University Journal of Medicine and Medical Specialities

ISSN 2455- 2852 2021, Vol. 7(2)

A Study on Haematological Abnormalities in Chronic Liver Disease

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Abstract

Aim of The Study

1. To assess the hematological abnormalities in chronic liver disease
2. To determine severity, morphology & most common type of anemia in chronic liver disease.
3. Quantitatively assess WBC abnormalities
4. To detect platelet abnormalities in chronic liver disease
5. To assess the coagulation profile of patients with chronic liver disease.

Materials and Methods

To assess the hematological abnormalities in chronic liver disease, a cross sectional analytical study was conducted

All patients taken up for the study were evaluated in detail. Oral consent was obtained for clinical examination and lab investigations. Written consent was obtained for procedures such paracentesis, Upper GI endoscopy and viral marker studies.

Inclusion Criteria

1. All patients with liver disease whose symptoms and signs persists for more than 6 months
2. Alcoholic cirrhosis, post-necrotic cirrhosis, metabolic causes of liver diseases were taken up for the study

Exclusion Criteria

1.Patients with underlying malignancy or known primary hepatocellular carcinoma were excluded
2. Patients with primary coagulation disorder or primary abnormalities of haemostatic function were excluded.
3. Acute hepatic failure was excluded
4. Patients with preexisting anemia due to other causes were excluded.
5. Patients suffering from end stage medical diseases like COPD, Coronary artery disease, cardiac failure, CKD were excluded

Observation & Data Analysis

A descriptive study to assess the haematological abnormalities in Decompensated chronic liver disease was conducted at Department of Digestive Health and diseases , Kilpauk medical college , Chennai from August 2016 to January 2017. 50 patients with chronic liver disease were taken for the study; this included 43 males (86%) and 7 females (14 %).

The age range was from 24 to 70. The average age of the patients in the study was 48 yrs. 70 % of the patients were between 40 and 60 years of 52% of the patients had alcoholic cirrhosis were males. The aetiology of chronic liver disease could not be determined in 24 % of cases but all of them had clinical and radiological features of cirrhosis. 6 patients had Hepatitis B and 2 had Hepatitis C; all these 8 patients had cirrhosis. Autoimmune hepatitis and cirrhosis were present in 2 females

Results

90% of the patients were anemic with only 10% of patients having a normal. Hb level above 12 g/dL. About 14 % of patients had severe anemia with an Hb value less than 6 g/d L. All these patients had upper GI bleed. The most common type of blood picture was normocytic red cells seen in 22 patients, of which 5 patients had a normal Hb value. Macrocytic picture was observed in 15 patients. Of these 14 patients had alcoholic liver disease and the etiology was undetermined in the other. 11 patients had a microcytic blood picture of which 8 patients had an upper GI bleed and the one patient with hemochromatosis had sideroblastic anemia that was proved with bone marrow and iron studies. Dimorphic blood picture was seen in 2 patients.

Among the 50 patients Leucocytosis was observed in 8 patients, 4 patients with a count above 15000 had SBP. The other 4 had low-grade fever probably as a result of endotoxemia. Leucopenia was observed in 13 patients. Eosinophilia was observed in 5 cases, neutrophilia in 8 patients

50 % of the patients had thrombocytopenia (<1 lakh). Of the 13 patients who had an upper GI bleed 3 patients had normal platelet counts and the rest had counts below 1 lakh. The average platelet count of patients who experienced an upper GI bleed was 92000 vs. 1.2 lakh in patients without a GI bleed.

The bleeding time was prolonged only in 6 patients with thrombocytopenia indicating BT as an insensitive test. 36 patients had a prolonged INR. Among the 13 patients with upper GI bleed 9 had prolonged INR; indicating other factors play a role in GI bleed

Conclusions

Many conclusive results regarding the haematological abnormalities in decompensated chronic liver disease were obtained with this limited study involving 50 patients with decompensated cirrhosis

⇒ 90% of the patients were anaemic of whom 14% had severe anaemia with a Hb less than 6 g/dL

⇒ In this study males had a worse Hb compared to females

⇒ Patients with an upper GI bleed had significantly lower levels than patients without bleed.

