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Clinical Research of Viral Hepatitis in Sickle Cell Disease

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ABSTRACT

Patients with sickle cell anaemia experience sickle cell crises throughout their life. Jaundice in a patient with sickle cell hemoglobinopathy is quite common and can be attributed to the sickle cell crisis, sickle cell hepatopathy, intrahepatic cholestasis or cholelithisis. In addition, occurrence of viral hepatitis is not uncommon in them and it is difficult to distinguish this aetiology clinically. In this study attempt has been made to identify the criteria to help differentiate amongst sicklers which patients should be investigated for viral hepatitis. Also, sicklers with hepatitis have been studied against non sicklers with hepatitis and also complications of hepatitis in these two groups.

KEY WORDS: SICKLE CELL ANAEMIA, VIRAL HEPATITIS, JAUNDICE, HAEMOGLOBINOPATHY.

INTRODUCTION

Eighty five years ago sickle cell disease was reported for the first time by Dr Herrick J. B. (1910) a Chicago cardiologist. Since then, during the last eight decades, that have ensued, a magnanimous acquaintance has accumulated concerning the clinical manifestations, pathology, pathophysiology, morphologic and rheologic features of sickle erythrocytes, kinetics of sickling, and complications in sickle cell disease.

Sickle cell disease is quite common in Vidarbha region of Maharashtra, India. It has predilection for particular communities and occurs in Boudha, Kunbi, Koshti, Teli communities in descending order of frequency. Sicklers are vexed throughout their life by different crises which characterise this disease. The word 'crisis' was for the first time coined by Sydenstricker (1924), who noted that abdominal pain, increase in jaundice, and in urobilinogen content in the urine resembled crisis in congenital haemolytic anaemia. However, the accepted definition of sickle cell disease was given by Diggs L. W. (1963).

Viral infections, particularly viral hepatitis is not uncommon in sicklers. It is the multiplicity of blood transfusions, injections, frequent exposures to the hospital environments and the socioeconomic environs, to which sicklers are exposed to, are the factors responsible for the frequency with which hepatitis occurs in sicklers (Green TW 1953 & Jorgensen T 1989).

Whenever viral hepatitis affects a sickler it poses problems in the diagnosis for the physician. This is because these are the chronically jaundiced persons with superimposed jaundice and malaise because of which hepatitis may go

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unnoticed. Clinically, it is difficult to differentiate it from other modalities by which liver gets involved in sicklers i. e. to say haemolytic crisis, sickle cell hepatopathy, intrahepatic cholestasis and cholelithiasis (Charlotte F 1995 et al.,). There are no well-defined haematological and biochemical criteria to diagnose and differentiate these simulating conditions. Serology and liver biopsy is the answer for this dilemma. But then conditions do not always permit these investigations as for example lack of facilities for serological investigation for viral markers or acute stage of viral hepatitis where liver biopsy is contraindicated. In the present study, an attempt has been made to diagnose viral hepatitis clinically, biochemically and histopathologically in sicklers and compare the same with non-sicklers.

MATERIAL AND METHODS

Setting: The study entitle "Study of viral hepatitis in sickle disease" was conducted in infectious unit of Government Medical College Nagpur from August 1994 to September 1995 in the Department of Medicine. This is case control study. Total no. of patients (n =88) i.e. 44 cases and equal no. of age and sex matched controls (n =44) were studied. Further sub division of cases was mad e in to two groups depending upon the haemoglobin electrophoresis pattern i.e. SS group (n =9), AS group (n =35).

Inclusion Criteria: All cases of hepatitis with sickle hemoglobinopathy and their age and sex matched controls without any hemoglobinopathy are included in the study.

Exclusion Criteria: Patients having historical or laboratory evidence of liver disease of aetiology other than viral hepatitis were excluded from the study.

Assessment criteria:
Subjective Criteria: Fever, anorexia, nausea, vomiting, yellowness of eyes, dark urine, altered mentation/ sleep rhythm, pain in abdomen, bleeding diathesis.

