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Original Research Article

Clinico-Etiological Profile of Bacterial Infections in Children with Sickle Cell Anemia

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ABSTRACT

Objective: In sickle cell anemia, fever is a common presenting symptom and is frequently the first indication of serious and life-threatening bacterial infection. There is a lack of study in central India, which has high prevalence of sickle cell anemia, showing causes of fever in them. So we studied various causes of fever and bacteremia in patients with sickle cell anemia and to provide data which will help to reduce morbidity and mortality by early intervention in patients of sickle cell disease.
Methods: This was a cross sectional observational study which contains 163 patients of sickle cell anemia (SS) presenting with fever in the age group between 6 months to 12 years. All cases were investigated with CBC, blood culture, urine examination, chest X-ray and other investigations as indicated.
Result: Amongst 163 cases enrolled, most common system to involve was respiratory system (44%), followed by gastrointestinal system (24%) and genitourinary system (8%). In these cases pneumonia was the most common clinical diagnosis (23%). Streptococcus pneumoniae along with the, *Klebsiella pneumoniae* and *E. coli* were found to be the common pathogens causing a febrile illness in sickle cell anaemia. Gram negative bacteria were responsible for 56. 25% of bacteremia.
Conclusion: We concluded that, the respiratory system was the most common one to get involved in patients of sickle cell anaemia presenting with fever and pneumonia was the most common diagnosis in it. Streptococcal pneumoniae along with *Klebsiella pneumoniae* and *E. coli* were found to be the common pathogens causing a febrile illness and bacteremia in patients of sickle cell anemia.

Key Words: Sickle cell anemia, Fever, Bacteremia.

INTRODUCTION

Sickle cell disease is an inherited hemoglobinopathy resulting from the inheritance of HbS gene either homozygously (also known as sickle cell anemia), or as a compound heterozygote with other interacting abnormal hemoglobin gene. [1] Sickle cell disease (SCD) is prevalent in central Africa, Middle East and Saudi Arabia, Mediterranean and in parts of India. [1] SCD has a high prevalence in India and poses considerable health burden. [2,3]

Fever is a common presenting symptom in many manifestations of sickle cell anemia. In particular, fever is frequently the first indication of serious and life-threatening bacterial infection amongst them. Infection is a significant contributor to morbidity and mortality in sickle cell anemia. [4,5]

Since fever is the most consistent finding in SCD with severe bacterial infections, early intervention in febrile children with sickle cell disease may reduce rates of complication and death. [4,5]

There is a lack of study in central India showing causes of fever in sickle cell disease. So we felt the need to study various

infectious causes of fever in patients with sickle cell anemia presenting with fever and to provide data which will help to reduce rates of morbidity and mortality by early intervention in patients of sickle cell disease.

MATERIALS & METHODS

This was a cross sectional observational study. We enrolled 163 patientsof sickle cell anaemia(SS pattern) in the age group of 6 months -12 years admitted with fever ≥100 ^{0}F inpediatric wards of tertiary care hospital in central India. We enrolled patients of sickle cell anemia (SS pattern). It was done from December 2012 to September 2014.

Considering the prevalence of 31% of acute febrile illness in sickle cell anemia from previous studies (R), absolute allowable error of 7%, and normal deviate of 1.96% the minimum required sample size (n) was 163. The study was approved by the institutional ethics committee and a written informed consent was obtained from parents of all study participants.

At the time of enrollment detailed history, physical examination and investigations were done like complete blood count(including the hemoglobin estimation, total and differential leukocyte counts) peripheral smear, blood culture, retic count and other investigations were done as per indicated.

RESULT

In this study, amongst 163 patients enrolled, respiratory system was the most commonly involved with 72(44.17%) cases, followed by 39(23.92%) cases of gastrointestinal system, then 13(7.97%) cases of genitourinary system and 3(1.84%) cases of central nervous system.

