ANNALS OF HEPATOLOGY

Volume **4** *Number* **4** *October-December* **2005**

Artículo:

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Annals of Hepatology 2005; 4(4): October-December: 261-263

Annals of Hepatology

Original Article

Liver dysfunction in steady state sickle cell disease

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Abstract

The Liver is one of the organs involved in the multiorgan failure that occurs in sickle cell disease, the pathophsiology of liver disease in this condition is complex because of the interrelated multifactorial causes. Liver dysfunction was assessed in both paediatric and adult sickle cell disease patients in the steady state. The transaminases and alkaline phosphatase were analysed by automation while coagulation studies were done manually. The mean (range) of Alanine transaminase (ALT), Aspartate transaminase (AST) and alkaline phosphatase (ALP) were 23.0 (2-77) IU, 48.5 (15-120) IU, 227.5 (37-1200) IU respectively. ALT and AST levels were less than 100 IU in over 95% of the patients. The gender or age of the patients did not significantly affect the level of these three enzymes. There was close association between the liver size and elevation of the liver enzymes except for alkaline phosphatase (ALT = .017, AST = .009, ALP = .056). Twenty-five percent of the patients had normal enzymes while 13% had derangement of the three enzymes, 19%, 50% and 74% had abnormal ALT, AST and ALP respectively. Only 22% and 5% had deranged PT and APTT respectively. In conclusion minimal elevation of the tramsaminases which is not gender or age dependent were observed in steady state sickle cell disease, higher levels of alkaline phosphatase may be due to associated vasoocclussive crises involving the bones rather than a pathology of the liver.

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Manuscript received: 19 September, 2005 and accepted: 12 October, 2005.

Key words: Liver disorder, liver enzymes, transaminases, alkaline phosphatase coagulopathy.

Introduction

The incidence of liver disease in sickle cell disorders is difficult to ascertain despite being a component of the multiorgan failure that occurs in sickle cell disease,[1] this is because dysfunction of the liver in sickle cell disease is multifactorial[2] and therefore there are no definite diagnostic criteria.[3] The clinical manifestation of the different causes of liver failure is also similar and interrelated thus making the pathophysiology complex[4] besides, enlargement of the liver does not connote disease, also a normal size liver may be diseased. The hepatic complications of the sickle cell disorders can be separated into the following; disorders related to hemolysis, the problems of anemia and transfusion management, the consequences of sickling and vaso-occlusion, and defects unrelated to sickle cell disorder.[2] Elevation of the different liver enzymes correlates with the different categories; haemolysis raises plasma aspartate transaminase (AST) while plasma alanine transaminase (ALT) levels more accurately reflects hepatocyte injury.[2] High levels of serum alkaline phosphatase are commonly seen in patients with sickle cell anaemia, this may be because of either cholestasis or bone disease.[5]

Evidence of liver disease in sickle cell disease is obtained either from abnormal biochemical tests or postmortem liver biopsy specimen rarely an antemortem liver specimen, studies using biochemical tests have more often included only the liver enzymes. Our study investigated the frequency of derangement of the liver enzymes by both biochemical and coagulation tests in sickle cell disease patients who are free of any acute illness i.e. in steady state, and also included both adult and paediatric patients.

Patients and methods

Fifty-two adult patients who attend the adult sickle cell clinic of a tertiary institution and fourteen paediatric sickle cell patients of the same institution were selected. Informed consent was obtained from the adult patients and the caregiver of the paediatric patients (< 16 years). Only patients who were in the steady state were selected,

this included both HbS and HbS +C, children below 10 years were excluded because majority of their parents will not give consent. A general examination was done on all the patients before blood samples were taken for biochemical and coagulation studies. The general examination included assessing the conjuctiva for jaundice, which was classified subjectively as mild, moderate or severe. Enlargement of the liver below the costal margin was classified as mild if it is not more than 5 cm, moderate if 5-10 cm below the coastal margin and massive if more than 10 cm. The liver enzymes and bilirubin were analyzed by Hitachi 912 autoanalyser (Beckman) while Prothrombin time (PT) and Activated Partial Thromboplastin time (APTT) were done manually.

Statistical analysis: Data were analyzed using SPSS version 11 software. Frequency tables were generated for nominal and ordinal variables while continuous variables were analysed using descriptive statistics. Association between clinical data was assessed by cross tabulation and one sample T- test used for laboratory parameters; the reference value of the community was used as the test value. The degree of jaundice and liver enlargement were recorded and age stratified, analysis of variance (ANOVA) was then used to compare the parameters of each group. Pearson's correlation coefficient was used to study the relationships between the liver enzymes. Level of significance for all tests was set at 95% confidence interval except for Pearson's correlation where 99% confidence interval was used as the level of significance.

Results

Clinical data: The mean age of the patients was 24 years (range, 10- 72), 59% were female. There was no clinical evidence of jaundice in 15% of the patients while 70% had mild jaundice. Twenty-three percent had no palpable liver; only 5% had liver size greater than 10 cm. Twelve percent had never received blood transfusion. There was close association between the degree of jaundice and the size of the liver (p = 0.024) but no association was observed between the total number of pints transfused and the degree of jaundice (p = 0.89). No significant association was found between the number of units transfused and liver size (p = 0.65).