Objective criteria: temperature, pulse, blood pressure, pallor, icterus, bony tenderness, malena, level of consciousness, bleeding spots, gastrointestinal bleeding, urine output, signs of hepatocellular failure, liver spleen free fluid in per abdomen examination.

Investigations: After detail history and clinical examination, investigations were divided into following categories:

1. To confirm the diagnosis of sickle cell disease.
2. Investigation for the diagnosis of hepatitis.
3. Investigations to rule out haemolytic crisis.

- Routine haemogram, reticulocyte count using brilliant cresyl blue stain was done all patients.
- Sickling was done by method described by Donald and Castle (1948)8. It is based on principle that deoxygenated cells containing haemoglobins sickle. The process of deoxygeneration is enhanced by adding a reducing substance to the preparation.
- To know type of sickle cell disease or trait, haemoglobin electrophoresis was done by paper electrophoresis method described by Goldberg

Table 1. Symptomatology

Symptoms	SS Group (n=9)		AS Group (n=35)		Control Group (n=44)	
	No.	%	No.	%	No.	%
Yellowness of Eyes	9	100.00	35	100	44	100
Fever	7	77.8	31	88.6	39	88.4
Dark coloured urine	7	77.8	30	85.7	37	84.09
Anoerexia	5	55.6	24	68.6	31	70.5
Nausea	6	66.7	10	28.6	30	68.2
Vomiting	6	66.7	21	60.0	30	68.2
Abdominal Pain	3	33.3	16	45.7	23	52.3
Altered level of consciousness	2	22.2	9	25.7	8	18.2
Bleeding Tendencies	2	22.2	4	11.4	3	6.8

- **Liver Function Tests**
- Australia antigen was done by reversed passive hemagglutination method10
- Coagulation profile was done in all patients with hepatic encephalopathy
- Ultrasonography abdomen was done in patients with serum bilirubin exceeding 10mg/dl.
- **Ultrasonography abdomen:**
- Ultrasonography abdomen was done in patients who had bilirubin value exceeding 10mg/dl. It showed that liver was enlarged in size and uniform in echotexture. There was no evidence of focal lesion. Gall bladder appeared normal in all and there was no evidence of gall stones in any patient.
- **Liver Necropsy:**
- Liver necropsy using Vim Silverman Needle was

performed in fatal cases.

- Liver biopsy being contraindicated in acute phase of viral hepatitis was not done in any patient.
- Liver necropsy was done in six fatal cases out of eight. Necropsies in all 6 patients were suggestive of viral hepatitis, and in no patient changes of sickle hepatopathy were seen on necropsy.

The cases were studied and observations were made which are tabulated below:

Table 2. Positive Findings on Clinical Examination

Signs	SS Group (n=9)		AS Group (n=35)		Control Group (n=44)	
	No.	%	No.	%	No.	%
Icterus	9	100.00	35	100.00	44	100.00
Pallor	9	100.00	32	91.4	-	-
Fever	7	7.8	31	88.6	39	88.4
Hepatic encephalopathy	2	22.2	7	20.0	8	18.2
Grade I	-	-	2	28.6	2	25
Grade II	1	50.0	2	28.6	3	37.5
Grade III	-	-	1	14.2	1	12.5
Grade IV	1	50.0	2	28.6	2	25
Bleeding tendency	1	11.1	5	14.3	7	15.9
Hepatomegaly	9	100.00	35	100.00	44	100.00
Spleenomegaly	0	00.00	35	100.00	7	15.9

Table 3. Comparison of LFT in Patients with Hepatitis

Sr Bilirubin (Mean levels)	SS Group (n=9)	AS Group (n=35)	Control Group (n=44)
Total Bilirubin (upto 1mg/dl)	15.49	12.48	8.86
Conjugated Sr Bilirubin (upto 0.25mg/dl)	12.13	9.66	6.38
Unconjugated Sr Bilirubin	3.36	3.11	2.42
Serum Transaminases			
SGPT (2-49 IU/L)	195.10	141.66	122.50
SGOT (2-48 IU/L)	138.30	106.69	98.30
SGPT/SGOT (0.75-1.0)	1.41	1.32	1.24
Other Parameters of LFT			
Sr Alkaline Phosphatase (3-13 KAU)	9.37	9.78	9.71
Sr Proteins (6.3-7.9 g/dl)	6.02	5.96	5.73
Sr Cholesterol	173.78	170.49	169.50

