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Review article

Viral hepatitis in patients with sickle cell disease

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ABSTRACT

Sickle cell hemoglobinopathy patients are vexed with sickle cell crises crises all through their life. Occurrence of jaundice in these patients is quite common and when present gets ascribed to the sickle cell crisis, sickle cell hepatopathy, intrahepatic cholestasis or cholelithisis. Further, incidence of viral hepatitis is extremely common in these patients. Clinically it is difficult to distinguish this aetiology. We have attempted 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.

Keywords: Viral hepatitis, Sickle Cell Disease, Jaundice, Haemoglobinopathy

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INTRODUCTION

Viral infections, particularly viral hepatitis is common in sicklers. However when sicklers develop jaundice, it can be attributed to superimposed hepatitis or more commonly hemolytic crisis, sickle cell hepatopathy, intrahepatic cholestasis and cholelithiasis. Clinically, it is difficult to differentiate these modalities. There are no precise hematological and biochemical criteria to diagnose and differentiate these mimicking conditions. Although serology and liver biopsy can be helpful, circumstances do not always permit these investigations as facilities for serological investigation for viral markers may not be available or liver biopsy being contraindicated in acute stage of viral hepatitis. In this review, an attempt has been made to diagnose viral hepatitis clinically, biochemically and histopathological in sicklers and comparison made with non-sicklers.

REVIEW OF LITERATURE

Haemoglobinopathies are molecular diseases resulting from the substitution of any single amino acid out of 144 or 146 amino acids of alpha or beta chains respectively of hemoglobin molecules1. Sickle cell disease is the hereditary hemoglobinopathy which results from inheritance of a gene for a structurally abnormal beta globin chain subunit of adult hemoglobin, the Bs chain of HbS.

In one Ghanian family symptoms of sickle cell anemia could be traced to the year 16706. Disorders of hemoglobin synthesis were, for the first time recognized by the scientific community Dr. James B Herrick (1910)2, a cardiologist of Chicago, recorded observations in a 20 year old West Indian student. This opened up a remarkable era of diseases called “Haemoglobinopathies”. Washburn (1911)3, Cook and Mayer (1915) reported subsequent cases. Emmel (1917) described the sickling phenomenon in a father and a son. He noticed that number of sickle cells very much increased when a blood drop was placed under a cover slip, sealed and seen after some time. Mason (1922) described the fourth case and was the first person to name “sickle cell anemia” to this condition. Deoxygenation was shown to be responsible for sickling by Haln and Gillespic in 1927.Neel (1947)4 put forward a hypothesis that heterozygous (AS) present as sickle cell trait and homozygous (SS) manifest as sickle cell anaemia. The percentage of sickle cell hemoglobin is 42-45% in sickle cell trait and more than 90% in sickle cell anemia.

Ingram (1957)5 demonstrated that the only detectable difference between haemoglobin ‘S’ and haemoglobin ‘A’ is that the glutamic acid at the sixth position of beta chain is substituted by

valine encoded by sickle mutation which substitutes thymine for adenine in sixth codon of beta gene (GAG-□GTG).Jensen W. N. (1970)6 demonstrated that when haemoglobin 'S' was deoxygenated a gel like substance was formed, spindle like bodies similar to crystal were visible by phase microscopy and they formed tactoids and sickling of red blood corpuscles took place.

During uterine life and a few months of infancy the presence of foetal haemoglobin protects the individual against the sickling of red blood corpuscles, vascular occlusion and anaemia. After the second month, symptoms are produced due to a decrease in foetal haemoglobin and an absolute increase in haemoglobin 'S'. The important factors in prevention of sickling in vivo, as suggested by Jensen are accelerated blood flow due to anemic state and oxygen dissociation curve towards right. In the regions where blood flow is perhaps slow because of the multiple sinusoidal pools, the infarction seems to be common.

Other important factors which play role are the intracellular concentration of haemoglobin S, state of degree of oxygenation and Deoxygenation of haemoglobin. There are other numerous factors, like stress situations such as trauma, strenuous physical exertion, competitive sports and emotional disturbances.

Diggs (1965)7 defined crisis (Greek-Krisis-turning point) as a short turn or a definite change in the course of the disease with the development of new symptoms and signs. The term sickle cell crisis refers to any new syndrome that develops rapidly in patients with sickle cell disease.

