CHANGES IN FIBRINOGEN LEVEL IN LIVER CIRRHOSIS

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Background: Liver cirrhosis causes significant morbidity and mortality in our country, however early diagnosis prevents complications and carries good prognosis. Estimation of fibrinogen level may be helpful in preventing bleeding tendencies. **Methods:** Plasma fibrinogen level of 82 confirmed liver cirrhosis in 18–60 years age admitted patients of Khyber Teaching Hospital were determined and compared with normal controls, to establish it as a marker for diagnosis in cirrhosis liver and prognosis. Fibrinogen level was determined by Fibriprest-2. **Results:** Significantly low levels in patients were recorded as compared to controls. 40% cases showed low fibrinogen level, while nearly 44% had normal levels. **Conclusion:** Fibrinogen level was low in early and terminal cirrhosis and high in advancing cirrhosis as compared to controls that showed normal levels.
KEY WORDS: Cirrhosis, Liver, Fibrinogen.

INTRODUCTION

The role carried out by the liver in the production of different proteins involved in the coagulation and fibrinolysis has been already demonstrated. Liver diseases can cause both quantitative and qualitative abnormalities in the clotting factors. Fibrinogen is synthesized at the level of the hepatic microsomes[1,2], and the existence of multiple coagulation defects, including a thrombin time prolongation with normal or high fibrinogen levels has also been frequently observed in patients with severe liver disease. In liver cirrhosis there is diffuse fibrosis which destroys the liver lobules. Regenerative nodules press on the liver substance leading to a vicious circle of further necrosis and fibrosis[2]. Fibrinogen is a glycoprotein of molecular weight approximately 340,000 daltons, present in the plasma at a concentration in the range of 2–4 g/l. It is synthesized in the liver (1.7–5 gm/day), and by the megakaryocytes[3]. It is an acute phase reactant and is often elevated in liver disorders especially in hepatoma and cirrhosis[4].

When the liver disease is advanced there is not only impaired synthesis of albumin but also fibrinogen, prothrombin and coagulation factors V, VII, IX and X. Although some of these changes may have serious consequences such as bleeding diasthesis, they are significant for the most part as clinical clues to the presence of advanced liver disease and cirrhosis. Liver diseases not only alter the concentration of circulating fibrinogen, but also make it functionally abnormal. As most coagulation proteins are synthesized by the liver, patients with liver diseases often exhibit multiple coagulation defects. Normal or even elevated levels of plasma fibrinogen is often observed in patients of severe liver disease with liver damage. In several cases this abnormality has been explained on the basis of increased antithrombin activity in the plasma probably due to circulating fibrinogen/fibrin degradation products whose clearance by the diseased liver is delayed[5]. However the phenomena can also be explained by the abnormal fibrinogen synthesis displayed by the damaged liver. This finding has been observed in liver cirrhosis and aggressive chronic hepatitis[6,7]; as well as in hepatocellular carcinoma[8,9].

Various hypothesis have been made to explain the pathogenesis of acquired dysfibrinogenemia. The most frequently observed phenomenon is an alteration of the glucide fraction with an elevation of sialic acid content, which would explain the cause of this functional anomoly[10]. Although there is disparity between the quantity of fibrinogen measured with functional and immunological assays, most patients have moderate bleeding. However in some cases dysfibrinogenemias induce a hyper coagulable state and increased risk of thrombosis[11].

Coagulation defects including a thrombin time prolongation with abnormal fibrinogen level have been observed in severe liver diseases, especially in cirrhosis liver by previous research workers[12]. Acquired dysfibrinogenemias appear to be a common problem than previously thought in patients of liver diseases like carcinoma, cirrhosis, fibrinolysis and dissiminated intravascular coagulatoin (DIC). DIC is inordinate activation of the coagulation system, leading to deposition of microthrombi in small vessels and consumption of platelets, prothrombin, fibrinogen, factors V, VIII and XIII. This consumption results in depletion of these factors, activation of fibrinolytic system and production of fibrin degradation products. These products further interfere with normal platelet formation and fibrin polymerization[13]. Recent studies suggest that slow fibrin formation occurs as a result of structural changes induced in the fibrinogen molecule itself. These relatively minor alterations in structure cause a functional dysfibrinogenemia and abnormalities in the fibrinogen level[12].

The objective of the present study is to establish plasma fibrinogen level as a marker for diagnosis and prognosis of liver cirrhosis.

MATERIALS AND METHODS

This was a case control study. It was done from 9th June 1999 to 6th December 1999. Forty (40) age, sex and socioeconomically matched controls having no history of viral hepatitis and cirrhosis liver were selected from the family members of the patients, staff of Khyber Teaching Hospital, Khyber Medical College and Pakistan Medical Research Council (PMRC) Peshawar. Eighty-two (82) Cirrhotic patients of age between 18–60 years both males and females belonging to different socioeconomic classes were selected from the medical units of Khyber Teaching Hospital Peshawar. Past history of all patients and controls regarding blood transfusions, injections, jaundice, use of razors and history of dental or surgical procedure or haemodialysis was recorded, and the patients were clinically examined for signs of liver cirrhosis. Ultrasonography abdomen was the preliminary investigation to detect cirrhosis liver, and diagnosis was established by evidence of shrunken liver with coarse echotexture, features of portal hypertension like spleenomegaly, portal vein diameter greater than 14 mm, and presence of ascites. Ultrasound guided biopsy was done in selected cases where there was no contraindication. Ascitic fluid if present was sent for serology. Relevant biochemical tests were also done.

