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Case Report

Low alkaline phosphatase levels: a potential indicator of Wilson disease

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ABSTRACT

A young adult female patient presented with complaints of jaundice, intermittent vomiting, and weight loss. Upon examination, pedal oedema and abdominal distension were observed. Laboratory investigations indicated macrocytic anaemia, hemolysis, prolonged prothrombin time, mixed hyperbilirubinemia, elevated aspartate/alanine transaminase (AST/ALT), and a normal alkaline phosphatase (ALP). The investigations repeated showed an increase in bilirubin, AST, and ALT. However, the levels of ALP and the ALP: total bilirubin ratio (ALP:TB ratio) were found to be very low. This raised the suspicion of Wilson disease, and further laboratory workup was initiated. Urine (24-hour) and serum copper levels were elevated, while serum ceruloplasmin levels were lower. Based on this, the diagnosis of acute on chronic liver failure (ACLF) related to Wilson disease was made. The levels of ALP and the ALP:TB ratio remained low until the sixth day. This report demonstrates the clinical relevance of low levels of ALP and ALP: TB ratio and its diagnostic utility in establishing the diagnosis of Wilson disease.

Keywords: Wilson disease, Alkaline phosphatase, Total Bilirubin, Copper, Ceruloplasmin

INTRODUCTION

Wilson disease, an autosomal recessive disorder is caused due to mutation in ATP7B gene. This causes impaired biliary excretion of copper leading to its accumulation in the body, primarily in liver and brain. The data on community-wide prevalence of Wilson disease was lacking in India, and a hospital based study conducted in South India has shown registration of about 15-20 new cases annually.[1] The diagnosis is either delayed or missed, adversely affecting the prognosis and outcome.[2] The clinical presentation varies with hepatic, neurological, psychiatric, haematological and renal manifestations.[3] Establishing the diagnosis of Wilson disease in patients presenting with features of acute liver disease is challenging and requires detailed laboratory work up. There is a comprehensive diagnostic criteria for acute on chronic liver failure (ACLF) related to Wilson disease, which includes increased urine and serum cooper, low ceruloplasmin, elevated amino transferases, normal or subnormal/low alkaline phosphatase (ALP) and presence of non-immune hemolytic anemia and coagulopathy.[4] In routine clinical practice, low ALP is rare, and when present, it's usually associated with reduced bilirubin levels in patients with chronic liver disease.[5] Therefore, the presence of low ALP with an increase in total bilirubin and transaminases with clinical feature of acute liver disease should not be overlooked and should raise the suspicion of Wilson disease. This case report highlights the importance of recognising low ALP levels and its role in initiating the

laboratory workup for establishing the diagnosis of ACLF related to Wilson disease.

CASE REPORT

History of presenting illness

A 25 years old female admitted with complaints of dry cough, yellowish discoloration of eyes, tiredness, intermittent vomiting for past 3-4 days. She is experiencing loss of weight for one month. She denied a history of any drug allergy. However, she had taken Ayurvedic medications for her illness for over a month. On examination, she had icterus, pedal edema and a slightly distended abdomen. Her vitals were normal with blood pressure of 130/80 mmHg and a pulse rate of 86 beats per minute.

Table 1: Laboratory results.

Analyte	Reference interval	Day-0 (on admission)	Day-2	Day-5	Day-6	Day-7
Haematological manifestations						
Hb, g/dl	13-17	10.1		4.9	7.2	6.4
MCV, fl	83-101	102.2		117	101.1	103
Prothrombin time PT, in seconds (INR)	10-13	35 (3.1)	41(3.5)	21 (1.8)		
aPTT, in seconds	24-35	49	62	33		
Biochemical investigations						
Total Bilirubin, TB mg/dl	0.3-1.3	16.42	35.37	35.37	26.56	18.34
Direct Bilirubin, mg/dl	0.1-0.4	10.25	22.23	22.8	16.16	9.93
Indirect Bilirubin, mg/dl	0.2-0.9	6.17	13.14	12.57	10.4	8.41
Total protein, g/dl	6.4-8.3	5.9	5.8	5.2	5.1	5
Albumin, g/dl	3.5-5.2	2.8	2.5	3.1	3.2	3.2
Globulin, g/dl	2.5-3.5	3.1	3.3	2.1	1.9	1.8
AST, IU/l	12-38	137	116	83	63	58
ALT, IU/l	7-41	69	16	20	24	24
AST:ALT ratio	1.1	1.98	7.25	4.15	2.62	2.41
ALP, IU/l	42-98	56	4	23	41	49
ALP: TB ratio	>4	3.41	0.11	0.65	1.54	2.67

Laboratory investigations

On the day of admission, liver function tests (LFT) revealed mixed hyperbilirubinemia, elevated aspartate and alanine transaminases (AST and ALT) and normal alkaline phosphatase (ALP). The LFT was repeated next day, and it showed an increase in bilirubin, AST and ALT. However, the levels of ALP dropped significantly i.e., 4 IU/l on Day-2 (Table 1). ALP: total bilirubin ratio was also found to be low (0.11). 24-hour urine copper (>4300 µg/dl, ref. range: 15-60) and serum copper levels were higher (220 µg/dl, ref. range: 74-130) and serum ceruloplasmin levels were lower (9 mg/dl, ref. range: 15-45). Ascitic fluid analysis showed serum ascitic albumin gradient (SAAG) of 2.1 indicating portal hypertension. The Direct Coombs test was negative and serum LDH levels were elevated indicating non-immune hemolytic anemia. PT INR was elevated despite administration of Vitamin K, indicating a non-responsive coagulopathy. Computed tomography scan (CT) showed splenomegaly, moderate ascites and bilateral pleural effusion. Portal vein doppler indicated chronic liver disease with portal hypertension.