Prevalence and Geographic Distribution

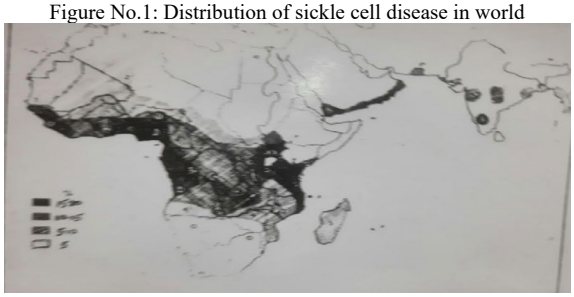
The highest prevalence of haemoglobin S is in tropical Africa and among blacks in countries that participated in the slave trade. It occurs with lower frequency in Mediterranean basin, Saudi Arabia and parts of India.

DNA polymorphism studies showed that beta gene from three independent mutations in the tropical Africa, most common beta chromosome is found in Benin (neighbouring Nigeria) and Central West Africa. A second haplotype is prominent in Senegal and the African West coast. Third haplotype is seen in the Central African Republic (Bantu speaking Africa). The same 3 haplotypes are associated with the beta gene in black Americans & Jamaicans8.

In some parts of Africa as many as 45% of the population has sickle cell disease. In the United States, Latin America and the Caribbean, approximately 8% of the blacks carry the sickle gene. In the United States the expected incidence of sickle cell anaemia at birth is one in 625.

The sickle trait was 1st reported in India by Lehman & Cutbush in 195217 among aboriginal tribes of South India. After that it has been reported in Western India, tribal population of Orissa & Bihar, workers of teagardens in Assam, in the tribal population of Uttar Pradesh and also among Marathi speaking population belonging to Mahar, Telis, Kunbis of Maharashtra in Nagpur. Dunlop & Muzumdar (1952)18 reported presumptive cases of sickle cell anaemia from labourers of teagardens in Assam.

Figure No.1: Distribution of sickle cell disease in world



In central India, work by Solanki& Shukla (1958)9, Subhedar et al (1961)10, Gupta V. L.et al (1981)11 increased the awareness of the disease. The distribution of disease in scheduled caste and tribes in Central India was studied by Solanki et al.

Table Showing Incidence of Sickle Cell Disease (%) In Various Communities in India

Authors	Mahar/ Navabouddha	Kunbi	Teli	Koshti	Gond	Muslim	Miscellaneous
Solanki& Shukla (1958)	22.20	9.4	11.3	-	-	-	-
Waikar (1972)	72.91	8.51	7.4	-	6.35	-	-
Gianchandani (1973)	82.35	5.88	0.00	-	3.95	-	5.88
V. L. Gupta (1977)	68.00	13.33	0.00	1.33	1.33	-	13.55

Table Showing Age and Sex wise Incidence of Sickle Cell Anaemia by Various Authors in India

Authors	No. of Cases	Age Group in Years					Male (%)	Female (%)
		0-10	11-20	21-30	31-40	>40		
Waikar (1972)	42	8	21	14	4	-	44.68	55.32
Gianchandani (1973)	51	11	14	12	6	8	62.74	37.26
V. L. Gupta (1977)	77	-	55	16	3	1	76.00	24.00

Pathophysiology

The varied manifestations of sickle cell disease are attributed to sickling compromising the circulation. The distortion of cells containing Hb-S is a result of Hb polymerization and tactoid formation. HbS differs from HbA in substitution of valine for glutamic acid at 6th position of beta chain which is responsible for profound changes in molecular stability and solubility.

The first visible change observed by phase microscopy revealed loss of red cell flicker movement. Sickling begins with the rim of cells becoming thicker on one side and thinner on opposite side. The mass of haemoglobin appears to flow to one side of cell. The cell becomes oval, elongated and crescent shaped. Under reduced oxygen tension and acidosis, HbS molecules are crystallized and an an isomorphic element is formed by union of two molecules of HbS. Subsequently, parallel alignment of these elements results in bifring

menttactoids forming aggregates. The aggregates then align themselves to form linearly arranged fibers that constitute a Para crystalline gel. This viscous gel decreases the flexibility of erythrocytes and red cell membrane assumes shape that is assumed by intracellular gel, the typical shape is “sickle or holly leaf shape”.

The polymerization process is reversible with re-oxygenation. With repeated sickling and unsickling, red cell membrane gets damaged irreversibly resulting in reduced life span. Occlusion of microvasculature by these cells leads tomicroinfarct and painful crisis. Physiologic determinants of sickling include haemoglobin concentration, temperature, pH, dehydration, stress and type of sickle cell disease, AS or SS.

