



RESEARCH ARTICLE

Clinico-Etiological Profile Of Acute Febrile Illness 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. Infection is a significant contributor to morbidity and mortality in Sickle Cell anemia.

High prevalence of Sickle Cell anemia & lack of study in central India showing causes of fever in them, we studied various causes of fever 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, Blood and Urine Culture 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 Pneumonia was the most common clinical diagnosis(23%).

Conclusion: We concluded that, the respiratory system was the most common one to get involved in a patients of sickle cell anaemia presenting with fever and pneumonia was the most common diagnosis in it.

Keywords: Sickle cell anemia, Fever, Bacteremia

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1 | INTRODUCTION

Sickle Cell Disease is an inherited hemoglobinopathy resulting from the inher-

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presence of HbS gene either homozygously (also known as Sickle Cell Anemia), or as a compound heterozygote with other interacting abnormal hemoglobin gene. 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 amongst various manifestations of Sickle cell anemia. In particular, fever is frequently the first indication of serious and life-threatening bacterial infection. Infection is a significant contributor to morbidity and mortality in Sickle cell anemia (4, 5)

There is lack of study in central India showing causes of fever in Sickle cell disease. So this study was planned to identify 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 (6).

2 | METHODS & MATERIAL

This study was a cross sectional observational study. We enrolled 163 patients of Sickle cell anaemia (SS pattern) in the age group of 6 months to 12 years admitted with fever $\geq 100^{\circ}\text{F}$ in Pediatric wards of tertiary care hospital in central India. The study period was from December 2017 to September 2019.

Considering the prevalence of 31% of acute febrile illness in Sickle cell anaemia 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

Supplementary information The online version of this article (XXXXXXX) contains supplementary material, which is available to authorized users.

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consent was obtained from parents of all participants (7, 8).

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

3 | 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.

1 shows, frequency of various clinical diagnosis found in patients of Sickle cell anaemia 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. Hyper reactive airway disease (HRAD)/asthma was the presentation in 4 patients. 2 patients found to have pulmonary tuberculosis and were receiving AKT.

Hepatitis antibody were positive in 4 patients and 16 patients had enteric fever with positive widal test, out of this salmonella was isolated in blood culture of 3 patients. Acute gastroenteritis was present in 10 patients with positive stool microscopy while 7 patients had splenic abscess. 2 patients had peritonitis out of these 1 patient died in whom streptococcus pneumoniae was isolated from peritoneal fluid.

Clinically and radiologically diagnosed osteomyelitis was found in 20 patients, in which salmonella typhi was isolated from blood culture of 2 patients in which 1 had concomitant enteric fever, and also staphalococcus was isolated from blood culture of 2 patients.

Urinary tract infection was found in 13 patients with clinical features of UTI and urine microscopy showed pus cells. Out of 13 patients, 3 were urine culture positive, E.coli was isolated in 2 patients and klebsiella was isolated from urine culture of 1 patient.

7 patients had dengue fever who were diagnosed clinically and serologically. 4 patients of malaria out of which 3 had positive for plasmodium vivax and 1 was positive for plasmodium falciparum. 3 patients were reactive for HIV.

Meningitis was the diagnosis in 2 patients in which CSF study shown increased WBC but no organism was isolated in CSF culture, and one patient presented with stroke. Mumps and Measles was the clinical diagnosis in 1 patient each and 1 patient 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 patients 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 were found in 2-2 patients of bacteremia. Pseudomonas aeruginosa was found in 1 patient of bacteremia. Culture of CSF were sterile in 2 patients of meningitis.

4 | DISCUSSION

In our study, out of 163 patients of Sick Cell anaemia presented 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 cases of pharyngitis, 7 cases of bronchopneumonia, 6 cases of tonsillitis, 4 cases of HRAD and 2 cases

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). (9) Akinyanju O, Johnson AO, 1987 in their study found, the commonest infections were pneumonia (35%), bacteraemia (32%), tonsillitis/pharyngitis (17%) and osteomyelitis (8%). (10)

Wierenga KJJ et al 2001 divided the diagnosis of fever in Sick 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. (11)

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

All 4 patients presented with features of Hepatitis were positive for Hepatitis A and out of 4 malarial patients 3 were positive for plasmodium vivax infection while 1 had plasmodium falciparum infection. Ambe JP et al 2001, stated that common problems associated with SCA patients in anaemic crisis were malaria and bacterial infections in 68 (66%) and 18 (17.3%) cases, respectively. (12)

In our study, CNS manifestations were, 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 (13). Similar results were also found in other studies also (4, 10).

