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POST-TRANSFUSION VIRAL HEPATITIS IN SICKLE CELL ANAEMIA: RETROSPECTIVE-PROSPECTIVE ANALYSIS

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ABSTRACT

Several complications of sickle cell anaemia (SCA) are well known including hepatobiliary dysfunction. We here present a study of 151 randomly selected SCA patients to highlight the contributory role of blood transfusion to the development of viral hepatitis in them.

Twenty (13.2%) had not received blood transfusion and no case of acute viral hepatitis (AVH) was recorded in them. One hundred and thirty one (86.8%) had received an average of 4.2 pints of blood as at the time of study. Sixteen (12.3%) of these developed post-transfusion hepatitis (PTH) out of which 8(50%) were positive for hepatitis B virus during the acute hepatitic phase. In the post-hepatitic state, 4 patients were positive for HBsAg only while 5 tested positive for anti-HCV only and 1 patient had both viruses. Six patients were seronegative for both HBsAg and anti-HCV. Three of the seronegative patients had previously been seropositive for HBsAg in the acute hepatitic phase. It is concluded that blood transfusion carries a significant risk for the development of PTH in SCA. We suggest more vigorous efforts by the government and the transfusion centers on strict adherence to blood safety guidelines.

INTRODUCTION

Hepatobiliary dysfunction was noticed in the first report on sickle cell anaemia in 1970(SCA)[1]. The spectrum of liver disease in SCA patients includes acute viral hepatitis, hepatic crisis, cholestasis, cholelithiasis and haemosiderosis. Sickle-cell hepatopathy has been attributed to anoxia, following sinusoidal obstruction by sickled erythrocytes and kupffer cell erythrophagocytosis[2]. This leads to progressive injury to the liver with significant fibrosis, often with cirrhosis and decreased liver function by adulthood[2,3]. However, some causes of liver disease in SCA patients can be explained by clinical disorders other than the heamoglobinopathy alone[4]. Sickle cell anaemia patients often require blood transfusion either as acute life-saving measure or to prevent organ damage, thus predisposing them to transmissible blood-borne organisms. Hepatotropic viruses are one group of such transmissible organisms, which can lead to the development of post-transfusion hepatitis (PTH) and its sequelae. This study was undertaken to define the role of blood transfusion in SCA patients with viral hepatitis.

PATIENTS AND METHODS

Data collecting sheets were administered to each of 151 randomly selected SCA patients from the outpatient unit of the Haematology Department of the University College Hospital, Ibadan, Nigeria. Information on biodata, past blood transfusion and development of liver disease following blood transfusion were obtained. Five millitres of venous blood was taken from each patient. The blood was allowed to clot and centrifuged. The sera were separated and stored at -20° C till analyzed. Samples were then screened for hepatitis B and C viruses using the second generation ELISA kits (Monolisa 2eme Sanofi Pasteur, Paris, France) to detect hepatitis B surface antigen (HBsAg) and antibody to hepatitis C virus (Anti-HCV). Hepatitis Be antigen (HBeAg), antibodies to core and surface antigens (anti-HBc, anti-HBs) were not tested. Clinical presentation, viral markers and liver function test results including the prothrombin time ratio (PTR) during the acute hepatitic phase were retrieved from the case notes of those who developed AVH following blood transfusion. Diagnosis of PTH was based on clinical features of acute viral hepatitis (AVH) such as jaundice, nausea, vomiting, dark urine, weakness, right upper abdominal pains, following blood transfusion in patients who have not had previous evidence of AVH, as well as marked rise in serum transaminase.

RESULTS

One hundred and thirty-one (86.8%) of the 151 patients had received blood transfusion. Indication for blood transfusion was anaemia in 92%. The mean packed cell volume (PCV) in steady state of the patients was 23 ± 3% while the pre-transfusion PCV range was 16- 19%. The average blood transfusion frequency was 4.2 per patient with a range of I to 20 units till date of study. No history of scarification, dental extraction, tattoos or indiscriminate injections were obtained. Data from questionnaire revealed that 19 (14.5%) had been managed for acute liver disease between 1987 and 1997. Sixteen (12.2%)of the 131 patients had documented clinical and laboratory evidence of AVH following blood transfusion which developed within 1 -4 months of the

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transfusion. All the 16 patients had hepatomegaly with liver span range of 13 to 23 cm below the right costal margin in the mid-clavicular line. Demographic characteristics of the 16 patients with clinical and laboratory evidence of PTH showed that the patients were between 13 - 39 years of age, with a male\female ratio of 2:1. Fifteen were single, the only married patient developed hepatitis 6 weeks after being transfused as a result of primary postpartum heamorrhage (PPH). There was no previous history of abortion or intrauterine death. Ten of the patients were students, 2 apprentices, 1 trader and 3 were civil servants/banker.

The liver function tests carried out in patients with PTH showed serum alanine and aspartate transaminase (ALT and AST) ranges of 305 IU/L to 2297 IU/L and 340 IU/L to 1759 IU/L respectively. The mean values of ALT and AST were 1244.5 IU/L and 1223.9 respectively. The PTR ranged between 1.5 to 3.8 with a mean of 2.25. Table 1. Liver function tests and PTR were not done in patients without PTH. Table 3 shows the details of viral markers for transfused patients with and without PTH. Hepatitis B surface antigen screening during the acute hepatitic phase showed that 8 (50%) were positive using monoclonal antibody latex agglutination method None of the patients was tested for anti-HCV or any other viral marker at this stage. During the post-acute hepatitic state, defined as 6 months or more post-recovery from acute viral hepatitis, HBsAg and anti-HCV screening results using ELISA method showed that 4 were positive for HBsAg, 5 for anti-HCV, 1 was positive for both viral

Table 1. **Abnormalities of Liver function Test in 16 Sickle Cell Anaemia Patients with Acute viral icteric hepatitis**

Parameters	**Fold rise of upper limit of normal range**						
	>2.5	>6	>12	>20	>30	>40	>50
Bil.Total	16(100%)	16(100%)	16(100%)	14(87.5%)	9(56.25%)	5(31.25%)	1(6.25%)
Conjugated	l6(100%)	16(100%)	16(100%)	16(100%)	16(100%)	14(87.5%)	12(75%)
ALT	16(100%)	13(81.25%)	13(81.25%)	10(62.5%)	4(25%)	1(6.25%)	1(6.25%)
L\ST	16(100%)	14(87.5%)	14(87.5%)	9(56.25%)	6(37.5%)	2(12.5%)	0

Fold rise of upper limit of normal range of PTR.