Clinical features

In individuals with SS genotype, haemoglobin F limits clinically important sickling during foetal and early postnatal life. As the amount of haemoglobin F decline, physiologic conditions for sickling are gradually met with-:Mild haemolytic anaemia is apparent by 12 weeks of age, splenomegaly is 1st noted after six months of age and 1stvaso-occlusive crisis is experienced in between 6-12 months by 50% subjects, before 6 years by vast majority. SS homozygotes have a severe haemolytic anaemia with haematocrit values between 18 and 30%. Haemoglobin S heterozygotes have minimal clinical problems with overall life expectancy and frequency of hospitalization not different from those of comparable group of individuals with Hb A.

A review of literature reveals that the pallor is a constant feature in the sickle cell patients with SS type of haemoglobin. Jaundice was reported in all cases of SS disease by Green et al (1953) and Song (1957) and Subhedar et al (1961).

Clinical features are eitheracuteplus episodic (crises) or chronic and unremitting12.

Sickle cell crisis

It is defined as a sharp turn or definite change in the course of the disease with development of new symptoms and signs.

Vasoocclusive crisis: Hand & foot syndrome, bone & joint crisis, abdominal crisis, CNS crisis and pulmonary crisis

Hematologic crisis: Aplastic crisis, splenic sequestration crisis, haemolytic crisis and megaloblastic crisis

Infectious crisis

As per Felix I.D., Kanotey (1974) 13 there is always a “Mixed crises” and according to severity these can be classified as-Mild or severe

The chronic unremitting features include

a. Growth and development retardation
b. Chronic and progressive destruction of bones and joints
c. Cardiovascular system manifestations like congestive cardiac failure, myocardial haemosiderosis, intermittent hypertension occurring during crisis and mitral valve prolapse.
d. Chronic pulmonary disease due to recurrent pulmonary embolism and infarction leading to pulmonary hypertension.
e. Sickle cell retinopathy
f. Sickle cell nephropathy
g. Sickle cell hepatopathy

Liver Involvement in Sickle Cell Disease

Hyperbilirubinemia usually punctuates the course of sickle cell anaemia, these episodes result from either of the following

- Haemolytic crisis
- Intrahepatic sickling (sickle hepatopathy)
- Choledocholithiasis
- Intercurrent hepatitis

Haemolytic crisis

Sydenstriker (1924) was first to realise that anaemia in sicklers was haemolytic. Sheen and Fleming (1949) demonstrated that sickled cells were usually lysed by mechanical trauma. Increased lipid peroxidation of sickled red cells by the reactive oxygen species derived from activated neutrophils is another possible mechanism for infection associated with haemolytic crisis.

Laboratory investigations show reticulocytosis more than 10% (usual range 17±5%), Urobilinogenuria, absence of bilirubin in urine and unconjugated Hyperbilirubinemia and absence of serological viral markers14. Patients are usually anaemic with haemoglobin averaging about 7.5 gm/dl and a range of 5.5 to 9.5 gm/dl. MCV and MCHC are low.

Blood smears contain variable numbers of sickled forms, cigar shaped cells, ovalocytes and target cells. Morphologic features of accelerated erythropoiesis like polychromatophilia, basophilic stippling, and normoblastosis are prominent. Presence of Howell Jolly bodies and Pappenheimer bodies reflect asplenia. Mean reticulocyte count is 17±5% during haemolytic crisis.

Chronic intravascular hemolysis results in an increase in endogenous carbon monoxide generation and elevated levels of unconjugated bilirubin. In patients with hemolysis the total bilirubin never exceeds 70-85 µmol /l (4-5 mg/dl) unless liver function is impaired.

Serum transaminases show modest elevation and serum alkaline phosphatase is normal. Diagnosis of hepatitis from hepatic sickle cell crisis is difficult. In general in viral hepatitis, pain is less, jaundice deeper and transaminase levels are more prolonged. Liver biopsy and serological viral markers usually help to make the distinction.

Intrahepatic sickling (“Sickle Hepatopathy”)

In about 10%, the crisis selectively affects the liver. It lasts for 2-3 weeks. It is marked by abdominal pain, fever, jaundice, an enlarged tender liver and a rise in serum transaminases.

