Original Research Article

Haemostatic Profile of Chronic Liver Disease Patients

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Abstract

Introduction: A wide spectrum of hematological disturbances is known to be observed in patients with chronic liver disease. **Aims:** Present study was planned to monitor the coagulation factors abnormalities during the gradual deterioration of liver disease. **Materials and methods:** Present study is retrospectively done on 60 patients of chronic liver disease who were enrolled in this study. Biochemical, Haemostatic and coagulation variables were estimated in patients and compared with the baseline levels of healthy subjects.This study was carried out at the department of Pathology, Fathima Medical College, Kadapa, Andhra Pradesh, during the period from April 2018 to November 2020. **Results:** In total 60 patients serum bilirubin levels were approximately four times average and showed a marked decrease in serum albumin levels. Patients with both serum bilirubin and albumin HCC (group III) levels were significantly affected, similar to the Child C cirrhosis patient pattern. These patients also had elevated ALT and AST, respectively. Platelet count in Child B, C and HCC revealed a significant thrombocytopenia, compared to both normal and child A cirrhotic patients. Compared to normal group, PT was significantly prolonged in patients with Child C and HCC, Compared to patients with Child A, PT was significantly increased only in cirrhotic patients with Child C.In HCC patients had lower plasma fibrinogen compared to all stages of cirrhosis. Plasma calciumwas above the baseline of normal subjects in cirrhotic patients with Childs A and B. Child C and HCC patients, however, showed normal calcium levels. **Conclusion:** The results indicated that the haemostatic abnormalities in PT, fibrinogen, and calciumwere deteriorated in parallel with the gradual regression of the constitutional function of liver.

Keywords: Chronic liver disease (CLD),Fibrinogen,Serum bilirubin, Calcium.

Introduction

The characterization of chronic liver disease (CLD) is defective liver synthesis of clotting factors and coagulation factors. Thrombo-cytopenia,caused mainly by portal hypertension and hyperfibr-inolysis, which can result in further hemostasis alterations. The liver parenchyma is gradually damaged and regenerated, which can lead to fibrosis and cirrhosis.A broad range of liver pathologies are associated with CLD, including: inflammation (chronic hepatitis), liver cirrhosis and hepatocellular carcinoma[1].With the concomitant increased activity of FVIII and von Willebrand factor (vWF) in cirrhosis, particular coagulation factors[5,7,9,10,11], prothrombin, protein C, and protein S are decreased. Platelet function (PF) is inhibited by thrombocytopenia, increased nitric oxide, and prosta-cycline, and greater vWF and FVIII activity supports platelet aggregation.Thrombocytopenia is the product of splenic sequestration due to glycoprotein IIb/IIIa platelet surface antigen-antibody interaction caused by inflammation or sepsis in portal hypertension, decreased hepatic thrombopoietin synthesis, and immune-mediated platelet destruction. Therefore, it is evident that patients with liver disease may experience both bleeding complications as well as thrombotic episodes[2,3].Spectrum of haemo-static defects in patients with chronic liver diseases,present study was planned to monitor the coagulation factors abnormalities during the gradual deterioration of liver disease.

Materials and methods

Present study is retrospectively done on 60 patients of chronic liver disease who presented in OP and referred to Department of Pathology, Fathima Medical College, Kadapa, Andhra Pradesh.

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Patients diagnosed with chronic liver disease were enrolled in study from April 2018 to November 2020.The study included 60 patients of 35–70 years aged admitted. Demographic and biochemical data as well as medical history including cause of liver cirrhosis, end stage kidney failure, other diseases and medication with anticoagulants were recorded. According to Child's classification[4], cirrhotic patients were divided into three grades (15 patients each): mild cirrhosis (Child A) (group IIA), moderate cirrhosis (Child B) (group IIB) and advanced cirrhosis (Child C) (group IIC), whereas HCC patients (n = 10) were included in group III. During the study period, patients did not receive anticoagulant treatment and those with active bleeding were not included. In addition, 15 healthy subjects were voluntarily taken as a normal control.Venous blood was collected via a cannula inserted into a cubital vein. Collection tubes for conventional coagulation analysis were prefilled with sodium-citrate. Hematological analyses were performed using collection tubes prefilled with ethylenediamine tetraacetate and analyzed. Platelet count was determined by fluorescence flow cytometry and biochemical parameters were assessed using serum collection and analyzed by autoanalyzer.To assess the integrity of liver function albumin and bilirubin serum levels of transaminases (ALT and AST)were investigated. Coagulation tests were done immediately were stored in cuvettes at temperature of -20 to-40 degree Celsius for later dates. Almost 2 ml blood was collected in EDTA vial for complete blood count by Haematology Fully Automated Autoanalyzer.The coagulation screening tests; pro thrombin time performed by the conventional methods. Plasma fibrinogen was measured by the Turbidometric method.