PTR	<1.5	1.5- 1.9	>2
1(6.25%)	15(93.75%)	11(68.75%)	

Table 2: **Viral markers during acute viral hepatitis and in the Post-hepatitic state in 16 patients with Sickle Cell Anaemia**

Viral marker	**Acute Viral Hepatitis**	**Steady State**
HBsAg positive	8(50%)	4(25%)
Anti-HCV positive	-	5(31.25%
HBsAg/Anti-HCV positive	-	1(6.25%)
HBsAg negative	8(50%)	-
HBsAg/Anti-HCV negative	-	6(37.5%)

Table 3: **Viral markers in transfused and non-transfused HBSS patients in steady state.**

Viral marker		**Transfused n=131**		**Non-transfused n=20**		**p-value**
		No	**%**	**N0**	**%**	
HBsAg	Positive	31	23.6	5	25	0.545
	Negative	100	76.3	15	75	
Anti-HCV:	Positive	26	19.8	4	20	0.595
	Negative	105	80.2	16	80	
HBsAg/Anti-HCV:	Positive	10	7.6	2	10	0.492
	Negative	121	92.4	18	90	

markers, while 6 were negative for both. Three of the 6 seronegatives were previously positive for HBsAg during the acute hepatitic phase (Table 2).

DISCUSSION

It is not surprising that 12.5% of our patients developed post transfusion hepatitis considering the inadequacy and lack of full implementation of blood screening policy in Nigeria. In tertiary health centers where blood is being screened for HIV and HBV, screening for HCV is yet to commence due to high cost of the kit. This finding is similar to findings in India; a developing country like Nigeria where the incidence of PTH in multiple transfused patients is 14.6%[5]. This picture is different from what obtains in economically developed countries of the world like Europe and North America where the incidence of PTH is negligible, as a result of stringent measures put in place for pre-donation blood screening, following establishment of National Blood Transfusion Services[6,7,8].

All our patients had hepatomegaly, this is similar to findings in a series of SCA patients where hepatomegaly with histopathological changes and liver function tests abnormalities were found in almost all even in steady state[9]. The high percentage of patients who had post- transfusion acute HBV infection is unexpected as all transfused blood at the UCH are screened for HBV and HIV, though latex agglutination is used for the former. Some of the patients may also have been transfused at several other centres where pre-transfusion screening of blood is not practiced. At 1 year only 3 (37.5%) of the HBsAg positive patients had cleared the virus, this will suggest a defective clearance of HBV in SCA, as most adults with HBV infection (>90%) usually clear the virus and become protected unlike childhood acquired HBV infection, which develops into chronic infection. The patients who were HBsAg negative at the time of the PTH might have had other viral agents as a cause or an HBV with superinfection with the delta antigen, which suppresses HBV replication and may render it undetectable[10]. The sensitivity of the screening method employed (monoclonal latex agglutination) which is less sensitive than the ELISA technique might also be responsible. In developed countries, HCV is the commonest cause of PTH[11] accounting for as high as 80% of post-transfusion hepatitis in some countries[12]. This finding calls for pre-transfusion screening for anti-HCV in all blood banks in Nigeria. The importance of pre-transfusion screening of blood for SCA cannot be over-emphasized as this group of patients who are likely to be multiply transfused stand a higher risk of infection by these viruses with subsequent chronic hepatocellular damage[13] especially with the high rate of chronicity of infection associated with HCV. The average transfusion per patient of 4.2 units in our study is high and complications like chronic hepatitis, liver cirrhosis and hepatocellular carcinoma should be anticipated in these patients. Hepatocellular carcinoma is however rarely reported in SCA[2], as the patients die of other complications of SCA beforehand. These aforementioned sequelae will further reduce the life expectancy of SCA patients, which is reported to be 42 years and 48 years in males and females respectively[14]. It is remarkable that 6(37.5)% of our patients are negative for both HBV and HCV markers in the study. This however does not suggest that these patients are negative for other hepatotropic viruses such as hepatitis G virus (HGV) that has been found to be common in some blood donors (1-2% in the USA) and transmissible by blood transfusion[15,16]. HGV has also been found in acute and chronic liver disease[17] . Seronegative hepatitis, in which all the known hepatitis viruses have been excluded, may also be responsible for some of these cases. Our patients cannot be categorised under this group as all the other known hepatitis viruses, including the recently discovered Transfusion Transmitted Hepatitis virus (TTV), which has also been associated with PTH[18,19] have not been excluded.

CONCLUSION

It is suggested that functional and well funded blood transfusion service with branches in state capitals and even local government headquarters be set up to enforce guidelines on blood safety. Efforts should be made to use blood rationally in SCD patients and alternatives to the use of blood transfusions should be considered while not withholding blood as a life saving measure in the management of SCA patients. We suggest that the national blood transfusion policy be implemented and funded by the government who should ensure that the transfusion centers keep to the guidelines on blood safety.

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