Urinary tract infection was found in 13(8%) patients with clinical feature and urine microscopy suggesting UTI. In 2 of these, E.coli was isolated and in 1 klebsiella pneumoniae was isolated from urine culture. Dipty et al 2013 and Wierenga KJJ et al 2001

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TABLE 1: DISTRIBUTION OF CLINICAL DIAGNOSIS IN SICKLE CELL ANEMIA WITH FEVER

CLINICAL DIAGNOSIS.	NO OF CASES
LRTI - Lobar pneumonia - Bronchopneumonia	37 (22.63%) 30 (18.4%) 7 (4.2%)
URTI - Pharyngitis -Tonsillitis	29 (17.79%) 23 (14.11%) 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 - Hepatitis A - Hepatitis B	4(2.4%) 4(2.4%) 0
Peritonitis	2(1.2%)
Osteomyelitis	20(12.2%)
UTI	13(7.9%)
Dengue fever	7(4.2%)
Malaria - Plasmodium Vivax - Plasmodium Falciparum	4(2.4%) 3(1.8%) 1(0.6%)
HIV	3(1.8%)
Meningitis	2(1.2%)
Measles	1(0.6%)
Mumps	1(0.6%)
Septicemia	1(0.6%)
Total	163 (100%)

TABLE 2: DISTRIBUTION OF DIFFERENT BACTERIAL PATHOGENS

ORGANISM	BLOOD	URINE	PERITONEAL FLUID	CSF	TOTAL
Streptococcus pneumonia	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%)
PseudomonasAeurogisa	1	0	0	0	1(0.6%)
Total	16(9.81%)	3(1.8%)	1 (0.6%)	0	20(12.26%)

also found UTI as cause of fever in a patients of SCD with fever (4, 10)

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 staphalococcus was isolated from 2 patients. Dipty Jain et al 2013 also found osteomyelitis in 21% of patients of sickle cell disease with fever (4) .

Wright Jet al 1997 and Chamber JB et al 2000, found the most common offending organism in osteomyelitis was Salmonella (eight of ten cases) (14, 15)

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 (16) .

7 patients had dengue fever who were diagnosed clinically and serologically. One patient had Measles, one had mumps infection, dignosed clinically and one had septicaemia in whome E. Coli was grown in blood culture. 2 patients had peritonitis out of these 1 died in whome streptococcus pneumoniae was isolated from peritoneal fluid (17) .

In our study, bacteraemia was identified in 16 (9.81%) patients. out of which *Streptococcus pneumoniae* was found in 3 patients, *Klebsiella pneumoniae* was positive in 3 patients of bacteremia, *E. coli* was found in 2 patients of bacteremia, *Salmonella typhi* was found in 3 patients, *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 (18).

Williams TN et al 2009, 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%) (19). Wierenga KJJ et al 2001, 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 (10). West et al 1994 and Wong WY et al 1992 also found that *Streptococcus pneumoniae* was the most common pathogen (20, 21).

Akinyanju O et al 1987 (11) found predominant bacteria isolated were *Klebsiella* sp (38%), *E. coli* (23%), *Staph. aureus* (23%), *Staph. albus* (23%) and *Pseudomonas* spp (23%), while Okuonghae HO et al 1993 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) (22). In the study of Dipty Jain et al, 2013 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) (4).

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 2001, also found positive urine culture

in (4/165) 2.4%, which is consistent with our findings (23). We found 1 positive peritoneal fluid culture in which *Streptococcus pneumoniae* was isolated. Culture of cerebrospinal fluid (CSF) were sterile in all the 3 patients.

5 | CONCLUSION:

Most patients with homozygous sickle cell disease presenting with fever >100°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. 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 a 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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