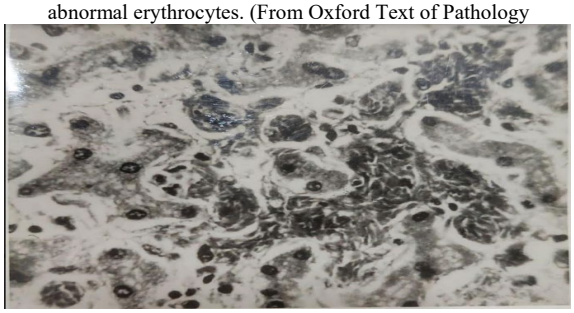
Liver enlargement is present by 1 year of age and persists to a moderate degree throughout life. In children, symptoms are mild

and transient; however, in adults progression to fulminant hepatic failure or diffuse nodular cirrhosis may also occur. Intrahepatic infarcts may be complicated by abscess formation. Jaundice is also deep, due to combination of haemolysis and impaired hepatocellular function. Other possibilities are lesions due to acute vascular spasm and liberation of a hepatotoxic agent during crisis and haemolysis responsible for parenchymal changes[19].

Histology

The histologic consequences of intrahepatic sickling include impaction of hepatic sinusoids with sickled erythrocytes, patchy areas of hepatocellular necrosis, enlargement of Kupffer cells and Kupffer cell erythrophagocytosis. Also there is round cell infiltration around portal spaces and marked atrophy of liver cells with pigmentation. In cirrhotic livers the changes appeared to be a macro nodular or a post necrotic type which is a unique manifestation of fatal sickle cell disease[16].

Figure No. 2: Sickle cell anaemia, liver sinusoids are occluded by clumps of abnormal erythrocytes. (From Oxford Text of Pathology



Hepatic damage is more prominent in sickle cell anaemia than in sickle cell trait. Sicklers with other hepatic pathologies have shown features of intrahepatic sickling as nearly universal findings at liver biopsy, irrespective of the clinical disorder[48]. As per Charlotte et al (1995)[50] in sickle cell disease hepatic lesions are mainly vascular[20].

Choledocholithiasis

Frequency of pigmentary gallstones is high because of sustained increase in heme catabolism. The incidence increases with age, being 12% in age group 2-4 year; 42% in15-18 year's age groups and about 60% in adults21.

Table: Showing Incidence of Gallstones

Author	No of cases	Age (yrs)	No of patients with stones	Percentage
Diggs	18	7	3	16.7
Green et al	18	1-70	5	27.8
Song	31	1-45	2	6.5
Weens	44	1-70	12	27.3

Acute cholecystitis and Choledocholithiasis may simulate hepatic crisis or viral hepatitis. Percutaneous or endoscopic cholangiography is helpful investigations in excluding biliary tract obstruction. Ultrasound is the technique of choice to detect gallstones56 with diagnostic accuracy of 90-95%.

Hepatitis in sickle cell disease

Viral infections in sickle cell disease are common. Viral hepatitis may remain unrecognized jaundice is usually attributed to either haemolytic crisis or liver disease of sickle cell anaemia; hepatitis is very rarely considered in the diagnosis12. Also, cholelithiasis and intrahepatic cholestasis without extrahepatic obstruction confuse the diagnosis22. Therefore, it is very important to have definitive criteria to diagnose and differentiate these conditions from each other and to rule out hepatitis as prognosis of each disease varies.

CLINICAL MANIFESTATIONS

Symptomatology

Duration of prodromal symptoms in patients of sickle cell disease is similar to those without any hemoglobinopathy[62]. Patients of SS group were jaundiced maximally. Fever and anorexia has been found to be more in AS group than in SS group (66.67%) and non sicklers (68%).Vomiting was experienced more by non sicklers. Incidence of acholic stools is slightly less in those with Haemoglobinopathies SS (33.33%) and AS (50%) than those without any hemoglobinopathies (56%).History of blood transfusions in past 6 months was most frequent in SS group. Average duration of hospitalisation was maximum in SS group than non sicklers followed by AS group.

Physical findings

Maximum number of patients in SS group was febrile as compared to AS and non sicklers. Hepatomegaly was more common in nonsicklers, however tender liver was maximally seen in sicklers with SS haemoglobin (83.33%) and less with nonsicklers (72%) and least with those who had AS haemoglobin (60%).Splenomegaly was present in 30% of patients with hepatitis and AS haemoglobin; whereas there was no splenomegaly in non sicklers and in SS group.

Hematological investigations

A significant worsening of anaemia, leucocytosis and reticulocytosis was seen in sicklers of both AS and SS group and no patient with viral hepatitis alone. Reticulocytosis with value of 17± 5% is the feature of haemolytic crisis in sickle cell disease which helps in differentiating it from viral hepatitis. Measurement of prothrombin time is important in these patients and it was maximally deranged patients with SS haemoglobin, followed by AS group and was least prolonged in nonsicklers [62].

