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Research Article

SICKLE CELL HEMOGLOBINOPATHIES AND MALARIA INFECTION: AN EXPERIENCE IN TERTIARY CARE LEVEL REFERRAL HOSPITAL, AHMEDABAD, GUJARAT, INDIA

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A B S T R A C T

Introduction: Malaria is major public health threat in India. . Hb S carriers are protected from malaria infection. Despite this advantage, individuals with sickle cell disease exhibit significant morbidity and mortality due to malaria.(1)

Aims and Objective: This study aims to highlight malarial infection in sickle cell hemoglopathies and to emphasis upon the need for detailed research to find out association between sickle cell hemoglobinopathies and severity of malaria. In this study our aim was to study the occurance of malaria and its incidence, severity, clinical features,complications and role of spleen in sickle cell hemoglobinopathies.To know the effect of malaria infection on the maternal and child health.

Material and Method: This was a retrospective analysis of the data collected from children age 1 to 18 years and adults admitted to civil Hospital during July 2011 to july 2018. A total of 10 samples received in hematology, department of pathology ,B.J.Medical College,Ahmedabad were studied, relevant information regarding age,sex,accompanying clinical symptoms, complications has been documented radiological and other biochemical test parameters were also recorded. Various parameters were recorded from automated cell counter machine. Peripheral smear was prepared.Rapid Diagnostic Test test,Sickling test and High Performance Liquid Chromatography test was done.

Result: Out of 10(100%) cases,7(70%) males including pediatric males(3) and 3(30%) female patient including (1) pediatric female patient with sickle cell hemognopathies were positive for malarial infection. Amongst 3 females 1 patient was presented with 8 months of pregnancy with sickle cell disease and p.vivax infection. All the patients had sickle cell hemognopathies and had positive sickling test. Ratio of male:female was 2.3:1. Affected patients showed anemia with complications like high grade fever, sickle painful crisis, jaundice followed by acute respiratory distress.

Conclusion: Malaria and sickle cell anemia are still major public health problems. The need for detailed research to find out association between sickle cell hemoglobinopathies and severity of malaria. Males are more commonly affected than females. Poor outcome of malaria in pregnant woman and children with sickle cell disease. In malaria endemic countries patient with SCA and particularly children, be protected from malaria by appropriate prophylaxis like vaccine. Systematic screening for malaria and sickle cell anemia should be integrated into maternal and child health services for conflict affected populations in highly endemic tribal areas especially during rainy season to reduce maternal and fetal complications.

INTRODUCTION

Sickle cell disease is caused by a variant of the β-globin gene called sickle hemoglobin (Hb S). Inherited autosomal recessively, either two copies of Hb S or one copy of Hb S plus another β-globin variant (such as Hb C) are required for disease expression. Hb S carriers are protected from malaria infection. Despite this advantage, individuals with sickle cell disease exhibit significant morbidity and mortality due to malaria. (1) Malaria is major public health threat in India(2).

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Malaria caused by the intracellular parasite plasmodium,affect more than 160 million people worldwide and kills more than 500,000 people each year(3) .Hemoglobin S is particularly frequent in Africa,Middle East and Central and Southern India.Hbs has a high prevalence in those part of world where malaria is common. This relationship is explained by the theory of balanced polymorphism.Theory of balanced polymorphism proposes that selective advantages gained by sickle cell heterozygote (i.e protection against severe falciparum malaria) is balanced by disadvantage of homozygous state (i.e. sickle cell anaemia) (4).We present a retrospective study of 10 patients of sickle cell

hemoglobinopathies with malaria admitted at Civil hospital, B.J.Medical college, Ahmedabad, Gujarat, a state on western coast of India. All were positive for malaria. All the patients were treated with antimalarial and transfusion therapy when needed with symptomatic treatment. Primaquine was given to prevent recurrence.