Table 4. LFT in patients with Hepatic Encephalopathy

LFT (Mean values)	Cases SS Group=2, AS group= 7 (n=9)	Control Group (n=8)
Total Bilirubin (mg/dl)	17.47	12.69
Conjugated Sr Bilirubin (mg/dl)	14.17	8.96
Unconjugated Sr Bilirubin (mg/dl)	3.30	3.73
SGPT (IU/L)	186.90	132.40
SGOT (IU/L)	136.60	112.60

Table 5. Comparison of LFT in fatal cases

LFT (Mean values)	Cases SS Group=2, AS group= 7 (n=9)	Control Group (n=8)
Total Bilirubin (mg/dl)	17.05	12.50
Conjugated Sr Bilirubin (mg/dl)	13.74	8.93
Unconjugated Sr Bilirubin (mg/dl)	3.79	3.43
SGPT (IU/L)	192.00	140.00
SGOT (IU/L)	139.00	118.40

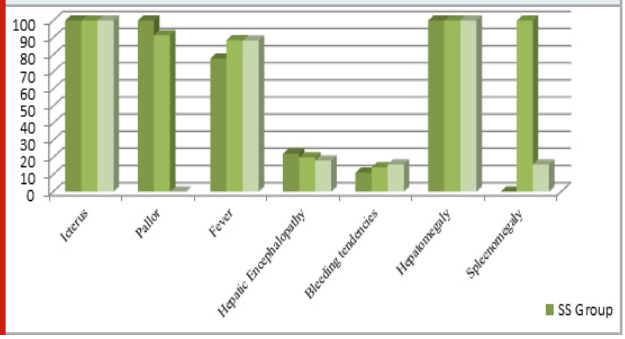
Table 6. Showing LFT in HBsAg positive patients

LFT (Mean values)	Cases (n=8)	Control Group (n=3)
Serum Bilirubin (mg/dl)	15.78	11.98
SGPT (IU/L)	177.10	116.80
SGOT (IU/L)	134.70	97.20

Table 8. Showing comparison of LFT in HBsAg positive fatal cases

LFT (Mean values)	Cases (n=8)	Control Group (n=3)
Serum Bilirubin (mg/dl)	17.05	15.78
SGPT (IU/L)	192.00	177.10
SGOT (IU/L)	139.90	134.70

Figure 1: Positive Findings of Clinical Examination



DISCUSSION

Clinical profile in cases of sickle cell disease with hepatitis and their age and sex matched controls was studied in Govt. Medical College and hospital, Nagpur between August 1994 to September 1995. All the cases were divided into two groups on the basis of haemoglobin electrophoresis pattern, SS group comprising 9 cases and AS group comprising of 35 cases. Detailed history and clinical examination along with haematological, biochemical, serological investigations and ultrasonography abdomen was done. Liver necropsy was done in fatal cases. Maximum numbers of patients were in the age group 11-20 years of SS group (55.56%) and in the age group of 21-30 years of AS group (57.14%). Males outnumbered females with 55.6% in SS group and 54.3% in AS groups.

Table 6. Showing comparison of LFT in HBsAg positive patients with hepatic encephalopathy

LFT (Mean values)	Cases (n=8)	Control Group (n=3)
Serum Bilirubin (mg/dl)	15.78	11.98
SGPT (IU/L)	177.10	116.80
SGOT (IU/L)	134.70	97.20

Table 9. Comparison of LFT in Cases with and without Hepatic Encephalopathy

LFT (Mean values)	With Hepatic Encephalopthy	Without Hepatic Encephalopthy
Sr. bilirubin (mg/dl)	17.47 (13.6-23.9)	13.18 (6.5-20.8)
SGPT (IU/L)	186.6 (139-340)	142.26 (96-215)
SGOT (IU/L)	136.6 (104-210)	114.33 (67-214)