The repeated LFTs demonstrated a progressive decline in bilirubin and transaminases. However, the levels of ALP and ALP:TB ratio remained low till Day 6 (Table 1).

Patient management

The patient was managed conservatively with diuretics, laxatives, cough suppressants and vitamin K injection. Three cycles of plasma exchange and packed cell transfusion were given. Liver transplantation was recommended as the treatment of choice, and the transplant workup has been initiated.

DISCUSSION

Copper (Cu), an essential trace mineral, functions as a cofactor for various enzymes. It is absorbed from the diet in the small intestine via the copper transporter 1 (hCTR1; SLC31A1). The liver cells take up copper, and delivers it to ATP7A and ATP7B. ATP7A, a copper containing P type ATPase is responsible for loading copper into apo-ceruloplasmin to form ceruloplasmin. ATP 7B is responsible for excreting Cu into bile and then feces,

which is the major route for copper excretion.[6] Wilson disease is caused due to a mutation in ATP7B gene, leading to excessive accumulation of copper primarily in liver. The diagnosis was made based on the following criteria: 24-hour urinary copper excretion greater than 100 µg/day in addition to a ceruloplasmin level less than 14 mg/dl.[4] Studies have demonstrated that the diagnosis of Wilson Disease is challenging due to its variable clinical presentation, particularly in cases presenting with signs of acute liver disease.[3]

The features of acute on chronic liver failure related to Wilson disease include non-immune hemolytic anaemia, coagulopathy, increased urine and serum copper, low ceruloplasmin, elevated amino transferases, and normal or low ALP.[4] In this patient, low ALP raised the index of suspicion for Wilson disease leading to initiation of the laboratory work up. This is in line with the fact that low ALP is pathognomonic of Wilson disease especially in patients presenting with non-immune hemolytic anemia.[7] It has been reported that ALP to total bilirubin ratio less than 4 (i.e., ALP:TB <4), has a sensitivity of 94%, specificity of 96% and a likelihood ratio of 23 in diagnosing fulminant liver failure in Wilson disease.[8] In this study, it was observed that the ALP:TB ratio was consistently below 4 throughout the patient's hospitalisation. The lowest value observed was 0.11 on D2, while the highest value was 3.47 on D1 of the hospitalisation. ALP is a metalloenzyme and requires zinc for its catalytic action. In patients with Wilson disease, excess copper displaces zinc leading to impaired activity of ALP.[9] A study has reported normal levels of ALP and ALP:TB ratio in ACLF related to Wilson disease in adults, this could be explained by duration of the disease and timing of blood sample in the study subjects.[10] Another study found normal ALP and ALP:TB ratios in patients with ACLF due to Wilson disease, unlike our study.[11] This could be because the later study was done in children.

In this patient, the AST:ALT ratio was 1.98 on the day of admission, which increased to 7.25 on Day 2 and showed a progressive decline to 2.41 on Day 7. It has been reported that AST to ALT ratio greater than 2.2 (i.e., AST:ALT >2.2), has a sensitivity of 94%, specificity of 86% and a likelihood ratio of 7 in diagnosing fulminant liver failure in Wilson disease.[8]

Ceruloplasmin, an acute phase reactant may not be reliable in the diagnosis of ACLF, as few studies have reported its levels to be normal in fulminant hepatitis.[8] In this patient, ceruloplasmin levels were found to be reduced. Kayser Fleisher ring (KF ring), formed due to the deposition of excess copper on cornea is seen in 95% of the patients presenting with neurological involvement and only in 50% of those with liver involvement.[12] In this patient, the slit lamp examination showed absence of KF ring. Hence, in this patient, low ALP and ALP:TB ratio and high AST:ALT ratio is crucial for initiating the laboratory work up and further diagnosis and management of Wilson disease.

The patient had non-immune hemolytic anemia as indicated by negative direct coombs test, elevated LDH and hemolysis. This could be the effect of copper induced oxidative stress on red cell membrane integrity.[13] The presence Vitamin K non-responsive coagulopathy could be due to loss of synthetic function of liver.

CONCLUSION

A high index of suspicion is necessary for a rare condition like Wilson disease when a jaundiced patient presents with subnormal or very low levels of ALP. Low ALP and the ALP: TB ratio are the diagnostic features of ACLF related to Wilson disease. Non-immune haemolytic anaemia and vitamin K non-responsive coagulopathy are other pathognomonic features. The ALP levels returned to normal upon conservative management, however, liver transplantation is the recommended treatment of choice.

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