Statistical analysis: Statistical analysis was done using SPSS 16.0. Comparisons between two group frequencies were made using Chi-square test. For the comparison of group means, Student's t-test was applied

Results

In total 60 patients 45 males and 15 females, aged 35–70 years were included in this study.15 patients were included in each group had following results.

Table 1: Biochemical parameters in all the stages of chronic liver diseases

Biochemical parameters	I (Normal) N=15	Cirrhosis			III(HCC) N=15
		IIa (child A) N=15	IIb (child B) N=15	IIc (child C) N=15	
Bilirubin(mg/dL)	0.7±0.2	0.8±0.2	2.0±0.6*	4.2±1.1*	3.7±1.3*
Albumin(grms/dL)	4.3±0.4	4.0±0.5	3.2±0.2*	2.5±0.38*	2.4±0.2*
AST	30±4	70±9*	78±10*	43±6*	56±7*
ALT	23±3	64±8*	79±11*	50±7*	58±6*

***Significant difference of the corresponding group versus the normal group**

Their serum bilirubin levels were significantly higher than average ($P < 0.001$), while serum albumin levels were significantly lower than those of all normal controls ($P < 0.01$) but slightly lower than those of Child A ($P > 0.05$). These patients also had elevated ALT and AST, respectively. Their serum bilirubin levels were approximately four times average and showed a marked decrease in serum albumin levels ($P < 0.001$). Patients with both serum bilirubin and albumin HCC (group III) levels were significantly affected, similar to the Child C cirrhosis patient pattern.

Table 2: Haemostatic Variables in all the stages of chronic liver diseases.

Haemostatic Variables	I (Normal)	Cirrhosis			III (HCC)
		IIa (child A)	IIb (child B)	IIc (child C)	
Platelets(cell/uL)	230±28	190±31	87±21*	82±15*	81±12*
Prothrombin time	12.1±0.3	14.2±1.2	17.3±2.2*	21.3±6.2*	20.1±4.8*
INR	1.3±0.07	1.4±0.15	2.2±0.8*	3.3±1.08*	3.2±1.2*

***Significant difference of the corresponding group versus the normal group**

Platelet count was normal in Child A cirrhotic patients. Patients with Child B, C and HCC (groups: IIb, IIc and III), however revealed a significant thrombocytopenia, compared to both normal and child A cirrhotic patients. Compared to normal group, PT was significantly prolonged in patients with Child C and HCC. Compared to patients with Child A, PT was significantly increased only in cirrhotic patients with Child C.

Table 3:Coagulation Factors in all the stages of chronic liver diseases

Coagulation Factors	I (Normal)	Cirrhosis			III (HCC)
		IIa (child A)	IIb (child B)	IIc (child C)	
Fibrinogen(g/L)	2.7±0.4	1.9±0.4*	1.7±0.5*	0.9±0.3*	0.99±0.2*
Calcium(mg/dl)	9.33±0.7	14.4±2.2*	14.8±2.2*	9.4±1.6	8.7±1.8

***Significant difference of the corresponding group versus the normal group**

Compared to healthy subjects fibrinogen significantly and gradually decreased, in parallel to the severity of liver disease. In HCC patients had lower plasma fibrinogen compared to all stages of cirrhosis. Plasma calcium was above the baseline of normal subjects in cirrhotic patients with Childs A and B. Child C and HCC patients, however, showed normal calcium levels.