Laboratory parameters: The mean (range) of Alanine transaminase (ALT), Aspartate transaminase (AST) and alkaline phosphatase (ALP) were 23.0 (2-77) IU, 48.5 (15-120) IU, 227.5 (37-1200) IU respectively. These were significantly different from the cutoff point for the general population (P = .00, .02, .00 for ALT, AST and ALP respectively). ALT and AST levels were less than 100 IU in over 95% of the patients. The cutoff point for ALT, AST and ALP are 35 units/L, 40 units/L and 106 units/L respectively for this population. The gender or age of the patients did not significantly affect the level of the three enzymes. There was close association between the liver size and elevation of the liver enzymes except for alkaline phosphatase *(Table I)*. Twenty-five percent of the patients had normal enzymes while 13% had the three enzymes deranged, 19%, 50% and 74% had abnormal ALT, AST and ALP respectively. There was significant positive correlation between the three liver enzymes at 0.01 level. The mean (range) of total bilirubin was 2.6 (0-13) mg/dL while for conjugated it was 1.3 (0-12) mg/dL. The mean bilirubin rises as the liver size increases *(Figure 1)*. The mean Prothrombin time (PT) of the patients differed significantly from that of the general population (p = 0.000) while the mean Activated Partial Thromboplastin Time (APTT) differ only minimally from that of the general population (p =. 046). Only 22% and 5% had deranged PT and APTT respectively. The reference values for PT and APTT are 12-14 seconds and 30-40 seconds respectively.

Discussion

There is no evidence to support the fact that the liver enlargement seen in seventy-seven percent of the patients is due solely to hepatic disease because abnormality of ALT which is specific for hepatic injury was noted in only 19% of the patients and similarly only 22% of the

Table I. Relationship between liver size and liver enzymes.

Liver size	Aspartate transaminase (units/L)	Alanine transaminase (units/L)	Alkaline phosphatase (units/L)
Nil	39.7	24.9	285
Mild	86.2	32.6	211.7
Moderate	70.5	49.4	416
Massive	87	19	658
Level of significance (p value)	0.09	0.17	0.56

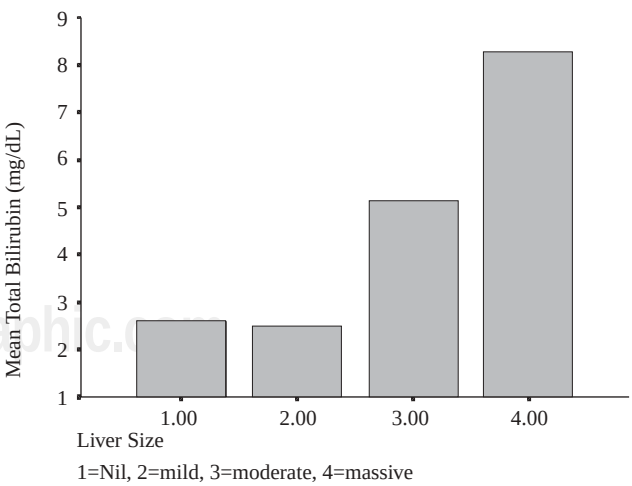

Figure 1. Mean total bilirubin in relation to liver size.

patients had a prolonged prothrombin time. *Postmortem* findings have also shown focal necrosis and fibrosis in 35-40% and cirrhosis in 5-16% of cases[6,7] with majority of the patients showing sinusoidal dilatation, erythrophagocytosis and haemosiderosis.[6-8] In a study of 100 patients over a five-year period, Johnson et al did not find clinical or laboratory evidence of liver disease,[9] the liver enlargement seen in sickle cell disease therefore may be because of acute sickle hepatic crisis or hepatic sequestration crisis rather than primary dysfunction of the liver. Acute intrahepatic cholestasis is however a common occurrence which may sometimes be fatal.[10,11]

Acute intrahepatic cholestasis may be a sequelae of widespread sickling within the sinusoid[2] or extreme haemolysis with resultant hyperbilirubinaemia, which is often accompanied by elevated alkaline phosphatase and variable levels of transaminases. Seventy-four percent of the patients showed elevated alkaline phosphatase but no significant association was found between it and liver size ($p = 0.056$), which will suggest that liver pathology may not account solely for the elevation of this enzyme. A previous study has identified bone alkaline phosphatase as the principal enzyme fraction that increases during sickle cell crises, there also appeared to be concordance between crisis severity, serum levels of alkaline phosphatase, and isoenzyme patterns. These abnormalities could also be detected even when the patients are asymptomatic.[5] This will suggest that the raised level of alkaline phosphatase may be due more to the recurrent vasoocclusive crises involving the bones in these patients. High levels of alkaline phosphatase are expected in children because of the growth spurts, this was not observed in this study, two patients had normal levels with other patients showing a marginal rise, this is similar to the observation of another study which showed normal values in paediatric sickle cell disease patients.[12]

Cirrhosis in sickle cell anaemia patients is usually secondary to chronic hepatitis B or C infection or to iron overload with serum ferritin levels correlating with the number of units transfused.[13] Similarly, the risk of hepatitis B and C infections have been related to the number of blood units transfused, the prevalence of hepatitis B and C is about 20%[14] in the same population of patients as ours. It is also worthy of note that a similar prevalence of about 20% is found in the control group of the same study so blood transfusion may not be solely responsible for the high viral markers in these patients. The high prevalence in both the sickle cell disease patients and the control group can be attributed to vertical and/or horizontal transmission, which has been noticed in sub-Saharan countries where anti HBc, persists in adults without the surface antigen (HBsAg) or its antibody.[15] No association was observed between the number of units transfused and liver size in the present study presumably because the liver enlargement may be due to erythrophagocytosis or haemosiderosis rather than to hepatic disease.

Mild elevation in liver function tests which is not related to age or gender is observed in sickle cell disease patients in the steady state so appreciable rise in the liver enzymes may be due to complications arising from management of the disease, moderate elevations of the liver enzymes especially of the transaminases should therefore be investigated.

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