Figure 2: Comparison of LFT in Patients with Hepatitis

Figure 3: LFT in Patients with Hepatic Encephalopathy

Figure 4: Comparison of LFT in Fatal Cases

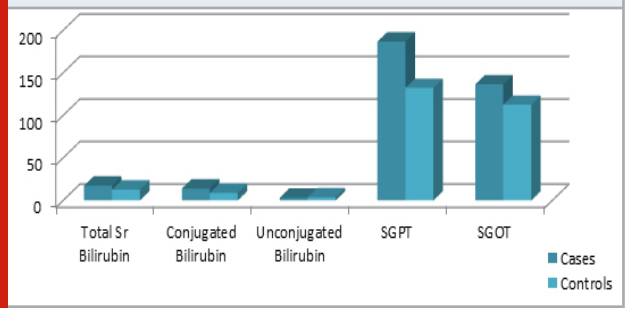


Figure 5: LFT In HBsAg positive Patients

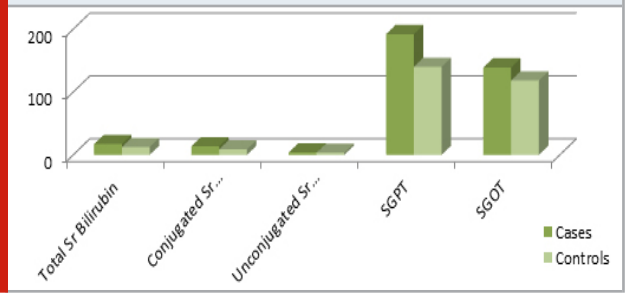


Figure 6: Comparison of LFT in HBsAg Positive Patients with Hepatic Encephalopathy

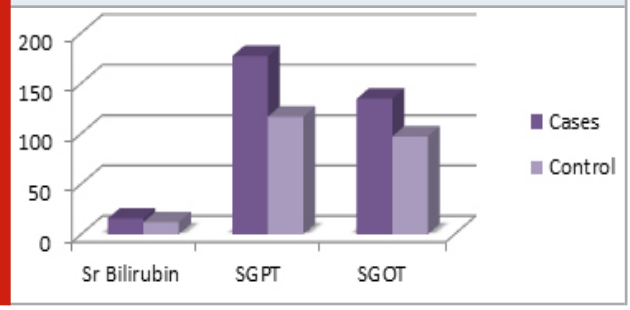


Figure 7: Comparison of LFT in HBsAg Positive Fatal Cases

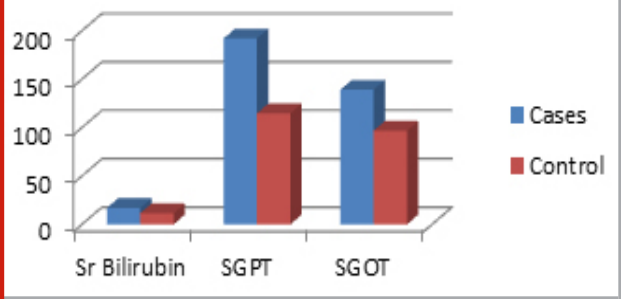


Figure 8

Of the symptoms, yellowness of eyes was present in all cases followed by fever in 77.8% of SS group and 88.6% of AS group and passing high coloured urine in 77.8% of SS group and 85.7% of AS group. History of blood transfusion in past 6 months was present in 33.3% of AS group and 11.9% of AS group. Clinical examination revealed presence of jaundice in all patients of all groups. Pallor was present in all patients of SS group and 91.4% of AS group. Tender hepatomegaly was present in all cases of both the groups (100%). Of the cases that had encephalopathy, 28.6% of AS group were in grade I, 50% of SS group and 28.6% of AS group were in grade II; 14.2% of AS group were in grade III and 50% of SS group and 28.6% of AS group were in grade IV encephalopathy.