⇒ The average Hb of alcoholic cirrhosis patients was 8.7 g/dL compared to 9.3g/dl of non-alcoholic cirrhosis indicating alcohol by itself worsens the haematological profile

⇒ The most common type of anaemia was a normochromic normocytic anemia seen in 44% of patients

⇒ Macrocytic picture was seen in 30% of patients; majority (93%) of whom were alcoholics

⇒ 22% patients had microcytic hypochromic anaemia of which roughly 73% patients had an upper GI bleed. . Dimorphic picture was observed only in 4 % of cases.

⇒ 44 % of patients had a normal WBC count. 26 % had low counts below 4000. Only 16% of patients had a count above 12000 of which 50% had spontaneous bacterial peritonitis.

⇒ 50 % of patients had thrombocytopenia.

⇒ The severity of thrombocytopenia had good correlation with spleen size

⇒ The average platelet count of patients with an upper GI bleed was 92000 compared to 1.2 lakh to those without an upper GI bleed; suggesting other factors such functional platelet defects may play a role as well. These need to be confirmed with platelet functional studies.

⇒ Bleeding time was prolonged only in 12 % of patients with thrombocytopenia indicating BT as an insensitive test of platelet number and function.

⇒ The PT-INR was elevated in 72 % of patients. However only 25 % of patients with a prolonged PT-INR had upper GI bleed indicating other factors such as a rebalanced hemostatic system at work, however this needs to be confirmed with more extensive studies. This result underlines the fact that clinical status of the patient and not lab values have to be treated, when correcting coagulopathy in a patient with cirrhosis.

From this study we can conclude that various haematological alterations are very common in cirrhosis patients that needs to be identified and corrected early to reduce morbidity and mortality.

Introduction

The liver is the largest organ in the body[1] and one of the most complex functioning organs with a wide array of functions.

It plays a major role in carbohydrate, protein, lipid metabolism; inactivation of various toxins, metabolism of drugs, hormones, synthesis of plasma proteins & maintenance of immunity (Kupffer cells).

Right from being a primary site of haematopoiesis in fetal life to maintenance of hematological parameters in postnatal life; the liver has an extremely important role in maintenance of blood homeostasis.

It acts as a storage depot for Iron, Folic acid & Vitamin B12, secretes clotting factors and inhibitors. Hence it's not surprising to see a wide range of hematological abnormalities in liver diseases.

In chronic liver disease the presence of jaundice, liver cell failure, portal hypertension and hypersplenism, reduced red cell half- life all influence peripheral blood picture[2]. Both Liver cell failure & cholestasis can derange the coagulation system. Dietary deficiencies, bleeding, alcoholism and abnormalities in hepatic synthesis of proteins used for blood formation or coagulation add to the problem liver disease[3].

This study was undertaken to describe the hematological abnormalities in decompensated chronic liver disease so that measures could be taken to correct them and reduce morbidity.

Aim of The Study

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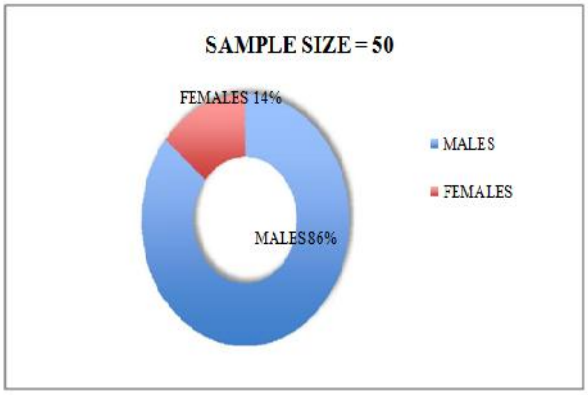


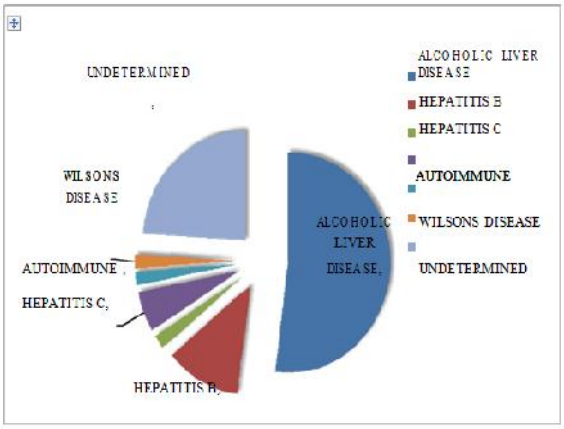
50 patients with chronic liver disease were taken for the study; this included 43 males (86%) and 7 females (14 %).