Urine analysis

Presence of both bilirubin and urobilinogen in urine during acute phase of hepatitis reflects hepatocellular damage and helps is distinguishing it from haemolytic crisis which is characterised by urobilinogenuriaalone. In viral hepatitis, bilirubin appears in urine before jaundice. Later it disappears. Urobilinogenuria is found in late - preicteric phase. Its reappearance commences the recovery.

BIOCHEMICAL INVESTIGATIONS

Liver function tests

Tests showed that Hyperbilirubinemia was most marked in cases of SS group with total serum bilirubin levels exceeding 20mg/dl62and conjugated bilirubin being 40 to 60% of the total bilirubin.

In cases of haemolytic crisis, 90% of the patients had

unconjugated Hyperbilirubinemia with indirectly positive Vandenberg test11While in hepatitis it was directly positive. Serum alkaline phosphatase level is usually less than three times the upper limit of normal. Serum aminotransferase AST and ALT (also designated as SGOT and SGPT) do not have any significant difference in patients of hepatitis with and without sickle cell disease.

Serological Investigations

As per Yohan Nan et al (1990) sicklers have possible predisposition to hepatic failure when infected with hepatitis A virus23.

Australia antigen or HBs Ag is the most widely studied among different viral markers of hepatitis.

Table Showing Incidence of HBsAg Obtained By Different Study Groups

Study Group	% Incident of HBsAg	
	Sickle Cell Disease Case	Controls
V. L. Gupta et al, 1981	13.6	0.0
Adani et al, 1982	-	-
Group 1	15.38	0.98
Group 2	14.63	2.04
Omata et al, 1986	44.44	-
El-Hazmi et al, 1989	9.4-27.5	5.8 -21.3
Abiodun et al, 1989	39.2	19.3
Al-Fawaz et al, 1993	14.3	20.1

Significantly higher incidence of HBsAg positivity has been found in patients of sickle cell disease by majority[24].

Exposure to HCV infection is higher among those with sickle cell anaemia (18.2%) than the control group (0.8%). Chances of detecting anti-HCV were higher in those sicklers who were transfused more than 10 units of blood products, as compared to those who received less than 10 units. In another series, highest HDV-Ab prevalence (62.5%) was obtained from sickle cell children[25].

Therefore early vaccination of patients of sickle cell disease against hepatitis is essential as also screening of all donated blood for HBsAg, by the most sensitive techniques.

Immunogenicity of hepatitis B vaccine in sickle cell disease patients undergoing long term transfusion therapy is confirmed to avoid the risk of potentially severe or chronic hepatitis[26].

Liver Biopsy

Essential lesion in viral hepatitis is an acute inflammation of the entire liver. Hepatic cell necrosis with leucocytic and histiocytic reaction and infiltration, polymorphs and eosinophilis, Zone 3 may show acidophil bodies, ballooning pleomorphism and cholestatis may be found. Reticulin framework is usually well preserved. During recovery reticuloendothelial activity increased throughout, apparently a ‘scavenger’ phenomenon.

Features of hepatopathy of sickle cell disease include active and healed areas of necrosis, vascular obstruction by impacted sickle cells or by kupffer cells swollen with phagocytosed erythrocytes following intra hepatic sickling. Classic findings are of intrasinusoidalsickling, kupffer cell erythrophagocytosis and ischaemic necrosis. These changes have been reported largely on autopsy specimen[27].

DISCUSSION

Maximum numbers of patients were in the age group 11-20 years with males outnumbering females. Of the symptoms, yellowness of eyes was present in all cases followed by fever and passing high coloured urine. History of blood transfusion in past 6 months was more in SS group sicklers. Clinical examination revealed presence of jaundice in all patients of all groups. Tender hepatomegaly was present in all cases of both the groups (100%).

Urine examination for both bilirubin and urobilinogen is positive in sicklers and only shows presence of only bilirubin in non-sicklers. Mean serum bilirubin levels are high in sicklers more in SS group. Serum transaminases show modest elevation and serum alkaline phosphatase is normal. Diagnosis of hepatitis from hepatic sickle cell crisis is difficult. In general in viral hepatitis, pain is less, jaundice deeper and transaminase levels are more prolonged. Liver biopsy and serological viral markers usually help to make the distinction.

