Original Article

FREQUENCY OF ACQUIRED DYSFIBRINOGENEMIA IN PATIENTS OF CHRONIC LIVER DISEASE

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ABSTRACT

Objective: To determine the frequency of acquired dysfibrinogenemia in patients of chronic liver disease.
Study Design: It was a descriptive study.
Place and Duration of Study: This study was conducted in the Haematology department, Army Medical College, National University of Science and Technology in collaboration with the department of Medicine, Military Hospital, Rawalpindi in one year (November 2012- October 2013).
Material and Methods: A total of 100 patients of chronic liver disease were included and those with previous history of coagulation disorders were excluded. It was a simple random sampling. A specifically designed proforma was used for the data collection. Mean and standard deviation (SD) were calculated from quantitative variables like fibrinogen levels and age. Frequency and percentages were calculated for qualitative variables like thrombin time, its correction with toluidine blue and gender. To find an association between all categorical variables Chi-square test was used. p-value <0.05 was considered significant.
Results: Frequency of acquired dysfibrinogenemia in patients was found to be 40/100 (40%). Child Pugh Score A, B and C was used for grading the severity of liver disease. The study showed that the frequency of acquired dysfibrinogenemia tends to increase significantly [3(7.5%), 8(20%), 29(72.5%)] with the progress in severity of liver disease graded by Child Pugh Score (p = 0.014).
Conclusion: The study shows that the frequency of acquired dysfibrinogenemia increases significantly with the progression of severity of liver disease. Thus, it can serve as a helpful tool in early management and follow up of patients of chronic liver disease.
Key Words: Thrombin time, Fibrinogen, Blood coagulation disorders, Thrombosis.

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INTRODUCTION

Dysfibrinogenemia is a coagulation disorder that is qualitative in nature and caused by different types of structural flaws in the molecule of fibrinogen that affects its function. It is of two types that is, inherited and acquired [1] [2]. The most frequently observed phenomenon in acquired dysfibrinogenemia is an increase of sialic acid content to carbohydrate side chain of fibrinogen molecule, which explains the cause of this functional anomaly [3][4]. Dysfibrinogenemia ultimately results in abnormality of fibrin clot formation. The normal clot forming ability of fibrinogen by thrombin is impaired due to functional abnormalities of fibrinogen [5].

It has been shown that dysfibrinogenemia is a feature of chronic liver disease and is a sensitive indicator to gauge the severity and progress of liver disorder, so in this study the frequency of dysfibrinogenemia in patients of chronic liver disease will be assessed. The frequency will be evaluated by using Child Pugh classification of severity of liver disease according to its respective grades.

As hepatitis leading to chronic liver disease is very prevalent in our country, so this study will help in early diagnosis and evaluation of the patients before developing further complications. It will also be of great help for hematologists and the gastroenterologists to pick the severity of coagulation defects and their accompanied complications e.g. bleeding / thrombosis in patients of chronic liver disease which will result in their better management and treatment [6] [7].

MATERIAL AND METHODS

This was a descriptive cross-sectional prospective study, completed in the Haematology department, Army Medical College, National University of Science and Technology in association with the department of Medicine, Military Hospital, Rawalpindi in one year. It was a simple random sampling.

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A total of 100 patients of chronic liver disease from the in-patient medicine wards were included and those with previous history of coagulation disorders and drugs intake like aspirin, heparin, warfarin were excluded. Permission was taken from the hospital ethical committee. Informed consents were taken from all the patients, enrolled in the study. A specifically designed questionnaire was used to take the history from the patients. The range of the age varied from 22 years to 63 years. Out of 100 patients, 68 (68%) were males.

A 5 ml syringe was used to withdraw venous blood from antecubital vein. 1.8 ml was taken in bottles containing tri-sodium citrate to measure prothrombin time, activated partial thromboplastin time, thrombin time and fibrinogen levels and 3 ml was separated in plain test tube for serum albumin and bilirubin levels. A laboratory number was allocated to the sample of each patient for record and then each sample was processed for results.