Table no 1 shows, frequency of various clinical diagnosis found in patients of sickle cell anemia with fever in which the respiratory system was divided into lower respiratory tract infection (LRTI) and upper respiratory tract infection(URTI), in this LRTI was further divided into lobar pneumonia which appeared in 30 patients, and bronchopneumonia which appeared in 7 patients. URTI was also further divided into pharyngitis which appeared in 23 patients and 6 patients were presented with tonsillitis. Hyperreactive airway disease (HRAD)/asthma was noticed in 4 patients. 2 patients found to have pulmonary tuberculosis and were receiving AKT.

Hepatitis antibody was positive in 4 patients and 16 patients had enteric fever with positive widal, out of this salmonella was isolated from 3 patients. 4 of malaria out of which 3 had plasmodium vivax and 1 was positive for plasmodium falciparum.

TABLE NO. 1: Distribution of Different Types of Clinical Diagnosis in Sickle Cell Anemia with Fever

CLINICAL DIAGNOSIS.	NO. OF CASES
LRTI	37 (22.63%)
- Lobar pneumonia	30 (18.4%)
- Bronchopneumonia	7 (4.2%)
URTI	29 (17.79%)
- Pharyngitis	23 (14.11%)
-Tonsillitis	6 (3.68%)
HRAD	4 (2.4%)
Pulmonary tuberculosis	2 (1.2%)
Enteric Fever	16 (9.8%)
Acute Gastroenteritis	10(6.13%)
Splenic abscess	7(4.2%)
Hepatitis	4(2.4%)
- Hepatitis A	4(2.4%)
- Hepatitis B	0
Peritonitis	2(1.2%)
Osteomyelitis	20(12.2%)
UTI	13(7.9%)
Dengue fever	7(4.2%)
Malaria	4(2.4%)
- Plasmodium Vivax	3(1.8%)
- Plasmodium Falciparum	1(0.6%)
HIV	3(1.8%)
Meningitis	2(1.2%)
Stroke	1(0.6%)
Mumps	1(0.6%)
Septicemia	1(0.6%)
Total	163 (100%)

Clinically and radiologically diagnosed osteomyelitis was found in 20 patients, in which salmonella typhi was isolated from 2 patients in which 1 had concomitant enteric fever, and staphylococcus was isolated from 2 patients.

Urinary tract infection was found in 13 patients with clinical feature and urine microscopy, in 2 of these, E.coli was isolated and in 1 klebsiella was isolated from urine culture.

Acute gastroenteritis was present in 10 patients with positive stool microscopy

while 7 patients had splenic abscess. 7 patients had dengue fever who were diagnosed clinically and serologically. 3 patients were reactive for HIV. 2 patients had peritonitis out of these1 died in whom streptococcus pneumoniae was isolated from peritoneal fluid.

Meningitis was positive in 2 patients in which CSF study shown increased WBC but no organism was isolated, and one patient had stroke. One patient had clinically diagnosed mumps and one had septicemia in which E.coli was isolated in blood culture.

Table no 2 shows the distribution of bacterial pathogens isolated from body fluids, in which amongst 163 enrolled patient's blood culture was positive in 9.8% cases, urine culture was positive in 1.8% cases and peritoneal fluid culture was positive in 0.6% cases. We found streptococcus pneumoniae in 3 patients of bacteremia, while it was also isolated from 1 peritoneal fluid culture. *Klebsiella pneumoniae* was positive in 3 patients of bacteremia and in 1 urine culture. *E. coli* was found in 2 patients of bacteremia and also isolated in 2 urine culture. *Salmonella typhi* was found in 3 patients of bacteremia. *Staphylococcus aureus* and Coagulase negative staphylococcus both of each was found in 2-2 patients of bacteremia. *Pseudomonas aeruginosa* was found in 1 patient of bacteremia. Cultures of CSF were sterile in all the 3 patients.

