

Original Research Article

Infections in sickle cell disease

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Abstract

Background: Infections are the most frequent complications in individuals with sickle cell disease. Infection is a significant contributor to morbidity and mortality in sickle cell disease.

Materials and methods: A prospective study was carried out in a total of 100 patients to study prevalence and type of infections in homozygous sickle cell disease patients in both sexes and all age groups at Department of Pathology of our institute. All homozygous (SS) sickle cell disease patients with high grade fever of temperature $\geq 101^{\circ}\text{F}$ (38°C) from all age groups and both sexes were included without administration of first antibiotic dose. The identification of the infecting organism was done by staining, and culture studies.

Results: The results were analyzed using standard microbiological techniques. In present study, maximum cases were seen in 0-5 years of age group, the cases of infection were more in males (62%) than in females (38%) with M: F ratio of 1.63:1. In the present study, respiratory tract infection was present in 37% cases. The positivity of blood culture was 27% (27 out of 100). Out of 27 blood culture positive cases, Gram negative organisms isolated were Klebsiella (51.55%), Escherichia coli (14.81%), Salmonella (7.40%), Acinetobacter (3.70%) and Gram positive isolates were Enterococcus (7.40%), Staphylococcus aureus (11.11%), Streptococcus Pneumoniae (3.70%). Therefore this study was conducted out to assess the patterns of morbidity and mortality due to infections in sickle cell disease and to implement various measures of preventive care and treatment in future.

Conclusion: The incidence of infection was more common in age group 0-5 years. The incidence of infection was more common in males as compared to females. Respiratory tract infection was the most common infection. Gram negative organism - Klebsiella pneumoniae was the most common organism isolated followed by E. coli, Salmonella and Acinetobacter. Among Gram positive organism - staphylococcus aureus, enterococcus, Streptococcus pneumoniae were common bacterial isolates. Among non-bacterial causes - Malaria was common infection.

Key words

Sickle cell disease, Infection, Culture studies.

Introduction

Infections are the most frequent complications in individuals with sickle cell disease [1]. In children from 0 to 6 years of age, splenomegaly is observed resulting from congestion in the red sequestered sickle-shaped erythrocytes in the Bill-Roth and sinusoidal cords, which progress with thrombosis and infarction culminating in atrophy and fibrosis of organ. This phenomenon known as auto-splenectomy, generally occurs by about 5 years of age [2, 3, 4]. As a consequence of this asplenia, there will be increased susceptibility to infections by capsulated organism notably Hemophilic influenza type b and pneumococcus [5, 6].

The most common bacterial infections in decreasing order of frequency, the main etiologic agents associated with episodes of invasive bacterial infection of individuals with sickle cell anemia are: streptococcus pneumonia, salmonella, H. influenzae b, Klebsiella pneumonia, E. coli [7]. Historically, infection is a major cause of mortality in SCD, particularly in children. Worldwide, it remains the leading cause of death, particularly in less developed and developing nations. In developed countries, measures to prevent and effectively treat infection have made a substantial contribution to improvements in survival and quality of life, and are continually being developed and extended [8]. However, progress continues to lag in less developed and developing countries where the patterns of morbidity and mortality are less well defined and implementation of preventive care is poor. Therefore this study was conducted out to assess the prevalence and type of infections in homozygous sickle cell disease patients, and its age and sex-wise incidence.

Materials and methods

The present study was conducted to study prevalence and type of infections in homozygous sickle cell disease patients in both sexes and all age groups at Department of Pathology of our institute.

Study Design: Hospital based prospective study.

Study Period: July 2010 to October 2012.

Inclusion criteria: All homozygous (SS) sickle cell disease patients with high grade fever of temperature $\geq 101^{\circ}\text{F}$ (38°C) from all age groups and both sexes.

Exclusion criteria: Administration of first antibiotic dose.

Methodology

Known already diagnosed cases of homozygous sickle cell anemia with "SS" pattern were included with detailed history and complete clinical examination. After taking informed and written consent, venous blood sample was collected for complete blood count, peripheral smear, blood culture studies, serum Bilirubin and serum creatinine and blood urea estimation. The following investigations were done.

Specimen collection

Blood for complete blood count, culture and sensitivity was collected before first antibiotic dose. Other specimens investigated were sputum, urine, pleural fluid, ascitic fluid, CSF, wound swab according to primary infection present and respective culture were performed.

Blood culture

Volume of blood collected: In adult, 10 ml of blood was collected and in children 5 ml of blood was collected.

Timing: Blood was obtained immediately once the sepsis was suspected within 24 hours of admission to hospital before starting treatment.

Procedure: A smear was prepared and stained by Gram-staining method for early presumptive diagnosis and inoculated on Blood agar and Mc Conkey's agar by streak method using Nichrome wire loop. The plates were incubated at 37°C overnight for 18-24 hours. Identification of isolates was done by morphology and colony characteristics according to CLSI guidelines.

Identification of growth: Direct gram stain report of specimens was correlated with the growth in the culture plates. Growth on the plates was taken and examined under microscopically

to group them into Gram positive and Gram negative organism.