About 1.8 ml of blood was drawn from the antecubital vein of the subjects and was immediately transferred to tubes containing 0.2 ml of an anticoagulant, trisodium citrate 0.9 M (3.2 percent) for the determination of fibrinogen and some other tests. Quantitative determination of fibrinogen was done by Fibriprest-2, supplied by Diagnostic Stago France.

RESULTS

A total of 40 controls (Group-A) and 82 patients (Group-B) suffering from cirrhosis liver were investigated during the course of present study. There were variations in fibrinogen level in the patients of liver cirrhosis (shown in Table-1), however the level remained within normal range in controls (mean ± SD, 3.02 ± 0.05).

Out of total, 36 patients had normal fibrinogen level. In 21 patients it was above normal (mean ± SD, 11.90 ± 5.5) and in 25 patients fibrinogen level was below the normal range (mean ± SD, 1.37 ± 0.08 g/l). The results showed that there was a highly significant difference in plasma levels of fibrinogen (P<0.001) in patients (Group B) when compared to controls (Group A). Fibrinogen level was variable in different stages of cirrhosis liver (Table-2).

Table-1: Fibrinogen Levels of Controls and Patients of Cirrhosis Liver

Group	**Subject**	**Fibrinogen (g/l)** Mean ± SD
A	Controls (n= 40)	3.02 ± 0.05
B	Patients (n= 82)	3.50 ± 2.07
B	Below normal range (n= 25) (Early and terminal stage)	1.37 ± 0.08
B	With in normal range (n= 36) (Advanced stage)	2.76 ± 0.94
B	Above normal (n= 21) (Advanced stage)	11.90 ± 5.5*

* P< 0.001 (Highly Significant).
Normal plasma fibrinogen level= 2–4 g/L.

Out of total 25 patients in which the level of plasma fibrinogen was below the normal Range, 12 % (10) were in the early stage of the disease who had not developed complications of cirrhosis and 18 % (15) were in the terminal stage who had developed complications of the disease. Seventy percent of the patients (57) out of total were in an advanced stage of cirrhosis and they had developed either one or more complications of the disease (Table-2). In these patients who presented with advancing cirrhosis, fibrinogen level was normal in 36 patients and rose above normal in 21 (Table 1).

Table-2: Plasma Fibrinogen Levels in Uncomplicated and Complicated Liver Cirrhosis

Type	Stage	Patients %	Fibrinogen in g/l Mean ± SD
Uncomplicated Cirrhosis	Early Stage (n= 10)	12	1.8 ± 0.90

Complicated Cirrhosis	Advanced Stage (n= 57)	70	3.5 ± 1.02
	Terminal Stage (n= 15)	18	1.2 ± 2.48

DISCUSSION

The existence of acquired dysfibrinogenemia in patients of liver cirrhosis is a relatively frequent finding[12]. Most of the dysproteinemias described in patients with liver disease have been due to quantitative abnormalities. However the presence of quantitative abnormalities of plasma proteins in this group of patients is now becoming increasingly recognized. In several patients with cirrhosis liver and hepatoma an acquired abnormality of fibrin monomer polymerization has been reported[14].

Functional abnormalities of fibrinogen or dysfibrinogenemias are initially differentiated on the basis of abnormal clottability of fibrinogen by thrombin[7]. A low fibrinogen level was recorded in 12% of our patients who were in early stage of liver cirrhosis, and in 18% patients at terminal stage of the disease. Massive destruction of liver hepatocytes results in poor production of plasma proteins and fibrinogen leading to decrease in their level, and showing that the occurrence of dysfibrinogenemia with low fibrinogen level may be a consequence of liver damage rather than the manifestation of any single type of liver disease[6]. Sallah and Bobzien are of the opinion that low fibrinogen levels may occur in DIC and hyperfibrinolysis but levels less than 100 mg/dl are found only in fulminent hepatitis and severely decompansated cirrhosis[15].

The normal fibrinogen level recorded in our study may be due to compensation by the normal liver as also inferred by Martinz *et al*.[9] from their study. The demonstration of a functional abnormality of the circulating fibrinogen molecule does not necessarily mean that the molecule secreted by the diseased liver is abnormal. It is conceivable that a normal fibrinogen is secreted by the abnormal liver and it undergoes rapid alteration in circulation due to abnormal plasma environment. In 50% cases of advanced cirrhosis and nearly 100% of cases of fulminant hepatic failure the structure of fibrinogen is abnormal, although the level may be normal. Abnormalities in fibrinogen structure may impair fibrin polymerization and clot formation despite normal levels16.

Elevated fibrinogen level, as noted in the plasma of the patients in our study may occur due to their impaired removal by the diseased liver. Most of the asialoglycoproteins are rapidly removed from the circulation by the liver as a result of binding of their terminal galactosyl residues to the hepatocyte membrane. Impairment of this clearance mechanism might be responsible for the finding of elevated levels of altered thyroxin binding proteins in the patients with liver disease. The liver also appears to play a role in the removal of altered coagulation factors. Abnormal removal of altered coagulation proteins by the diseased liver may result in high fibrinogen balance in these patients.

The occurrence of dysfibrinogenemias in our patients suggests that abnormality may be a consequence of liver damage resulting in abnormal fibrinogen level in these patients.

CONCLUSION

The estimation of fibrinogen level is an important diagnostic index permitting us to follow the dynamics of the disease and it may also be helpful in diagnosing the haemorrhagic tendencies before they are clinically manifested. Further investigations into the nature of these alterations in fibrinogen level may provide a basis for better understanding of the pathogenetic mechanism responsible for it in the patients of cirrhosis liver.

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