CONCLUSION

Patients of sickle cell disease with jaundice can have viral hepatitis. 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 recommendations can be observed to diagnose viral hepatitis and to rule out haemolytic crisis and sickle cell hepatopathy in sickle cell hemoglobinopathy patients: Patients history of injections or blood transfusion, recticulocyte count in normal range, presence of bilirubin and urobilinogen in urine, presence of conjugated hyperbilirubinemia, markedly raised serum transaminases and serological 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.

REFERENCES

1. Mehta BC, 1990. Hemolytic anemia API Text Book of Medicine 4, 945.
2. Herick JB, 1910. Peculiar elongated and sickle shaped red blood cells Arch of Int Med 6: 517-521.
3. Washburn RE, 1911. Peculiar and sickle shaped red blood corpuscles in case of severanemia. Virginia Med Semi Monthly 15: 490.
4. Nell JV, 1947.The inheritance of sickle cell anemia, Science 110: 64.
5. Ingram VM, 1957. Gene mutation in human haemoglobin. The chemical difference between normal and sickle haemoglobin, Nature (London) 180: 326 -327.
6. Jensen WN, Lessin LS, 1970. Membrane alterations in haemoglobinopathies, Semin Haemol 7: 409 -426.

7. Diggs LW: Sickle Cell Crises AM J clinPatho44 : 1, 1965
8. Antonarakis SE, 1984. Origin of the Bs gene in blacks: The contribution of the recurrent mutation or gene conversion pr both, ProcNatlAcadSci USA 81; 853.
9. Shukla RN, Solanki BR, 1958. Study of sickle cell anemia in central India Lancet 1: 297.
10. Subhedar BJ, Choubey BS, 1961. Sickle cell anemia in adolscents and adults, JAPI 9: 419.
11. Gupta VL, Dubey GK, Kelkar SS, 1981. Clinical study of sickle cell crisis Indian Medical Gaz CXV 5: 158 -161.
12. Green TW Conley CL, Berthorng M, 1953. The liver in sickle cell anemia, John Hopkins Med J: 92: 99.
13. Felix ID, Konotey A, 1974. The sickle cell disease, Arch Int med 133: 64.
14. Lee RG, 1993. The haemolytic disorders: General considerations, Wintrobe's clinical Hematology 1 (9): 956.
15. Bogoch A, Casselmann WGB, Morgolies MP, Bockus HL, 1948. Liver disease in sickle cell anemia, a correlation of clinical biochemical, histologic and histochemical observations Am J Med Sci 216: 11.
16. Song YS, 1957. Hepatic Lesions in sickle cell anemia, Am J Path 33: 331.
17. Lehman, Cutbush, 1952. Report of Sickle cell anemia from South India BMJ :2.
18. Dunlop KJ, Mumumdar UK, 1952. The occurenceof sickle cell anemia among group of ten garden workers in Assam, Ind Med Gaz 87: 387.
19. Lukens JN, 1993. Hemoglobinopathies S, C, D, E, O and associated diseases. 1 (9): 1074.
20. Charlotte F, Bachil D, Nenert M, Mavier P, Galacteros F, Dhumeaux D, Zafrani ES, 1995. Vascular lessions of the liver in sickle cell disease, a clinicopathological study in 26 living patients, Arch pathol lab Med (US) 119 (1): 46-52.
21. Schubert TT, 1986. Hepatobiliary system in sickle cell disease, Gastroenterology (US) 90 (6): 2013-21.
22. Weens HS, 1988. Cholelithiasis in sickle cell anemia, Ann Int med 22: 182.
23. Yohannan MD, Arif M, Ramia S, 1990. Aetiology of icteric hepatitis and fulminant hepatic failure in children and possible predisition to hepatic failure by sickle cell disease, Acta Pediate Scand (Seden) 79 (2) 201-5.
24. Abiodum PO, Fatunde OJ, Flach KH, Buck T, 1989. Increased incidence of hepatitis B markers in children with sickle cell anemia, Blut (Germany West) 58 (3): 147-50.
25. De-Vault KR, Friedman KLS, Westerberg S, Martin P, Hosein b, Ballas SK, 1994. Hepatitis C in sickle cell anemia, J ClinGastroentrol (US) 18 (3): 206-9.
26. Sarnaik SA, Merline JR, Bond S, 1988. Immunogenicity of hepatitis B vaccine in children with sickle cell anemia J of Pediatr (US) 122 : 429-38.
27. Conner EB, 1968. Sickle cell disease and viral hepatitis, Ann Int Med 69: 517.

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