MATERIAL AND METHOD

This was a retrospective analysis of the data collected from children (age 1 to 18 years) and adults admitted to civil Hospital during July 2011 to july 2018. A total of 10 samples received in hematology, department of pathology ,B.J.Medical College,Ahmedabad were studied, relevant information regarding age,sex,accompanying clinical symptoms, complications has been documented radiological and other biochemical test parameters were also recorded. Various parameters were recorded from automated cell counter machine.Peripheral smear was prepared. RDT test, Sickling test and HPLC test was done. All the parameters were analyzed and compared.

RESULT

Total 10 cases,7 males and 3 female patient with sickle cell hemognopathies were positive for malarial infection. All cases had sickle cell hemoglobinopathies and had positive sickling test after 1 or 24 hour. All patients had positive findings in HPLC analysis for sickle cell trait or sickle cell disease.
Ratio of male:female was 2.3:1.

Table 1 Sex specific incidence of sickle cell hemoglobinopathies. In our result male preponderance was seen.

	Male	Incidence(%)
Male	7	70
Female	3	30
Total	10	100

Table 2 Patients (Total 4 no.) of sickle cell anemia affected by malaria. In our result high incidence of p.vivax with sickle cell anemia was seen.

Malarial species	No.of pediatric patients	Percentage (%)
p.vivax	9	90
p.falciparum	1	10
Total	10	100

Table 3 Sickle cell hemoglobinopathies incidence in all cases. In our result high incidence of sickle cell disease was seen

Sicklecell hemoglobinopathy	No.of cases	Percentage(%)
Sickle cell trait (HbAS)	3	30
Sickle cell disease (HbSS)	7	70
Total	10	100

Table 4 Age specific incidence of sickle cell hemoglobinopathies.

Age in years	No.	Percentage (%)
5-14	3	30
15-24	5	50
25-34	1	10
35-44	1	10
45-54	0	0
>55	0	0
Total	10	100

In our result out of 10 patients 5(50%)patient was from the age group of 15-24 years, 4(40%)patient was from the age group of 1-18 years. Age specific incidence was higher in younger age group followed by children.

Table-5 Clinical conditions in patients of sickle cell anemia affected by malaria. In our results 10(100%) patients showed anemia with complications like high grade fever in 10(100%), sickle painful crisis in 9(90%), jaundice in 9(90%), acute respiratory distress in 7(70%), 3 (30%) patients showed autosplenectomy, 3 (30%) patients showed spenomegaly, 3 (30%) patients showed hepatomegaly,intra uterine growth reduction (IUGR) of fetus was seen in 1(1%) pregnant female and 1(10%) patient showed splenic infarct.

Clinical complications	Total No.	Percentage (%)
High grade fever	10	100
Anemia	10	100
Painful crisis	9	90
Jaundice	9	90
Acute respiratory distress	7	70
Hepatomegaly	3	30
Splenomegaly	3	30
Autosplenectomy	3	30
Splenic Infarct	1	10
IUGR	1	10

Vasoocclusive episodes results in progressive infarction, fibrosis and contraction of the spleen-so called autosplenectomy[16] . Of special note is the fact that normally the spleen plays an important role in filtering and removing parasitized red cells: but patients with SCA regularly have an impaired splenic function: Often to the extent of functional asplenia, and sometimes the functional asplenia evolves to anatomical atrophy of the spleen from multiple infarcts (so-called auto-splenectomy)[18].

Pregnant women with SCD are known to be at high risk of obstetrical complications and perinatal mortality as well as sickle-related complications. The maternal and fetal complications include prepartum and postpartum painful crises, pulmonary complications, anemia, preeclampsia, eclampsia, premature delivery with associated risks, and intrauterine growth restriction (IUGR)[14] .

Table 6 Laboratory parameters in sickle cell anemia affected by malaria.