Statistical analysis

Statistical analysis was done using Student-t test for continuous variables. Categorical variables were analyzed using Chi square test. Probability value of $p < 0.05$ were considered significant while $p < 0.01$ is taken as highly significant.

Results

In the present study, 100 cases of homozygous sickle cell anemia with high grade fever, from all age groups and both sexes were studied in the Department of Pathology and sickle cell OPD from July 2010 to October 2012.

Maximum cases (37%) were in 0-5 years age group. Males were more commonly affected than females as per **Table – 1**.

Table - 1: Age and Sex wise distribution of cases in present study.

Age (years)	Male	Female	Total	M:F ratio
0-5	22	15	37	1.46:1
6-10	17	13	30	1.30:1
11-15	12	6	18	2:1
16-20	3	1	4	3:1
21-25	7	0	7	7:0
26-30	1	1	2	1:1
>30	0	2	2	0:2
Total	62	38	100	1.63:1

Percentage of clinical diagnosis (foci of infection) in present study was as per **Table - 2**. The commonest foci of infection were Respiratory tract infection in 37% cases, in which 6 cases (6%) presented with Acute chest syndrome, 6 cases (6%) presented with fever, cough with expectoration, 2 cases (2%) presented with consolidation of lung, 1 case (2%) presented with asthma, 1 case (2%) presented with Mycobacterium tuberculosis and the remaining cases presented with fever, cold, cough without expectoration. In the present study, mixed

infections were seen in 6% cases. In mixed infections, 2 cases were of respiratory tract infection and cholecystitis, 3 cases were of respiratory tract infection and gastrointestinal tract infection and, 1 case was of respiratory tract infection and urinary tract infection.

Table - 2: Clinical diagnosis (foci of infection) in SCD patients in present study (n=100).

Clinical diagnosis	No. of cases	%
Respiratory infection	37	37
Septic arthritis	15	15
Pyrexia of unknown origin (PUO)	18	18
Malaria	9	9
GIT infection	9	9
Mixed infection	6	6
Skin/ soft tissue infection	4	4
Hepatitis	3	3
Osteomyelitis	2	2
Typhoid	2	2
Urinary tract infection (UTI)	2	2
Hepatic encephalopathy	1	1
Diabetic ketoacidosis	1	1
Septicemia	1	1

Out of 100 cases, 27 were blood culture positive cases. Out of 27 blood culture positive cases, bacteria isolated were Klebsiella Pneumoniae in 14 cases (51.85%), E-Coli in 4 cases (14.81%), Enterococcus in 2 cases (7.40%), Salmonella in 2 cases (7.40%), Streptococcus Pneumoniae in 1 case (3.70%), Staphylococcus Aureus in 3 cases (11.11%), and Acinetobacter in 1 case (3.70%) as per **Graph - 1**.

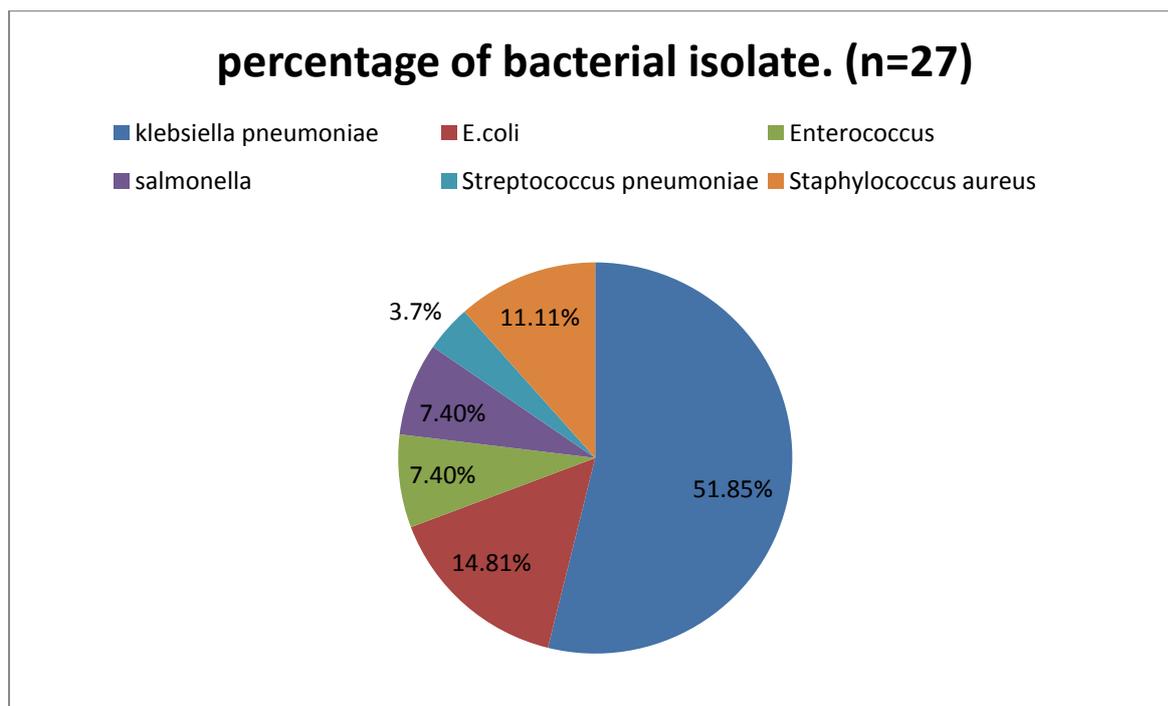
2 cases (2%) having urinary tract infection showed bacterial growth on urine culture, the organism isolated was E. coli in a 23 year/male and 34year/female having UTI.

