ORIGINAL ARTICLE

Pattern of Elevated Serum Alkaline Phosphatase (ALP) Levels in Hospitalized Patients: A Single Centre Study

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Abstract

Background: Persistent elevation of serum ALP is frequently encountered and can pose a diagnostic dilemma due to its association with a wide range of clinical conditions. However, the significance of ALP in these clinical conditions in routine practice is often underestimated or overrated. Objectives: This study was determined to assess the pattern of ALP with an aim to elucidate its clinical utility among hospitalized patients. Method & materials: The inpatients with high ALP level were enlisted & analysed between January to December 2012 excluding cases of (a) patients who have bone involvements with malignancies and (b) HIV-seropositive patients attending a tertiary care Hospital at Dhaka. Extremely high levels of ALP were defined as being more than 1000 U/L. These patients were divided into different groups according to their final diagnosis. Results: A total of 154 hospitalized patients with eligible medical records were identified (98 male and 56 female, mean age 36 years). Their ALP levels are ranging from 1,006 to 3,067 IU/L; very extreme values of > 3000 IU/L being rarely (only about 2%) documented. Patients with sepsis can have an extremely high alkaline phosphatase level (1,648.2 ± 328.4 IU/L) and a normal bilirubin. Conclusion: High serum ALP levels in hospitalized patients were commonly found in three major groups having obstructive biliary diseases, infiltrative liver disease and sepsis. A variety of other causes were also noted. This routine laboratory test should receive more attention in clinical decision-making than has previously been given.

Keywords

Serum alkaline phosphatase, pattern of elevation, hospitalized patient, single centre study.

Introduction

Serum Alkaline Phosphatase (ALP) is an established routine test commonly practiced either as a part of biochemical evaluation of hepatic functions or as an independent marker of certain other medical conditions. Alkaline phosphatase comprises a group of enzymes that catalyze the hydrolysis of phosphate esters in an alkaline environment, generating an organic radical and inorganic phosphate.[1] Like other enzymes, this enzyme has many isoenzymes. In healthy adults, the highest concentration of ALP is present in liver and bone; an elevated AP concentration is therefore generally attributed to either liver or bone disease.

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However, AP is also present in other organs including intestine, kidney, placenta and leucocytes. It is impossible to tell from a routine lab test whether the elevated alkaline phosphatase arises from the liver or bone.

To find out the source, a sample can be sent to the lab for fractionation to determine its source.[2] Serum ALP levels vary with age, gender and blood type.[3]

Mild elevation of ALP is seen in the first 3 months of life, puberty and a gradual increase is also noted between ages 40–65 years, especially in women. ALP in adolescent boys may be 2–5 times greater than normal adults and correlates with bone growth.[4]

Likewise, African Americans have a 10–15% higher serum ALP and smokers may have up to 10% higher ALP compared to nonsmokers. Finally, individuals with Blood type O and B may have elevated ALP following a fatty meal due to influx of intestinal ALP.[5]

An increase in serum ALP levels is frequently associated with a variety of diseases. Such disorders as extrahepatic bile obstruction, intrahepatic cholestasis, infiltrative liver disease and hepatitis are mentioned.

Unfortunately, the elevation of ALP less than three times the normal level is considered non specific and insufficient to provide a definite diagnosis.[6]

Markedly elevated serum ALP, hyperalkalinephosphatasemia, is seen predominantly with more specific disorders, including, malignant biliary obstruction, primary biliary cirrhosis, primary sclerosing cholangitis, hepatic lymphoma and sarcoidosis.[7,8] On the other hand, according to a recent study[9], sepsis and malignant obstruction are identified as common causes of hyperalkalinephosphatasemia, whereas diffuse liver metastases, as well as a number of benign disorders, are relatively less common causes of hyperalkalinephosphatasemia. The utility of ALP has long been discussed since the 80's.[4,6-8] However, the number of such studies in recent years has declined.[9,10] Studies with similar objectives in our country are also very limited and underreported. So, this study was focused on the pattern of markedly elevated serum ALP among adult hospitalized patients and to determine the associated disease conditions.