2 cases of SS group and 6 of AS group died. Complications included hepatic encephalopathy in all and aspiration pneumonia in 1 (50%) of SS group, probably pulmonary embolism in 1 (16.67%) of AS group and prolonged postpartum haemorrhage in 1 (16.67%) of AS group. Urine examination for both bilirubin and urobilinogen in all the cases of SS group (100%). 88.6% of SS group and 11.4 % of AS group had only presence of bilirubin in urine. Mean values of serum proteins, alkaline phosphatase and cholesterol were within normal range in both the groups. Mean serum bilirubin was 15.49 mg/dl in SS group, 12.48 mg/dl in AS group and 8.86 mg/dl in control group. Mean conjugated serum bilirubin was 12.2 mg /dl in SS group, 9.66 mg/dl in AS group and was 6.38 mg/dl in control group.

Mean serum SGOT was 138.3 IU/L in SS group, 106.69 IU/L in AS group and 98.3 IU/L in control group. Mean serum SGPT was 195.1 IU/L in SS group, 141.66 IU/L in AS group and 122.5 IU/L in control group. When liver function tests were compared in cases and controls with hepatitis, serum bilirubin, SGOT and SGPT were statistically significantly higher in SS group and AS group compared to the control group and in SS group compared to the AS group. Serum bilirubin levels were significantly higher in cases compared to control

group with hepatic encephalopathy and there was no statistically significant difference in them as far as SGOT and SGPT levels are concerned.

Serum bilirubin levels were significantly higher in fatal cases compared to controls of the same group and difference in SGOT and SGPT levels was insignificant statistically. Of 9 patients with hepatic encephalopathy coagulation profile was deranged in 7 cases (77.8%) and it was normal in 1 case (11.11%). Of 44 cases 2 of SS group (22.2%) and 8 of AS group (22.86%) were HBsAg positive.

Thus in present study

- Mean serum bilirubin values in sicklers are higher than non sicklers with hepatitis.
- Patients with mean serum bilirubin level of 14 mg/dl. SGPT of 169.4 IU/L and SGPT of 128.7 IU/L landed up in hepatic encephalopathy.
- Fatal cases had mean bilirubin level of 17.05 mg/dl, SGPT level of 192 IU/L and SGOT of 139 IU/L.
- HBsAg status not only increased the occurrence of hepatic encephalopathy but also increased the mortality in the cases.

Patients of sickle cell disease showed higher HBsAg positivity and this was significant statistically($p < 0.05$). Significantly higher number of sickle cell disease patients went into hepatic encephalopathy compared to the control group ($p < 0.005$). Difference in number of HBsAg positive sicklers who died was more than controls, and it was statistically significant ($p < 0.005$).

HBsAg positive cases had significantly higher serum bilirubin levels compared to controls and difference in SGOT and SGPT levels was insignificant. Parameters of liver function tests in HBsAg positive cases going into hepatic encephalopathy were significantly higher compared to the controls. Parameters of liver function tests in HBsAg positive fatal cases did not show any statistically significant difference ($P > 0.05$). A number of related studies on hepatitis12-16, Sickle cell disease and childhood anaemia were reviewed.

CONCLUSION

Patients of sickle cell disease with jaundice can have viral hepatitis. They have complications like encephalopathy with or without bleeding tendencies. The prognosis is better without encephalopathy. Occurrence of HBsAg in sicklers is higher than non sicklers with viral hepatitis. It increases the complications like encephalopathy or fatality in patients with sickle cell disease as compared to the controls. Following guidelines can be observed to diagnose viral hepatitis and to rule out haemolytic crisis and sickle cell hepatopathy in sickle cell disease patients:

1. History of injections or blood transfusion.
2. Reticulocyte count in normal range.
3. Presence of bilirubin and urobilinogen in urine.
4. Conjugated hyperbilirubinemia.
5. Markedly raised serum transaminases with ratio of SGPT/SGOT exceeding normal limit (0.75 -0.11).
6. Serologic presence of viral markers.

This would help in differentiating the clinically simulating and confusing conditions and would provide help in recognizing these conditions earlier which is essential as the management and prognosis for each of them is quite different. Vaccination of sickle cell disease patients who are at risk against hepatitis B, as early as possible, should prove helpful.

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