Prothrombin time (PT) was measured using Pacific Hemostasis Thromboplastin –DS kit provided by Fisher Diagnostics. Activated partial thromboplastin time (APTT) was measured by using Pacific Hemostasis Activated Partial Thromboplastin Time reagents provided by Fisher Diagnostics. The reference range for PT was 12-15 sec and APTT was 26-33 sec. The Thrombin time was measured using Thrombin time kit provided by Weiner Laboratory. Reagent (bovine thrombin) was prepared and added to centrifuged plasma sample. The starting time of clot formation was measured as the thrombin time. The normal reference range was 13-17sec. In cases where thrombin time was found prolonged, its correction was checked using a reagent toluidine blue provided by British Drug House Ltd for diagnosis of acquired dysfibrinogenemia. Toluidine blue is a charged reagent and it normalizes the thrombin time in dysfibrinogenemia by interacting with excess of sialic acid attached to the fibrinogen molecule. Centrifuged plasma sample and prepared toluidine blue reagent were taken in a plain glass tube. Bovine thrombin reagent was added to it and time of start of clot formation was noted.

Fibrinogen levels were measured by using Hemostat Fibrinogen kit provided by Human Diagnostics. The thrombin reagent in optimized quantity was added to 1:10 prediluted plasma sample. The measured clotting time was entered on standard chart and levels are measured. The normal reference range was 150-350mg/dl. Serum albumin and bilirubin levels were determined using commercially available kit on fully automated chemistry analyzer Selectra XL made in Netherlands. Prothrombin time, serum albumin, bilirubin levels, degree of ascites and encephalopathy were used to grade the severity of liver disease according to Child Pugh Score.

A specifically designed proforma was used for the collection of all the data. Data analysis was done by operating SPSS version 20. The data was described by using descriptive statistics. Mean and standard deviation (SD) were calculated for quantitative variables like fibrinogen levels and age. Frequency and percentages were calculated for qualitative variables like gender.

RESULTS

A total of 100 patients of chronic liver disease were screened for the frequency of acquired dysfibrinogenemia. The range for the age of the patients was 22 years to 63 years. The cause of chronic liver disease in the study group was hepatitis B in 2 (2%) patients and hepatitis C in 98 (98%) patients (Figure-1).

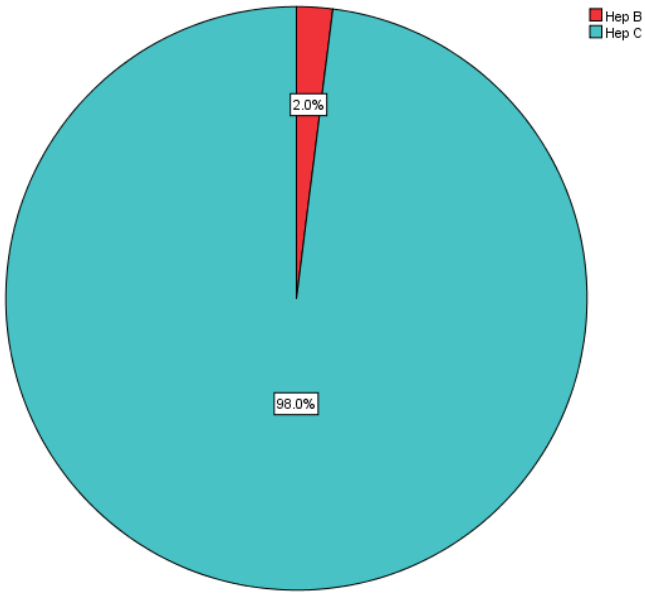

Figure-1: Causes of chronic liver disease.

Among the total of 100 patients, prothrombin time was prolonged in 41 (41%) patients where the rest of the 59 (59%) patients had prothrombin time within normal limits. Similarly, activated partial thromboplastin time was prolonged in 28 (28%) patients and was normal in the rest of the 72 (72%) patients. Liver function tests were deranged in all the patients.

The range of fibrinogen levels (mg/dl) of the patients was found to be between 69 and 451. Mean fibrinogen level was found to be 192.5±991.19. Regarding fibrinogen levels, 6 (6%) patients showed increased levels, 39 (39%) patients had decreased levels whereas 55 (55%) patients had normal fibrinogen levels.