TABLE NO. 2: Distribution of Different Bacterial Pathogens

ORGANISM	BLOOD	URINE	PERITONEAL FLUID	CSF	TOTAL
Streptococcus pneumoniae	3	0	1	0	4(2.4%)
Klebsiellapneumoniae	3	1	0	0	4(2.4%)
Salmonella typhi	3	0	0	0	3(1.8%)
E.coli	2	2	0	0	4(2.4%)
Staph aurease	2	0	0	0	2(1.2%)
Coagulase negative staphylococcus	2	0	0	0	2(1.2%)
PsedomonasAeurogisa	1	0	0	0	1(0.6%)
Total	16(9.81%)	3(1.8%)	1 (0.6%)	0	20(12.26%)

DISCUSSION

Table No. 3:Distribution of Different types of clinical Diagnosis

Clinical diagnosis	Present study (e-163)	Wierenga KJJ et al (e-165) [6]	Dipty Jain et al (e-56) [4]	Akinyanju O Johnson AO (e-60) [7]	McIntos et al (e-182) [8]
LRTI	37	-	-	35%	14
-Lobar Pneumonia	30	-	-	-	-
-Broncopenumonia	7	-	-	-	-
URTI	29	27	-	17%	23
-Pharyngitis	23		-	-	-
-Tonsillitis	6	28	-	-	-
HRAD	4	2	-	-	-
Pulmonary Tuberculosis	2		-	-	-
Enteric fever	60	1	-	-	-
Acute Gastroenteritis	10	-	-	-	-
Splenic abscess	7	-	'*'	-	-
Hepatitis	4	-	-	-	-
-Hepatitis A	4	-	-	-	-
-Hepatitis B	0	-	-	-	-
Peritonitis	2	-	-	-	-
Osteomyelitis	20	1	21%	8%	-
UTI	13	4	'*'	-	2
Dengue fever	7	1	-	-	-
Malaria	4	-	-	-	-
Plasmodium Vivax	3	-	-	-	-
Plasmodium Falciparum	1	-	-	-	-
HIV	3	-	-	-	-
Meningitis	2	1	-	-	-
Stroke	1	-	0.6%	-	-
Mumps	1	1	-	-	-
Septicemia	1	-	'*'	-	6

(*)- Number not specified. e= Number of episodes.

In our study, out of 163 patients of sickle cell anaemia with fever, many patients had localising signs of infections and respiratory system was most commonly involved with 72(44.17%) cases which include 30 cases of lobar pneumonia, 23 were of pharyngitis, 7 were of bronchopneumonia, 6 were of tonsillitis, 4 were of HRAD and 2 were of pulmonary tuberculosis, followed by 39(23.92%) cases of gastrointestinal system, then 13(7.97%) cases of genitourinary system and 3(1.84%) cases of central nervous system(CNS). Akinyanju O, Johnson AO,1987 [7] found, the commonest infections were pneumonia (35%), bacteraemia (32%), tonsillitis/ pharyngitis (17%) and osteomyelitis (8%). [9]

Wierenga KJJ et al 2001 [6] divided diagnosis of fever in sickle cell anaemia in five groups of systemic bacterial, local bacterial, presumed viral, ACS and painful crisis and had Acute tonsillitis in 28 cases, Urinary tract infection in 4, Acute bacterial conjunctivitis in 1, Proven bacterial enteritis in 1, Upper respiratory tract infection in 27, Presumed viral enteritis in 3. 2 of asthmatic attack, Dengue haemorrhagic fever in 1, Varicella zoster infection in 1, Mumps infection in 1, Viral meningitis in 1.

In present study gastrointestinal system account for 16 cases of enteric fever, 10 cases of acute gastroenteritis, 7 were of splenic abscess, 4 were of Hepatitis, and 2 were of peritonitis. Dipty Jain et al 2013, [4] also found superficial abscess, urinary tract infection, splenic abscess and septicaemia, osteomyelitis were the causes of fever in SCD. Out of 16 patients of enteric fever with positive widal, salmonella was isolated from 3 patients.