	Total No	Percentage(%)
Hemoglobin (g/dL)		
<7	4	40
7–9.9	5	50
≥10	1	10
Mean corpuscular Volume(MCV)(fl)		
<80(Microcytic)	5	50
80-100(Normocytic)	5	50
>100(Macrocytic)	0	0
Platelet count(10^3/ul)		
<50(Severe)	1	10
50-150(Mild)	9	90
>50(Normal)	0	0
RBC ($3.8\text{-}4.8\times10^6$/cmm)	2	20
$<3.8\times10^6$/cmm	8	80
WBC ($4\text{-}11\times10^3$/cmm)	1	10
$<4\times10^3$/cmm	1	10
$>4\times10^3$/cmm	8	80

MCH(27-31 pg)	2	20
<27pg	7	70
>31pg	1	10
MCHC(33-37)	4	40
<33	6	60
>37	0	0
HCT(36-46%)	1	10
<36	9	90
>46	0	0
Normoblasts(<10%)	3	30
10-30%	4	40
30-50%	1	10
Parasitemia in blood film(grading system)		
+	8	80
++	1	10
+++	1	10
++++	0	0
S.Bilirubin(Total)		
0.2-1.0mg/dl	0	0
>1.0mg/dl	9	90

In our findings 4(40%) patients had Hb <7g/dl,5(50%), patients had Hb >7g/dl. RBC count was significantly low in 8(80%) patients, MCH was significantly low in 7(70%), S.Bilirubin(Total) level was >1.0mg/dl in 9(90%) patients. WBC count was significantly high in 8(80%) patients which showed that Infection was a major cause of morbidity in patients with sickle cell disease that required hospitalization. Anemia was the major cause for the transfusion therapy in many of these patients.

Sickle cell hemoglobinopathies in pediatric age group(1-18 years)

In our study 4 pediatric patients(1-18years) had sickle cell disease. Among them 3 patients (75%) had p.vivax infection and 1(25%) patient had p.falciparum infection proven by smear as well as RDT.

Table 7 Pediatric patients (Total 4 no.) of sickle cell anemia affected by malaria.

Malarial species	No.of pediatric patients	Percentage(%)
p.vivax	3	75
p.falciparum	1	25
Total	4	100

In our result 3(75%) patients had p.vivax and 1(25%) patients had p.falciparum malaria.our study is comparable with Bhupeshvari at all who had total 44 patients with SCD either p. vivax(26 i.e. 58%), or p.falciparum (18 i.e.42%) malaria proven by smear as well as RDT[17].

Table 8 Incidence of Sickle cell hemoglobinopathy in pediatric patients (total 4 no.).

Sicklecell hemoglobinopathy	No.of cases	Percentage(%)
Sickle cell trait (HbAS)	1	25
Sickle cell anemia (HbSS)	3	75
Total	4	100

Table 9 clinical conditions in pediatric patients (Total 4 no.) of sickle cell anemia affected by malaria.

Clinical complications	Total No.	Percentage (%)
High grade fever	4	100
Anemia	4	100
Painful crisis	4	100
Jaundice	4	100
Acute respiratory distress	4	100
Splenomegaly	3	75
Hepatomegaly	1	25
Autosplenectomy	1	25
Splenic Infarct	0	0

In our result 2 patient(50%) had complicated malaria clinically. All the pediatric patients was in sickle cell crisis (100%), high grade fever(100%),Acute chest pain(100%), jaundice (100%). our study is comparable with study of Bhupeshvari at all who had all studied children were in some form of crisis like: all patients had bodyache and limb pain as chief complaints with high grade fever, in these 44 patients 48%(22) had complicated malaria clinically and/or by laboratory parameters.[17]

Table 10 Laboratory parameters in pediatric patients (Total 4 no.)of sickle cell anemia affected by malaria.

	Total No	Percentage(%)
Hemoglobin (g/dL)		
<7	3	75
7–9.9	1	25
≥10	0	0
Mean corpuscular Volume(MCV)(fl)		
<80(Microcytic)	3	75
80-100(Normocytic)	1	25
>100(Macrocytic)	0	0
Platelet count(10^3/ul)		
<50(Severe)	1	25
50-150(Mild)	3	75
>50(Normal)	0	0
RBC ($3.8\text{-}4.8\times10^6$/cmm)	2	50
$<3.8\times10^6$/cmm	2	50
WBC ($4\text{-}11\times10^3$/cmm)	1	25
$<4\times10^3$/cmm	1	25
$>4\times10^3$/cmm	2	50
MCH(27-31 pg)	1	25
<27pg	3	75
>31pg	0	0
MCHC(33-37)	1	25
<33	3	75
>37	0	0
HCT(36-46%)	1	25
<36	3	75
>46	0	0
Normoblasts(<10%)	1	25
10-30%	2	50
30-50%	0	0
S.Bilirubin(Total)		
0.2-1.0mg/dl	0	0
>1.0mg/dl	4	100