Age Distribut Ion of Cases

Age	Males	Females	Total	%
20 to 30	2	0	2	4
30 to 40	4	3	7	14
40 to 50	16	2	18	36
50 to 60	17	0	17	34
>6 0	4	2	6	12

The age range was from 24 to 70. The average age of the patients in the study was 48 yrs. 70 % of the patients were between 40 and 60 years of age

AETIOLOGY OF CHRONIC LIVER DISEASE



AETIOLOGY OF CIRRHOSIS

Aetiology of cirrhosis	Male	Female	Total
Alcoholic liver disease	26	1	27
Hepatitis B	5	1	6
Hepatitis C	2	0	1
Autoimmune	0	2	2
Wilsons disease	0	1	2
Un determined	9	3	12

52% of the patients had alcoholic cirrhosis were males. The aetiology of chronic liver disease could not be determined in 24 % of cases but all of them had clinical and radiological features of cirrhosis. 6 patients had Hepatitis B and 2 had Hepatitis C; all these 8 patients had cirrhosis. Autoimmune hepatitis and cirrhosis were present in 2 females

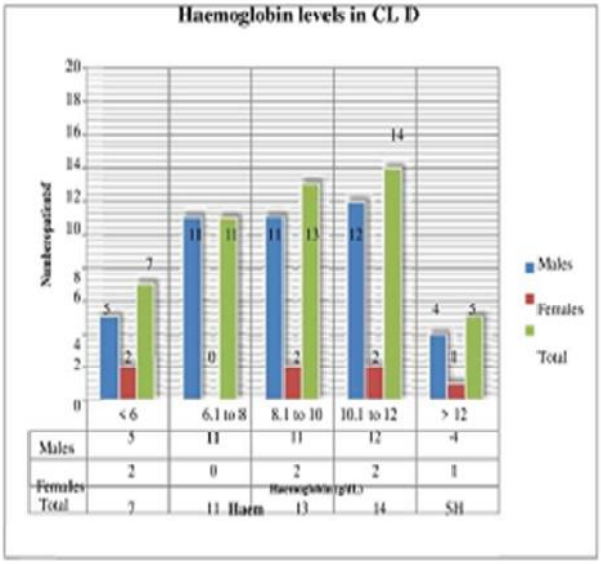
Past History of Jaundice

Of the 50 patients with Cirrhotic liver only 14 patients gave past history of jaundice. Serology proved that 4 patients had hepatitis B and 2 had hepatitis C. One female patient had recurrent history of jaundice and was diagnosed as a case of Wilsons disease.

Analysis of Haemoglobin

Patients were analyzed for the presence or absence of anemia; & if present the type of anemia was characterized with help of peripheral smear.

HAEMAGLOBIN LEVELS IN CLD



90% of the patients were anemic with only 10% of patients having a normal Hb level above 12 g/dL. About 14 % of patients had severe anemia with an Hb value less than 6 g/d L. All these patients had upper GI bleed.

From the above data males had a worse Hb compared to females. This can be explained by the following facts

- Males had more severe liver disease compared to females (average CPS of males – 11. 2 Vs CPS of females – 8.1)

- Eleven males had an upper GI bleed compared to only two females

-60 % males were alcoho lics, which contributes to anemia by various mechanisms like direct toxicity on the bone marrow, direct liver injury, impaired folate absorption and malnutrition etc.

In this study 13 patients had a history or presented with Upper GI bleed. This included 11 males and 2 females. The source of bleed was confirmed to be variceal by upper GI endoscopy in all 13. The rest 37 patients did not give a history of upper GI bleed and they had a negative stool occult blood test (though 35 patients had evidence of portal hyper tension).