All 4 patients were of Hepatitis A and out of 4 malarial patients 3 were positive of plasmodium vivax infection while 1 had plasmodium falciparum infection**.** Ambe JP et al 2001, [10] stated that common problems associated with SCA patients in anaemic crisis were malaria and bacterial infections- 68 (66%) and 18 (17.3%) of cases, respectively.

In our study, CNS manifested with 2 cases of meningitis and 1 case of stroke, and CSF study in all these 3 cases were sterile. Meningitis is a major cause of death in young children with sickle cell anaemia. [11] Similar results were also found in other studies also. [4,6]

Urinary tract infection was found in 13(8%) patients with clinical feature and urine microscopy, in 2 of these, E.coli was isolated and in 1 klebsiella was isolated from urine culture. Dipty et al 2013 [4] and Wierenga KJJ et al 2001 [6] also found UTI as cause of fever in a patients of SCD with fever.

In our study, osteomyelitis was found in 20(12.56%) patients, in which salmonella typhi was isolated from 2 patients in which 1 had concomitant enteric fever, and staphylococcus was isolated from 2 patients. Dipty Jain et al 2013, [4] also found osteomyelitis in 21% of patients of sickle cell disease with fever.

Chambers JB [12] et al 2000, and Wright Jet al [13] 1997**,** found the most common offending organism in osteomyelitis was Salmonella (eight of ten cases). [12,13]

In the present study 3 patients of sickle cell anaemia with fever found to be HIV positive. Kourtis AP et al 2007 in their study stated that hospitalized children with SCD and HIV infection have higher odds of infection than those with SCD alone. [14]

7 patients had dengue fever who were diagnosed clinically and serologically. One patient had clinically diagnosed mumps and one had septicaemia in whose E. Coli was grown in blood culture. 2 patients had peritonitis out of these1 died in whom streptococcus pneumoniae was isolated from peritoneal fluid.

Table no. 4: Percentage of bacteremia in sickle cell anaemia patients with fever in different study.

Study	Percentage of Bacteremia
Williams TN et al [15]	6%
Wierenga KJJ et al [6]	6.1%
Akinyanju O et al [7]	32%
Okuonghae HO et al [16]	32.5%
Dipty Jain et al [4]	35.71%
Present study	9.81%

Infection is the major presenting manifestation of sickle cell anemia in early childhood and is the most common cause of death in these patients. [17] Amongst the infections, bacterial infections are important as they cause a large number of deaths in children with sickle cell disease. [18-20]

Different studies had different percentage of bacteremia likely Williams TNet al [15] 2009 found in 6%, Wierenga KJJ et al [6] 2001 found in 6.1%, Akinyanju Oet al [7] 1987 found in 32%, Okuonghae HO et al [16] 1993 found in 32.5% and Dipty Jain et al [4] 2013 found in 35.71%. In present study we found bacteremia in 9.81%.

Also study from central India done by Patel AB et al 2004stated that the infection was the main cause for hospitalization of SCD patients along with blood transfusion and sickle cell crisis. [21] Various similar studies show that septicemia was the most common infection found in the patients with sickle cell disease. [22-25]

Table no. 5: Number of bacteria found on blood culture in different study.

Organism	Williams TNet al [15]	WierengaKJJet al [6]	Akinyanju O et al [7]	Dipty Jain et al [4]	Present Study
Streptococcus Pneumoniae	41%	30%	-	-	19%(3)
Klebsiella Pneumoniae	-	-	38%	25%	19%(3)
Salmonella Typhi	-	20%	-	-	19%(3)
E.Coli	7%	10%	23%	25%	12.5%(2)
Staph aureus	-	-	23%	40%	12.5%(2)
Coagulase Negative Staphylococcus	-	-	-	-	12.5%(2)
Pseudomonas aeruginosa	-	-	23%	10%	6.25(1)
Non-Typhi Salmonella Species	18%	-	-	-	-
Haemophilus influenzae Type B	12%	20%	-	-	-
Acinetobacter Species	7%	10%	-	-	-
Enterobacter Sp	-	10%	-	-	-
Staph. Albus	-	-	23%	-	-

In our study, bacteraemia was identified in 16 (9.81%) patients. out of which Streptococcus pneumoniae was found in 3patients, *Klebsiella pneumoniae* was positive in 3 patients of bacteremia, E.coli was found in 2 patients of bacteremia, *Salmonella typhi* was found in 3patients, *Staphylococcus aureus* and Coagulase negative staphylococcus both of each were found in 2-2 patients of bacteremia. *Pseudomonas aeruginosa* was found in 1 patient of bacteremia.