Table 11 HPLC interpretation of sickle cell anemia in pediatric age group

No.	HbA%	HbF%	HbS%	HbA2%	Sickle cell hemoglobinopathy
1	3.5	8.0	84.0	4.5	SCD
2	8.8	40.7	45.5	5.0	Sbeta thal trait
3	2.5	8.5	85.5	3.5	SCD
4	3.0	9.5	83.5	4.0	SCD

DISCUSSION

Sickle haemoglobin (Hbs) is the result of substitution of valine for the normally occurring glutamic acid residue at the 6th position of the beta-chain and so, is designated as: Hb β 6(A3) Glu-Val.This substitution creates a sticky hydrophobic contact point which is on the outer surface of the molecule. These

sticky spots cause deoxygenated haemoglobin (Hb) molecules to associated abnormally with each other to form the long fibrous aggregates responsible for sickling of the red cells. Deoxygenated Hbs then polymerizes and the polymers are in the form of long needle-like structures that distort the cell. This reduces the flexibility of the red cell making it more mechanically fragile and as it passes through capillaries, the cell sickles, decreasing its life span and leading to anaemia[8].Hemoglobin S (Hbs) reportedly confers protection against uncomplicated *p.falciparum* malaria in sickle cell trait[5] . Spleen also plays a mechanical role in phagocytosis of parasitized red blood cells [6] In contrast to *p. falciparum* malaria, no studies investigated the protective effect of Hb S against *p. vivax* malaria [7] there were earlier reported in a case report by Muley et al.they emphasized that malaria is not so rare in current scenario as thought earlier.

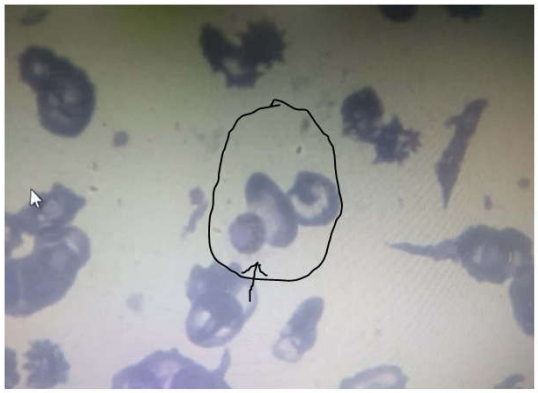

Image 1 Peripheral smear (stained with Gimsa stain) showing Sickled cells with p.vivax trophozoites(100x)

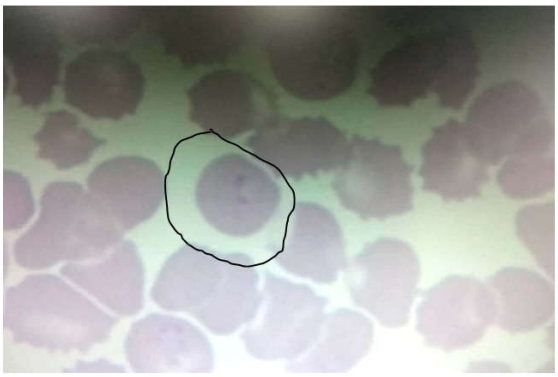

Image 2 Peripheral smear (stained with Gimsa stain) showing Sickled cells with p.vivax ring(100x).

