summer than in spring and winter.

In a study by Rawat et al., 567 epilepsy patients were evaluated, and ALP levels were elevated, especially in uncontrolled epilepsies. It was shown that ALP levels decreased as seizures were controlled [8]. Reken et al. detected elevated ALP in a patient with cystic fibrosis they followed and showed that ALP regressed spontaneously in their follow-up [9]. Sakurai et al. investigated patients with elevated ALP admitted to the hospital over five years. In their study, the results of 1097 patients were examined. High ALP was detected in 12 patients, Fanconi syndrome was found in 1 of them, and acute upper respiratory tract infection was detected in the remaining 11 patients. This study emphasized that there might be an increase in ALP secondary to upper respiratory tract infection. It was concluded that if ALP elevation is detected in patients with upper respiratory tract infection, there is no need for further investigation, and follow-up is sufficient [10]. In a study by Mori et al., increased ALP values were detected in 3 patients using cyclosporine, 2 for nephritic syndrome and 1 for aplastic anemia, and an immediate improvement in ALP level was detected in 2 patients who were suspended from cyclosporine. In their study, it was determined that the elevation of ALP was related to cyclosporine since there was an improvement in ALP values with the discontinuation of cyclosporin. In the other patient, the elevation of cyclosporine lasted for approximately four months [11]. In a study by Dori et al. on 60 patients, an infectious cause was found in 33% of patients diagnosed with transient hypophosphatemia, malnutrition in 28%, gastroenteritis in 15%, and other causes in 23%. Based on these results, the study concluded that there was no apparent cause in the etiology of transient hypophosphatemia. However, multifactorial causes caused this condition with a complex mechanism [12]. Etiology has been investigated in many studies to detect transient ALP elevation. In our study, patient's complaints, diagnosis, and follow-up were examined to determine the transient ALP elevation. In our study, upper respiratory tract infection was the most common cause. This finding supports the work of Sakurai et al. However, other causes, gastroenteritis, growth retardation, anemia, and chronic diseases, were also detected at high ALP levels, and we think that the etiology of ALP is multifactorial in our country. It is difficult to base it on a specific etiology.

Teitelbaum et al. followed up with 20 patients with isolated ALP elevation who had no other disease. In their follow-up, they found improvement in all patients within a few months. In this study, it was emphasized that isolated ALP elevation is usually a temporary condition, and it was stated that unnecessary and expensive examinations should be avoided [13]. In our study, there was an improvement in all patients with no other disease with elevated ALP. No other disease was observed in the follow-up of the patients, and our study supports that ALP elevation is a temporary and benign condition. In a study by Asami et al., three patients aged 2.9 and 13 years were found to have elevated ALP incidentally, and when these patients were investigated, no underlying cause was found. These three patients were followed for 6-10 years, and it was observed that there was no decrease in ALP levels. There was no clinical or laboratory deterioration in the follow-up of the patients. This study used a definition that was not previously available in the literature, and these patients were defined as persistent non-familial hyperphosphatemia. This definition was evaluated as a condition similar to transient hypophosphatemia but as the persistence of elevated ALP levels [14]. Although persistent ALP elevation was detected in some studies, all ALP elevations returned to normal in our study. Since persistent ALP elevation is less common than transient ALP elevation, it may not have been detected in our study.

Ranchin et al. detected elevated ALP levels after transplantation in 6 patients, 3 of them had liver transplants, and three had kidney transplants and found that ALP levels regressed and returned to normal in their follow-up. Their study concluded that transient hypophosphatemia might also occur after organ transplantation, and this condition is benign and does not require further investigation [15]. Since organ transplantation was not performed in the center where our study was conducted, we did not have the chance to evaluate post-transplant patients.

Conclusion

Transient ALP elevation is a benign and temporary condition. ALP levels usually return to normal before four months, and ALP levels may persist in sporadic patients. Many diseases have been blamed for the etiology of transient ALP elevation, and it is challenging to connect its etiology to a precise mechanism. ALP elevation is usually multifactorial. For this reason, further research on children who appear clinically and laboratory well will result in unnecessary costs and workload for the patient and his family. Including these patients in routine follow-up would be appropriate and excluded from follow-up after ALP levels decrease.

Ethical approval

Ethical approval for this study was obtained from Adıyaman University Non-Invasive Clinical Research Ethics Committee (Decision Date: 23/06/2020. Number of decision: 2020/6-33).

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