Characteristics of the Anemia

The most common type of blood picture was normocytic red cells seen in 22 patients, of which 5 patients had a normal Hb value. Macrocytic picture was observed in 15 patients. Of these 14 patients had alcoholic liver disease and the etiology was undetermined in the other. 11 patients had a microcytic blood picture of which 8 patients had an upper GI bleed and the one patient with hemochromatosis had sideroblastic anemia that was proved with bone marrow and iron studies. Dimorphic blood picture was seen in 2 patients.

Characteristics & Morphology of Anemia

Peripheral smear	*Number*	*Average MCV*
Macrocytic	15	101.8
Normocytic	22	89.9
Microcytic	11	71.39
Dimorphic	2	78

Target cells were seen only in 3 patients and acanthocytes in 2 patients, these patients had severe disease with an average CPS of 13. One female patient with Wilsons disease was noted to have few spherocytes in the peripheral smear.

Wbc Abnormalities

The analysis of WBC was done with total and differential counts. Counts ranged from 2700 to 20800

WBC COUNT IN CLD

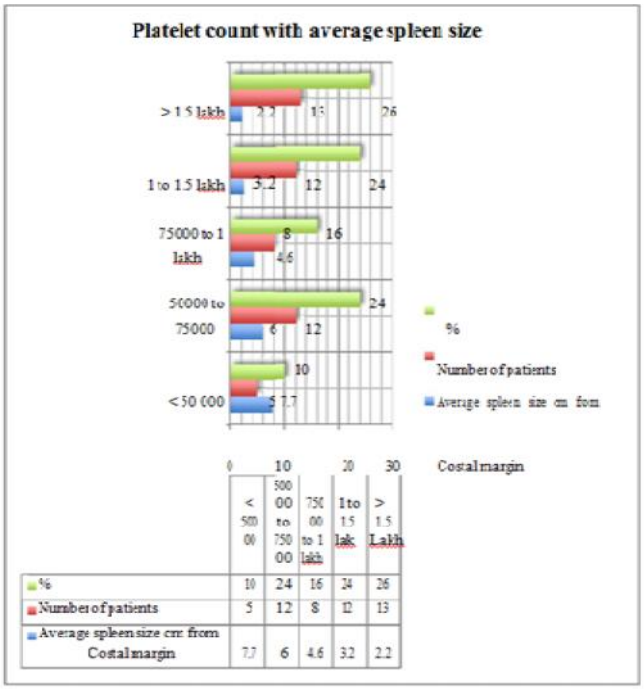
WBC Counts	Number of patients
< 4000	13
4000 to 8000	22
8000 to 12000	7
> 12000	8

Among the 50 patients Leucocytosis was observed in 8 patients, 4 patients with a count above 15000 had SBP. The other 4 had low-grade fever probably as a result of endotoxemia. Leucopenia was observed in 13 patients. Eosinophilia was observed in 5 cases, neutrophilia in 8 patients.

Platelet Abnormalities

50 % of the patients had thrombocytopenia (<1 lakh)

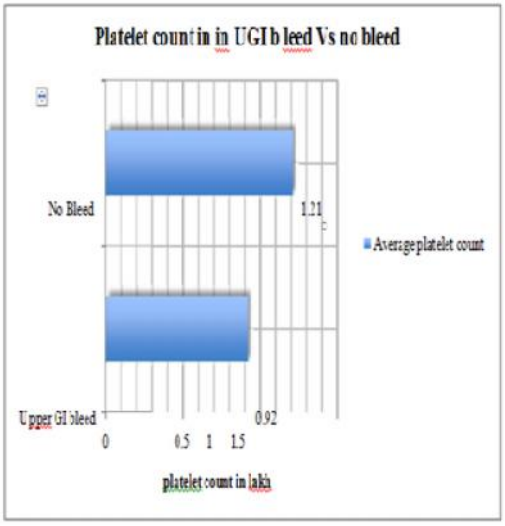
PLATELET COUNT COMPARED TO AVERAGE SPLEEN SIZE



A stastically significant correlation was noted between spleen size and thrombocytopenia (p value – 0.03) Patients with a count less than 50000 had an average spleen size of 7.7 cm.

Of the 13 patients who had an upper GI bleed 3 patients had normal platelet counts and the rest had counts below 1 lakh. The average platelet count of patients who experienced an upper GI bleed was 92000 vs. 1.2 lakh in patients without a GI bleed.