Among the total of 100 patients, the thrombin time was found to be prolonged in 44 (44%) patients where 56 (56%) patients had thrombin time within the normal limits. Out of 44 (44%) patients with prolonged thrombin time, 40 (40%) showed correction with toluidine blue and 4 (4%) were not corrected. The patients showing the correction of prolonged thrombin time with toluidine blue revealed the frequency of acquired dysfibrinogenemia to be 40 (40%).

According to the severity of the disease, 30 (30%) patients were categorized in Child Pugh Score A, 35 (35%) in Child Pugh Score B and 35 (35%) in Child Pugh Score C.

In Child Pugh Score A, 4 (13.3%) patients were found to have increased fibrinogen levels, 4 (13.3%) patients were with normal levels where 22 (73.3%) patients had decreased fibrinogen. In Child Pugh Score B, 1(2.9%) patient had increased fibrinogen, 11 (31.4%) patients were found to have decreased fibrinogen whereas 23 (65.7%) patients had normal fibrinogen levels. In Child Pugh Score C, 1(2.9%) patient was found to have increased fibrinogen, 24 (68.6%) patients had decreased fibrinogen levels and 10 (28.6%) patients showed normal fibrinogen levels.

In Child Pugh Score A, 26 (86.7%) patients were found to have normal thrombin time and 4 (13.3%) showed prolonged thrombin time. In Child Pugh Score B, 24 (68.6%) patients had normal thrombin time and 11(31.4%) showed prolonged thrombin time whereas in Child Pugh Score C, 6 (17.1%) patients had normal thrombin time and 29 (82.9%) showed prolonged thrombin time.

Regarding the correction of prolonged thrombin time with toluidine blue, in Child Pugh Score A, 3 (75%) patients showed correction and 1 (25%) showed no correction, in Child Pugh Score B, 8 (72.7%) patients showed correction and 3 (27.3%) showed no correction while in Child Pugh Score C, 29 (100%) patients showed correction. The correction of prolonged thrombin time with toluidine blue showed frequency of acquired dysfibrinogenemia in patients of chronic liver disease. The frequency of acquired dysfibrinogenemia observed individually in Child Pugh Score A, B and C was 3(7.5%), 8(20%) and 29(72.5%) respectively (Figure-2).

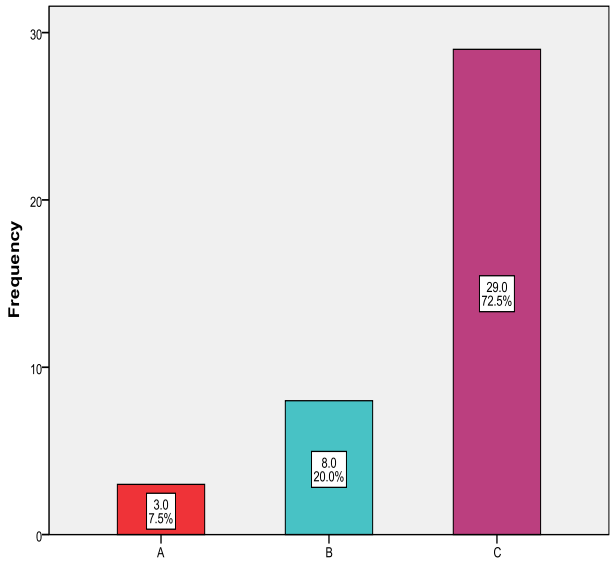

Figure-2: Association between child pugh score and corrected thrombin time (acquired dysfibrinogenemia) (n = 40).

The thrombin time was found to be increasing with the progression of liver disorder (p-value < 0.001) (Table-1). The frequency of correction of thrombin time with toluidine blue that is the acquired dysfibrinogenemia increases with the severity of liver disease (p-value = 0.014) (Table-2). The number of patients with decreased fibrinogen levels increase significantly as the severity of liver disease progress graded by Child Pugh Scoring (p value < 0.001) (Table 3) The thrombin time was found to be increasing with the progression of liver disorder (p-value < 0.001) (Table-1). The frequency of correction of thrombin time with toluidine blue that is the acquired dysfibrinogenemia increases with the severity of liver disease (*p*-value = 0.014) (Table-2). The number of patients with decreased fibrinogen levels increase significantly as the severity of liver disease progress graded by Child Pugh Scoring (*p* value < 0.001) (Table-3).