Discussion

Patients with chronic liver disease have profoundly altered hemodynamics and hemostatic pathways with procoagulant and anticoagulant mechanisms, resulting in a tenuous “rebalanced” state in the setting of portal hypertension. Pugh et al. and Truscott and Child,had introduced a modified method to assess the operative risk in cirrhotic patients. According to this classification, patients were classified into three grades (Child A, Child B and Child C), which respectively indicated mild, moderate or severe conditions of cirrhosis[3,5]. In present study serum bilirubin levels were significantly higher than average while serum albumin levels were significantly lower than those of all normal controls when compare child B(IIb) and child C (IIc) and HCC groups. Liver enzymes AST and ALT both elevated in cirrhosis and HCC patients.Violi et al.[6] have demonstrated that patients with higher fibrinogen degradation products have recorded higher levels of serum bilirubin indicating the association between the severity of liver disease and the low fibrinogen level. In present study patients with Child B, C and HCC (groups: IIb, IIc and III)revealed a significant thrombocytopenia, compared to both normal and child A cirrhotic patients.Afdhal N et al.[7] found that thrombocytopenia (platelet counts <150,000/dL) was a common complication in patients with CLD, reported in as many as 76% of cirrhotic patients. Various factors can lead to thrombocytopenia like splenic platelet sequestration, bone marrow suppression by chronic hepatitis C infection,and antiviral treatment with interferon-based therapy. Reduced level or activity of the Thrombopoietin (TPO) may also play a role. Similar to our study, Papatheodoridis GV et al.[8] found mean platelet count in chronic hepatitis to be within normal limit (208X $103/mm^3$) and Zocco MA et al.[9]found mean platelet count in cirrhosis to be reduced (96 X $103/ mm^3$).A mild to moderately reduced platelet count is frequently present in patients with acute or chronic liver failure. An important cause for thrombocytopenia in chronic liver disease is an increased platelet sequestration in the spleen as a result of congestive splenomegaly, which is related to portal hypertension.In our study PT was significantly prolonged in patients with Child C and HCC, Compared to patients with Child A, PT was significantly increased only in cirrhotic patients with Child C. Our study are in concordance with study done by Saray A et al., and Saja MF et al., and confirmed that prolongation of conventional coagulation screening tests appears in advanced liver disease and are not sensitive markers of liver damage[10,11].Furthermore, recent studies have shown that these global tests are not predictive of bleeding in patients with cirrhosis however PT has kept its place as one of the parameters of common prognostic indices in advanced liver disease.In our study fibrinogen significantly and gradually decreased, in parallel to the severity of liver disease. In HCC patients had lower plasma fibrinogen compared to all stages of cirrhosis. Desborough MJ et al showed low fibrinogen is associated with a 29% increase in mortality for every 1-g/L (100-mg/dL) reduction in decompensated cirrhosis[12]. Fibrinogen is

synthesized almost exclusively in the liver and low levels in cirrhotics are generally attributed to decreased liver synthetic capacity,consumption during Disseminating Intravascular Coagulation(DIC), destruction by abnormal plasma fibrinolytic activity or accelerated catabolism. Plasma calcium was above the baseline of normal subjects in cirrhotic patients with Childs A and B. Child C and HCC patients, however, showed normal calcium levels. In earlier studies, the progression of cirrhosis from compensatory (Child A and B) to uncompensative cirrhosis has been identified as calcium deficiency. The possible decrease in vitamin D and the decrease in calcium absorption have been explained by the improvement in calcium levels in early and moderate cirrhosis[13].This reduction causes PTH (secondary hyperparathyroidism) secretion, which can increase bone resorption and subsequent increases in blood calcium, which in turn prevents the release of PTH through feedback. For a healthy liver, this scenario is expected. Owing to the poor clearance efficiency of the liver, PTH remains elevated and maintains bone resorption in the early stages of cirrhosis.

Conclusion

In conclusion, the data demonstrate the steady degradation, along with the development of liver diseaseof the coagulation factors examined. Future work may be performed to use coagulation factors as primary indicators of non-invasive liver fibrogenesis monitoring.

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