Table 29: Comparison of Platelet Counts in Ptients with and without upper Gibleed



The bleeding time was prolonged only in 6 patients with thrombocytopenia indicating BT as an insensitive test.

Coagulation Profile

The liver secretes all clotting factors except VIII & VWBf. Coagulation profile was assessed using aPTT, PT-INR and fibrinogen levels. 36 patients had a prolonged INR. Among the 13 patients with upper GI bleed 9 had prolonged INR; indicating other factors play a role in GI bleed.

INR VALUES

INR	Number
1.3 to 1.6	17
1.7 to 2	10
2 to 2.5	7
>2.5	2

Discussion

This study conducted at Department of digestive health and diseases hospital, Kilpauk medical college involving 50 patients has thrown light on many of the hematological abnormalities that is seen in decompensated chronic liver disease.

Haemoglobin Abnormalities

According to an article –" Spectrum of anemia associated with chronic liver disease by Rosario Gonzalez-Casas, E Anthony Jones, and Ricardo Moreno-Otero" published in the World Journal of Gastroenterology in 2009; anemia of diverse etiology occurs in up to 75 to 80 % of cases of chronic liver disease. The mechanisms operating to produce anemia include the following;

- Haemodilution
- Portal hypertension and splenic sequestration of red cells
- Bleeding into the gastrointestinal tract from varices or bleeding peptic ulcers
- Nutritional deficiencies of folate, B12 and iron
- Suboptimal bone marrow response to chronic inflammation
- Reduced red cell survival
- Alcohol through diverse mechanisms.
- Reduced erythropoietin levels

In our study 90 % of the patients were anaemic; this value is significantly higher compared to the previously cited article. 76 % of the patients had a moderate degree of anemia whereas 14 % of the patients had severe anemia below 6 g/dL.

The reason for the more severe degree of anemia in this study population of 50 patients could be the following:

- 52 % of patients of this study population had alcoholic liver disease. Alcohol's adverse effects on the hematopoietic system are both direct and indirect. The direct consequences of excessive alcohol consumption include toxic effects on the bone marrow. Alcohol's indirect effects include nutritional deficiencies that impair the production and function of various blood cells.

In this study the average Hb of patients with alcoholic liver disease was 8.7 g/dL compared to 9.3 g/dL of patients with other causes of DCLD. This clearly shows alcoholism by itself contributes significantly to the causation & burden of anemia.

This study was undertaken in a Government medical college hospital where all patients belonged to the lower strata of the socio-economic circle; hence they probably had pre existing nutritional deficiencies that added on to burden of chronic liver disease.

Another interesting observation from this study was that males had a higher degree of anemia compared to females. The average Hb of males was 8.9 g/dL compared to 9.1g/dL in females.

The reasons probably are

- Males had a more severe liver disease compared to females. The Average CPS of males was 11.2 compared to 8.1 for females

- 11 males had an upper GI bleed compared to only 2 females. In this study the average Hb of patients with an upper GI bleed was 6.5 g/dL compared to 9.8 g/dL with those without a bleed.

- 60 % of the males had alcoholic liver disease compared to no alcoholic liver disease in females.

Type of Anaemia

Several studies have been published describing the morphology and frequency of the types of anemia in chronic liver disease; the type of anemia varying in frequency in different studies.

According to Sherlock's textbook of the liver & Oxford textbook of medicine the most common type of anemia is a normochromic normocytic anemia. A Chapter by Atul B Mehta & A Victor Hoffbrand in the postgraduate hematology, fifth edition mentions that 66 % of patients show a macrocytic picture, a view that is shared by Garnet Cheney – "Morphology of the erythrocytes in cirrhosis" published in the California & Western medicine journal 1967. A study by Mishra et al in 1982 said that the most common type of anemia is a normochromic normocytic anemia seen in 79% of the patients.

An article published by Eric William Camille et al in The Journal of French studies & research (volume 17, Number 2, 87-91, April-May-June 2010) elucidates that 43.3 % of patients had a normochromic normocytic anemia where as 20 % had a microcytic hypochromic anemia.

Our particular study conforms more closely to the French study; 44% of the patients had a normochromic normocytic anemia, 30 % had a macrocytic blood picture and 22 had microcytic hypochromic anemia. 16 % of the patients with a microcytic blood picture had an upper GI bleed and one patient with hemochromatosis had sideroblastic anemia that was proven with iron studies and bone marrow.