Materials and methods

This retrospective study was performed on hospitalized patients who had an ALP level equal to or greater than 1,000 IU/L (normal 98 – 279 IU/L) between July 2011 to June 2012 at a tertiary level teaching hospital at Dhaka. The cases of (a) patients who have bone involvements with malignancies (b) paediatric patients younger than 15 years old and c) HIV seropostive patients were excluded.

The review of the patients' medical records during this period identified 273 cases with a conclusive diagnosis for further analysis. The data from the discharge summary of these patients were then recorded including their age and sex, as well as the final diagnosis.

Descriptive statistics were used in analyzing the patient characteristics and laboratory parameters for each group. In addition, unpaired Student's T test was used to assess group differences when appropriate.

Independence was tested by Chi square test. A statistically significant difference was accepted as P value < 0.05. All the statistical analyses in this study were made using SPSS 7.0 for Windows Program.

Results

In this retrospective study, a total of 154 hospitalized patients with serum ALP level over 1000 IU/L were identified. They were 98 male and 56 female patients with ages ranging from 21 to 46 years old. The ALP levels ranged from 1,006 to 3,067 IU/L. ALP was done in all cases as a supporting diagnostic tool (Fig1). Other investigations noticed in these cases were CT scan (for operative plan), cholangiography (to assess pattern of obstruction), and ERCP were common in addition to a number of biochemical tests.

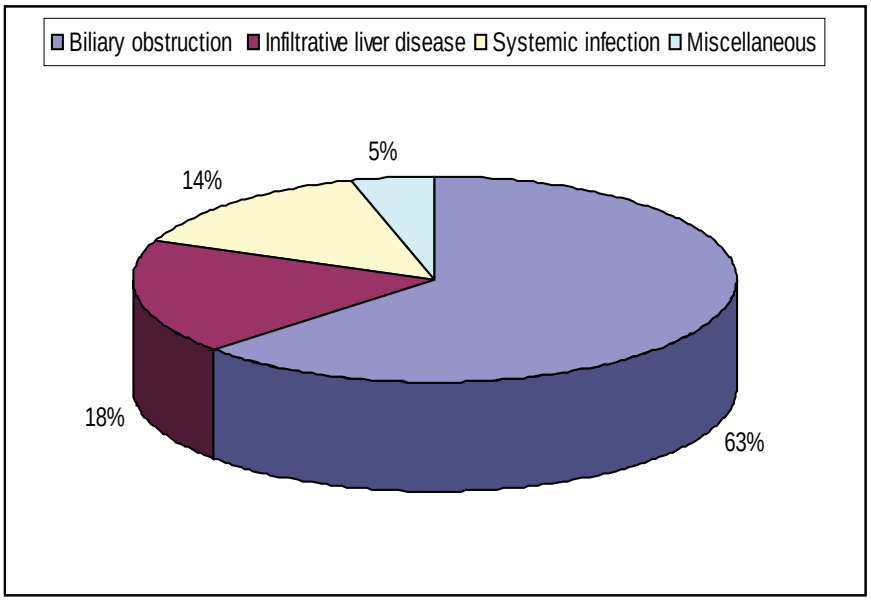

Fig 2: Three dimensional test positive but double disc synergy test negative for ESBL (Pseudomonas spp)

Out of 154 cases, Serum ALP level was commonly (75.9%) observed between 1000 to 1999 IU/L. Very extreme levels of ≥ 3,000 IU/L was found only in 3 (1.9%) cases; two in MBO and one with liver metastasis (Table I). However, no significant correlation between the level of ALP elevation and the group of disorders was detected (Chi-square test, P > 0.05)

Table I: Distribution of the study subjects according to diagnosed groups and serum ALP levels.