Table-1: Association between child pugh score and thrombin time (p-value < 0.001).

Child Pugh Score	Thrombin Time	
	Normal	Prolonged
A	26 (86.7%)	4 (13.3%)
B	24 (68.6%)	11 (31.4%)
C	6 (17.1%)	29 (82.9%)

Table-2: Association between child pugh score and corrected thrombin time (acquired dysfibrinogenemia) (p-value = 0.014).

Child Pugh Score	Corrected Thrombin Time	
	Yes	No
A	3 (75%)	1 (25%)
B	8 (72.7%)	3 (27.3%)
C	29 (100%)	0 (0%)

Table-3: Association between number of patients with variation in fibrinogen levels and Child Pugh Score

Child Pugh Score	Fibrinogen Levels		
	Increased	Normal	Decreased
A	4 (13.3%)	22 (73.3%)	4 (13.3%)
B	1 (2.9%)	23 (65.7%)	11 (31.4%)
C	1 (2.9%)	10 (28.6%)	24 (68.6%)

p-value < 0.001 (< 0.05 Significant)

DISCUSSION

In liver diseases acquired dysfibrinogenemia might be a contributing factor for bleeding but how strong a risk factor it is, not known because such patients have many other reasons for bleeding as well [2][8-10]. The study showed that as the acuteness of liver disease progresses, the number of patients with prolonged thrombin time increases significantly that goes in the favor of some other studies [11,12]. In the present study 40 (40%) patients were found with acquired dysfibrinogenemia whereas different studies reveal a slightly different result that is 50-78% [13, 14]. This study revealed statistically significant association of acquired dysfibrinogenemia with increasing severity of liver disease (3(7.5%), 8(20%), 29(72.5%)) and no such study has been carried out until now where frequencies of acquired dysfibrinogenemia according to Child Pugh Scoring is mentioned. There is a documented case report regarding acquired dysfibrinogenemia where a female who was hepatitis C positive, came with bleeding episode and after investigation thrombin time was found to be prolonged along with other coagulation tests abnormality and ultimately leading to diagnosis of acquired dysfibrinogenemia so was treated accordingly [8]. One study conducted in Pakistan showed that 50% patients with advanced cirrhosis and 100% patients with fulminant hepatic failure had abnormality in structure of fibrinogen ultimately resulting in acquired dysfibrinogenemia irrespective of normal levels [15]. In present study 44 (44%) patients were with prolonged thrombin time but 40 (40%) showed correction with toluidine blue showing the presence of acquired dysfibrinogenemia whereas 4 (4%) did not show correction so they were not the cases of acquired dysfibrinogenemia, they might have other causes for prolonged thrombin time for example decreased fibrinogen levels, fibrin degradation product, etc [2] [16].

Hence, this study will be helpful in early diagnosis of patients with acquired dysfibrinogenemia that is one of the frequently observed complications of chronic liver disease in our setup.

CONCLUSION

The study concludes that the frequency of acquired dysfibrinogenemia in patients of chronic liver disease is 40% and decreased levels of fibrinogen were observed in 39% cases. The frequency of acquired dysfibrinogenemia increases whereas the fibrinogen levels decrease with the progression of acuteness of liver disease graded by Child Pugh Score. Thus, the present study renders significant value in early diagnosis so early management of the complications associated with chronic liver disease. Much more studies, researches and knowledge are required to understand the coagulation disorders related to chronic liver disease in order to improve the prognosis and quality of life of the patients.

AUTHORS CONTRIBUTION

Ayesha Noor: Conceiving idea, running the tests on kit, compiling the results, writing discussion, correction of reviewers comment.

Maria Shafiq: Collection of samples, review of literature.

Nosheen Ali: Entering data in SPSS, writing introduction.

Amer Siddiq: Write up of materials and methods.

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