Various abnormal types of red cells have been described in cirrhosis.Target cells are bell-shaped RBC that assumes a target shape on dried films of blood. Cooper RA, Arner EC, Wiley JS

et al explained that target cells form due to loading of the red cell membrane with cholesterol and lecithin resulting from diminished lecithin cholestrol acyl transferase activity (LCAT). Bile acids are believed to inhibit LCAT activity.

Spur cells or acanthocytes are seen in severe liver disase. They are cells with unusual irregularly placed thorny projections & are believed to be formed from echinocytes or burr cells due to the interaction of abnormal HDL found in liver disease with the red cell membrane (Owen JS, Brown DJ, Harry DS et al – "Erythrocyte Echinocyte in liver disease." Role of abnormal plasma HDL-J Clini. Invst. 1985)

In our study only 3 patients showed target cells and 2 showed acanthocytes. One female patient with Wilsons disease showed few spherocytes suggesting Copper mediated non-immune haemolysis.

WBC ABNORMALITIES

According to Sherlocks textbook of Hepatology, in cirrhosis there is usually a leucopenia in the order of 1500 to 3000 cells/dL. It may be more severe in which case

- Hypersplenism
- Alcohol & cytokine induced bone marrow suppression
- Significant folate deficiency should be ruled out.

Studies by Rosenbloom, A.J. et al published in JAMA in 2010; elevated levels of IL-6 in patients with cirrhosis suggested ongoing leucocyte activation, and predicted the development of a systemic inflammatory response syndrome.

Altin et al have described abnormalities of Neutrophil function – adhesion and chemotaxis accompanied with low levels of C3 in DCLD. Very little is known about the role of granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) in leucopenia associated with cirrhosis. Gurakar et al have shown that GM -CSF treatment for seven days in patients with cirrhosis and leucopenia resulted in an increase in the WBC count.

Hypergammaglobulinemia is almost universal in chronic liver disease. It is due to immunization of the antigen presenting cells with enteric microbes and antigens with resultant lymphocyte activation. IgA is elevated in alcoholic cirrhosis whereas IgG elevated in autoimmune hepatitis.

In our study group of 50 patients the WBC count ranged from 2700 to 20800. 26% of patients had leucopenia with count less than 4000. 58% had normal count & 16 % of patients had Leucocytosis. 4 patients with count above 15000 had proven spontaneous bacterial peritonitis; the other 4 had low-grade fever and severe liver disease probably resulting from endotoxemia.

Eosinophilia was observed in 5 cases probably resulting from underlying parasitic infection.

It was not possible to obtain functional studies of WBC nor electrophoretically determine the type of immunoglobulin's elevated in cirrhosis due to lack of facilities. However all 50 patients had A:G reversal. It was due to both decreased synthesis of albumin with deteriorating liver function and increased synthesis of immunoglobulin.

An interesting observation that was made was the correlation of A:G ratio with severity of liver disease. When the ratio was lower, the severity of liver disease was higher – 6% of patients had A:G ratio of <.05 with an average CPS of 13.6 whereas when the A:G ratio was 0.8 to 0.9 the CPS was 8.3.

Platelet Abnormalities

Several studies on platelet defects in DCLD have been done before. According to an interesting article by Jody L Kujovich MD – "Haemostatic defects in end stage liver disease "; Critical care clinics 21 (2005) - mild to moderate thrombocytopenia occurs in 49 to 64 % of patients with DCLD. The platelet count is rarely less than 30 to 40 thousand. The etiology of thrombocytopenia is multifactorial –

- Splenic sequestration of platelets
- Low Thrombopoietin levels
- Hypersplenism
- Reduced platelet half-life related to autoantibodies
- Folate deficiency
- Alcohol induced bone marrow suppression
- DIC
- Sepsis
- Drugs

Functional platelet defects are well described in several studies.

Escolar G et al reports that platelet aggregation seems to be particularly affected in as much as 46% of patients with DCLD.