Williams TN et al 2009, [15] in their study, the organisms most commonly isolated from children with sickle-cell anaemia were Streptococcus pneumoniae (44/108 isolates; 41%), non-typhi Salmonella species (19/108; 18%), Haemophilus influenzae type b (13/108; 12%), Acinetobacter species (seven of 108; 7%), and Escherichia coli (seven of 108; 7%). Wierenga KJJ et al 2001 [6] found enteric Gram negative organisms accounted for 50% of positive blood cultures. Bacteraemia was found in 10 (6.1%) patients, three *Streptococcus pneumoniae*, two *Haemophilus influenzae* type b, two Salmonella sp, one *Escherichia coli*, one Enterobacter sp, and one Acinetobacter sp. West et al 1994 [26] and Wong WY et al 1992 [27] also found that Streptococcus pneumoniae was the most common pathogen.

AkinyanjuOet al 1987 [7] found predominant bacteria isolated were Klebsiella spp (38%), E. coli (23%), Staph. aureus (23%), Staph. albus(23%) and Pseudomonas spp (23%), while Okuonghae HO et al 1993 [16] found Gram-negative bacteria were the predominant organisms (70.4%) in SCA. The commonest organisms isolated were Salmonella (25.9%), Klebsiella (25.9%) and Staphylococcus aureus (22.2). In the study of Dipty Jain et al, 2013 [4] in central India bacteraemia was proved in 20 patients of 56 acute febrile illness in which Staphylococcus aureus (n=8) and Gram negative bacteria (n=12)

were responsible for all cases of bacteraemia. The isolated Gram negative bacteria included *Escherichia coli* (n=5), *Klebsiella pneumoniae* (n=5) and *Pseudomonas aeruginosa* (n=2).

In our study, urine culture was positive in 3(1.84%) cases out of 13 UTI patients in which 2 had E.coli infection while 1 had Klebsiella infection, Wierenga KJJ et al [6] 2001, also found positive urine culture in (4/165)2.4%, which is consistent with our findings. We found 1 positive peritoneal fluid culture in which Streptococcus pneumoniae was isolated. Cultures of cerebrospinal fluid (CSF) were sterile in all the 3 patients.

Most patients with homozygous sickle cell disease presenting with fever $>100^0$F had no evidence of bacterial infection, and the fever was assumed to be attributable to viral or atypical organisms. However, these events remain clinically important because more serious pathology such as bacteraemia cannot be excluded.

CONCLUSION

Most patients with homozygous sickle cell disease presenting with fever $>100^0$F had no evidence of bacterial infection, and the fever was assumed to be attributable to viral or atypical organisms. However, these events remain clinically important because more serious pathology such as bacteraemia cannot be excluded.

Although the greatest concern has traditionally been Streptococcal pneumoniae, getting Gram negative bacteria on blood culture has outnumbered it. It may be due to an effective prophylaxis and vaccination against S pneumoniae.

Despite the paucity of invasive bacterial disease in this study, it is wise to treat all febrile children with sickle cell disease with antibiotics pending the results of blood culture.

Hence we conclude that, the respiratory system is the most common one to get involved in patients of sickle cell anaemia with fever and pneumonia is the most common diagnosis in it. Streptococcal pneumoniae along with *Klebsiella pneumoniae* and *E. coli* were found to be the common pathogens causing a significant febrile illness and bacteremia in patients of sickle cell anemia.

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