Groups	Serum ALP level (IU/L)		
	1,000 – 1,999	2,000 – 2,999	≥ 3,000
1. Biliary obstruction (BO)	72 (74.2%)	23 (23.7%)	2 (2.06%)
Malignant (MBO)	28 (77%)	6 (16.6%)	2 (5.5%)
Benign	44 (72 %)	17 (27.8%)	0
2. Infiltrative liver disease	22 (78.5%)	5 (17.8%)	1(3.5%)
Hepatoma	3 (60%)	2 (40%)	0

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Metastatic	19 (82.6%)	3 (13.04%)	1 (4.3%)
3. Systemic infection/sepsis	18 (81.8%)	4 (18.1%)	0
4. Miscellaneous	5 (71.4%)	2 (28.5%)	0
Total	117 (75.9%)	34 (22%)	3 (1.9%)

The most common diagnosis in patients with high ALP in this series was biliary obstruction of which benign cases were more frequent (39.6%) followed by malignant biliary obstruction (MBO) (23.3%). Among the benign cases the associated causes were gall stone (41), stricture (17) and choledocal cysts (3). In MBO patients, carcinoma of head of pancreas, lymphoma and cholangicocarcinoma (CCA) was found in 18, 14 and 4 cases, respectively. All the cases invariably showed raised bilirubin; higher levels being confined to the MBO. Another common observation was Hypercholesterolemia (26%) in intrahepatic cholestasis.

The second common group of disorders associated with high serum ALP levels was infiltrative liver disorders. Among the 28 patients in the study, only 5 (3.2%) had hepatoma diagnosed based on histology and/or based on clinical features combined with serum AFP levels above 400 IU/ml. There were also 23 (15%) cases with liver metastasis in which a variety of primary cancers were identified, including colon, stomach, and breast cancer.

Then, high serum ALP above 1000 IU/L was also common in patients with sepsis. There were 22 such patients in whom the evidence of the biliary obstruction or local abscess was not demonstrated by imaging techniques. In this group, bacteria were among the most frequently identified organisms (12 cases). In addition, another two cases with fungal infections following systemic chemotherapy exhibited high serum ALP levels. Of interest, a common tropical infection; typhoid fever (2 cases), was also identified with extreme ALP. Furthermore, there were 6 patients with disseminated tuberculosis. Finally, there was this group of patients with high ALP levels associated with miscellaneous diseases. The 7 patients remaining from the three groups above had the following various disorders: 1) one patients with hematological malignancies; 2) two alcoholic cirrhosis cases (ALP levels ranged from 1,002 to 2,739 IU/L); 3) three pyogenic liver abscess (ALP levels ranged from 1,011 to 1,756 IU/L); 4) one severe preeclampsia cases.

The highest mean ALP was observed in patients of malignant biliary obstruction (MBO) followed by sepsis and liver metastasis. In the group of biliary obstruction (ALP ranged from 1,007 to 3,067 IU/L.) the mean ALP levels in the malignant biliary obstruction group was significantly higher ($P < 0.05$) when compared to the benign cases. For the cases with infiltrative liver disorders the ALP levels ranged from 1,205 to 3,007 IU/L. Interestingly, the mean ALP level in patients in the metastatic cancer group was significantly higher than that in the primary hepatoma group ($P < 0.05$). In the group of patients with sepsis, the ALP levels ranged from 1,010 to 2,734 IU/L where most of the cases (72.7%) showed normal bilirubin (Table II).

Table II: Serum ALP levels in different clinical groups.