The possible mechanisms have been postulated by a study by Ballard HS, Marcus AJ et al - "Platelet aggregation in portal cirrhosis"; Arch Intern Med 1996. They include

- Reduced availability of arachidonic acid for prostaglandin synthesis

- Reduced platelet ATP and serotonin

- Circulating factors that inhibits platelet aggregation - FDP and D- dimers, plasmin degradation of platelet receptors, dysfibrinogenemia, and excess nitric oxide synthesis.

- Nitric oxide is a powerful vasodilator and inhibitor of platelet adhesion and aggregation produced by vascular endothelial cells.

- HDL isolated from cirrhotic patients inhibit ADP induced platelet aggregation

- Platelet binding domains are abnormal thus preventing efficient binding to Von Willi Brand factor during adhesion.

Comparison of various studies showed conflicting reports regarding bleeding time as a test to assess platelet function adequately. Blake JC et al." Bleeding time in patients with hepatic cirrhosis". BMJ 1990 reports that bleeding time is prolonged in as much as 40% of patients with cirrhosis. However another study by Basili S et al. "Bleeding time does not predict gastrointestinal bleeding in patients with cirrhosis"; J Hepatol (1996) reports bleeding time as an inadequate and ineffective test for platelet function and correlates poorly with bleeding tendency.

In our particular study 50% of patients had thrombocytopenia (< 1 lakh) of which 80% had mild to moderate thrombocytopenia (50 to 100 thousand). This conforms to the article by Jody L Kujovich mentioned earlier. The rest 20 % had severe thrombocytopenia (below 50000).

Our study also compared the degree of thrombocytopenia to the spleen size clinically palpable from the costal margin. The average spleen size of patients with count between 75 to 100 thousand was 4.6 cm, those with a count of 50 to 75 thousand was 6cm and those with a count less than 50000 had an average spleen size of 7.7 cm. According to a study by Aster RH et al "Pooling of platelets in the spleen" J Clin Invest 1966 the normal spleen sequesters up-to 33% of the platelet mass exchanging freely with circulating platelets. Markedly enlarged spleens may sequester up-to 90 % of platelets. This report conforms closely with our study.

In our study, of the 13 patients who had an upper GI bleed, 3 patients had normal platelet counts and the rest had average platelet count of 92000. The bleeding time was prolonged only in 12% of patients with thrombocytopenia. This clearly indicates that bleeding time as an insensitive test for platelet function conforming to the result shared by Basili S et al; and functional abnormalities probably play a role. However due to lack of facilities platelet functional studies could not be taken up.

Coagulation Abnormalities

A deranged coagulation system is very common in chronic liver disease. There is reduce d synthesis of all coagulation factors (except factor VIII & Von Willi Brand factor), Vitamin K deficiency, Hyperfibrinolysis & dysfibrinogenemia, all contributing to increased bleeding tendency.

Tripodi et al HEPATOLOGY 2005 through an elegant study have shown in addition to the diminished hepatic synthesis of clotting factors, patients also have a profound deficit of natural anticoagulants, mainly of protein C (a protein synthesized by the liver), and also of anti-thrombin, which may counterbalance the bleeding tendency caused by the deficiency in procoagulants. This was the concept of the Rebalanced Haemostatic system, which can be tipped in favor of bleeding or thrombosis depending on the clinical situation.

In our particular study as much as 72% of patients had a prolonged PT-INR, though only 25 % of these patients had an upper GI bleed. This may suggest a rebalanced coagulation system in action to prevent bleed, however we did not have any patient with DCLD who presented with thrombosis. Individual assessment of procoagulants & endogenous anticoagulants were not possible due to lack of facilities and are definitely warranted for more conclusive results.

Thus from this limited study of 50 patients with chronic liver disease we were able to draw many inferences regarding the haematological abnormalities that contribute to the morbidity of patients.

Many of the results obtained conform to previously done studies mentioned earlier but whether these results can be extrapolated to the larger population of cirrhotic patients as a whole is not definitely known and needs larger, more comprehensive studies with a wider range of patient selection.

Conclusion

Many conclusive results regarding the haematological abnormalities in decompensated chronic liver disease were obtained with this limited study involving 50 patients with decompensated cirrhosis

- 90% of the patients were anaemic of whom 14% had severe anaemia with a Hb less than 6 g/dL

- In this study males had a worse Hb compared to females

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