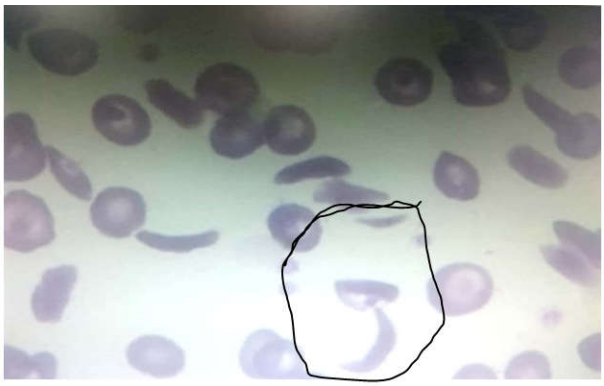

Image 3 Sickle shaped red blood cells in peripheral smear(Stained with Gimsa stain) (100x).

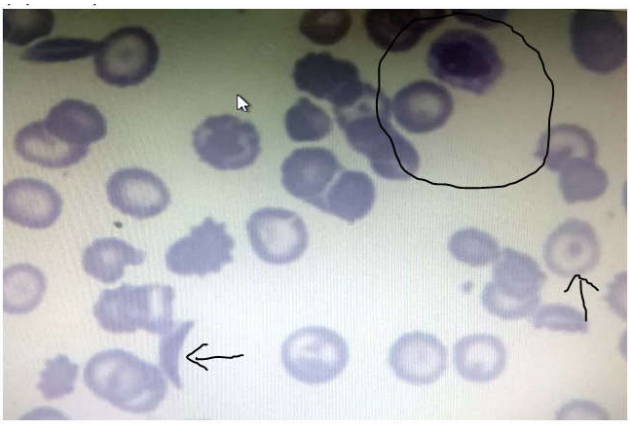

Image 4 Sickle shaped red blood cells in peripheral smear with normoblast and target cell. (Stained with Gimsa stain) (100x).

Image 5 Positive sickling test after 2 hour done by using 2% sodium metabisulphate(20x).

Severe complications and heavy parasitaemia is found in the patient with sickle cell anemia in contrast to current thought that sickle gene protect against heavy parasitemia[9].On the other hand ,patients who are homozygous for the sickle cell gene are therefore suffer from sickle cell anemia are highly susceptible to the lethal effects of malaria. The simplest explanation of this fact is that malaria makes the anemia of SCA more severe.

In addition,in SCA there is often hyposplenism,which reduces clearance of parasites.From the point of view of public health it is important that in malaria endemic countries patient with SCA and particularly children, be protected from malaria by appropriate prophylaxis[10]. Severe painful crises are nearly the pathognomonic symptoms of the SCDs, and they are precipitated by infection, operation, depression, or injuries. Although the painful crises may not be thought as a directly life threatening [15],The *var* gene products, a group of highly expressed surface antigens, bind in Fab and Fe fragments of human immunoglobulins in a fashion similar to protein A to *Staphylococcus aureus,* which may offer some protection to the parasite from the human immune system. Despite the poor prospects for a fully protective vaccine, it may be possible to develop a vaccine that would reduce the severity of malaria for children living in endemic areas [11] .Furthermore, individuals with HbAS tend to survive better than individuals with HbSS as they are not exposed to the same severity of risks yet still receive protection form malaria (Ashley *et al*., 2000)[12] .

The fact that *p. falciparum* is the predominant species in tribal areas may add substantial risk to pregnant women. *p. vivax* is theoretically less dangerous for this group of patients because it does not cytoadhere in the placenta, yet it may also cause low birth weight and maternal anemia [13].

CONCLUSION

Malaria and sickle cell anaemia are still major challenges to infectious disease medicine and to haematology respectively, and both are also major public health problems.

We concluded that, in our patients,Hb S did not confer any protective role in malarial infection in sickle cell hemognopathies. Need for detailed research to find out association between sickle cell hemoglobinopathes and severity of malaria. Males are more commonly affected than females. Poor outcome of malaria in pregnant woman and children with sickle cell disease. In malaria endemic countries patient with SCA and particularly children,should be protected from malaria by appropriate prophylaxis. Despite the poor prospects for a fully protective vaccine, it may be possible to develop a vaccine that would reduce the severity of malaria for children living in endemic areas. Systematic screening for malaria and sickle cell anemia should be integrated into maternal and child health services for conflict affected populations in highly endemic tribal areas specially during rainy season to reduce maternal and fetal complications.

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