Groups	Serum ALP level (IU/L) (Mean ± SD)
1. Biliary obstruction (BO)	1544.1± 278.2
Benign obstruction	1,398.3 ± 241.2
Malignant biliary obstruction (MBO)	1,689.8 ± 315.3
2. Infiltrative liver disorders	1541.1 ± 209.9
Hepatoma	1,449.9 ± 206.2
Liver metastasis	1,632.3 ± 213.6
3. Sepsis	1,648.2 ± 328.4
4. Miscellaneous	1,443.5 ± 212.5

Discussion

Primarily, three major categories of diseases, namely, obstructive biliary diseases (63%), infiltrative liver diseases (18.1%) and sepsis (14.2%), were identified as the three common disorders associated with serum ALP exceeding 1000 IU/L in our series. Unlike a similar previous study[11], high prevalence of benign biliary obstruction, accounting for approximately 40 % of patients in the study, was identified. This discordance was probably associated with high prevalence of cholangiocarcinoma (CCA) in the previous study conducted in Thai population. CCA is the most common cause of hyperalkalinephosphatasemia among the Thai cancerous cases. In fact, CCA is an important cancer in Southeast Asia, especially in Thailand and Laos.[12,13] The cases in group of BO in this study were commonly associated with hyperbilirubinemia and Hypercholesterolemia (26%). Hypercholesterolemia is a common feature of intahepatic cholestasis.[5]

Cholestasis, roughly divided into intrahepatic and extrahepatic forms, is a clinical challenge. Extrahepatic cholestasis, characterized by dilated bile ducts, is caused by either a bile duct stone or stricture, with stricture most often related to a malignancy. For years common liver function tests have been tested in separating patients with malignant bile duct strictures from those with stones. To a few plasma bilirubin seems to be the best liver function test in distinguishing patients with malignant bile duct strictures from those with bile duct stones.[14] However, like most of the previous researches, serum ALP in MBO of this study had significantly higher level compared to the benign cases.[9-12]

A total of 117 (75.9%) cases from different groups revealed high ALP of < 2000 IU/L; majority confined to benign biliary obstructions (37.6% of ALP range group). This could be associated with the acuteness of clinical symptoms driving patients to seek health care earlier. Serum ALP levels beyond 3,000 IU/L was documented only in 3 (1.9%) cases; two in MBO and one with liver metastasis (1.2% and 0.6% of total cases respectively). Among the infiltrative liver disorders; the second common clinical group, metastatic cancer patients showed significantly higher ALP values than that in the primary hepatoma group. Unlike the Thai

study11, hepatoma was the least reported cases (3.2%) of this series. Colon cancer was found to be the major primary source of liver metastasis.

So far the results of the present study are in accordance with studies in developing countries.[9-12] However, a few interesting findings unique to our setting were identified. One most interestingly was common tropical infections; typhoid fever (1.2%) and disseminated tuberculosis (3.8%) with extreme ALP which could be explained by the higher prevalence in our country. WHO estimates that the largest number of new TB cases in 2008 occurred in the South-East Asia Region, which accounted for 35% of incident cases globally. With a population of 150 million, Bangladesh ranks sixth among countries with a high TB burden.[15]

Besides, extremely high levels of alkaline phosphatase have rarely been emphasized as a manifestation of bacteremia in adults. But surprisingly sepsis with high ALP was found in 14% of cases like Maldonado et al[8] (27.02%) and Tung et al.[9] Another prominent feature was the presentation of normal bilirubin in 72% cases again supported by earlier reports.[9]

The present study is based on a single health care centre. As a specific population of hospitalized patients was particularly selected for this study, the results may not apply to the general outpatient population. Besides, no reference value of ALP for Bangladeshi population is available yet for valid comparison. Nonetheless, several interesting findings were observed in this study which might be worth notifying.

Conclusion

A wide range of disorders have been identified in addition to the common ones associated with high serum ALP levels in hospitalized patients. It is also demonstrated in this study that hepatic dysfunction during bacteremia may be manifested predominantly by extreme elevation of alkaline phosphatase with little abnormality in serum bilirubin. Measurement of the activities of alkaline phosphatase isoenzyme has been used for the identification and monitoring of diseases associated with the isoenzyme. Further large scale prospective studies may be undertaken to elucidate the abnormal level (cut-off) of ALP as per associated disease conditions for Bangladeshi population.

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