In 0-5 years age group, 3 sputum culture positive cases were present. In 6-10 years age group, 1 sputum culture positive case out of three was present. In 11-15 years age group, 1 sputum

culture positive case was present. Out of 7, klebsiella pneumoniae was isolated in 3 cases, having respiratory tract infection in a 7 year/male, 4 year/male and 3 year/male respectively. Streptococcus pneumoniae was isolated in a 4.5 year/female having fever, cough with expectoration. Mycobacterium tuberculosis

was isolated in a 15 year/female and on ZN stain, AFB bacilli were seen. Thus, the incidence of sputum culture positive cases was more in age group of 0-5 years. The common organisms isolated on sputum culture were Klebsiella pneumoniae.

Graph – 1: Percentage of bacterial isolate.



Wound culture was positive in 2 cases in a 30 year/male and another in a 24 year/male, who presented as foot ulcer. The organism isolated was Staphylococcus aureus in both cases. In 0-5 years age group, stool culture was positive in a 2 year/male and 4 year/female who presented as fever with diarrhoea. The organism isolated was E. coli in both cases. In 6-10 years age group, 1 stool culture positive case was present in a 10yr/male. The organism isolated was E. coli.

Hepatitis Bs Antigen was positive in 3 cases in a 12 year/female, 21 year/male and 4 year/male respectively, which clinically presented as fever with abdominal pain and jaundice. Plasmodium falciparum was detected in 4 cases and plasmodium vivax in 5 cases.

Discussion

Respiratory tract infections

In the present study, respiratory tract infection was present in 37% cases which were comparable with other study [8].

Acute Chest Syndrome: It is characterized by pleuritic chest pain, fever, rales on lung auscultation, and pulmonary infiltrates on chest X-ray [9]. In the present study, there were 6% cases of Acute chest syndrome, which was low than other studies [9].

Tuberculosis: In the present study, sputum culture was positive for Mycobacterium Tuberculosis and pulmonary Mycobacterium Tuberculosis was seen in 1% case, while one study reported higher incidence of tuberculosis

cases (6%) by Jacques Cadranel, et al., (2007), who reported that in SCD patients, lymph node tuberculosis appears to have a higher incidence than that in an epidemiologically comparable population, and has a rather indolent presentation and a favorable outcome. Pulmonary tuberculosis seems to be less frequent than expected [10].

In the present study, Fever with weakness was seen in 21% cases. Pyrexia of unknown origin was seen in 17% cases, Weakness may be due to weight loss and muscle wasting because of decreased food intake and associated infections.

Septicemia: Incidence of septicemia was 1% in present study, which was low as compared to study done by Mohamed Reda Bassiouny, et al. (1995) [11] (23%).

Osteoarticular system infections: In the present study, fever with joint pain was seen in 17% cases. Joint pains in sickle cell disease result from vaso-occlusive crises because of chronic hemolytic process. Vaso occlusive crisis was the commonest cause of hospitalization in Oman (91%), a very high incidence compared to Saudi Arabia, Jamaica, South London and Africa [12-15].

Septic arthritis: In the present study, incidence of Septic Arthritis was seen in 15% cases, which was higher than the other studies [16].

Osteomyelitis: The incidence of osteomyelitis cases was 2% in present study, which was low as compared to other studies [16].

Gastrointestinal tract infections: In the present study, fever with abdominal pain was seen in 15% cases. Seven cases had splenomegaly, one case had hepatomegaly and splenomegaly and three cases had hepatomegaly, and two cases had cholelithiasis. No cause was found in remaining cases of abdominal pain.

The abdominal pain in sickle cell anemia may be due to splenic sequestration resulting in acute enlargement of spleen or less commonly due to

hepatic sequestration, subcapsular infarction or hepatic vein thrombosis.

Cholelithiasis: Cholelithiasis is also a frequent cause of abdominal pain. High frequency of gall stones in sickle cell disease is due to sustained increase in heme catabolism. These gall stones had been documented in children less than 5 years of age [16].

Incidence of cholelithiasis cases was 2% in present study, which was low as compared to other studies [17-20].

In the present study, fever with diarrhoea was seen in 7% cases. Gastrointestinal tract infection was seen in 9% cases. In the present study, E. coli was isolated from stool culture in 3 out of 7 diarrhoeal cases.

Skin/ soft tissue infections: In the present study, skin/ soft tissue infection was seen in 4% cases, out of which fever with cellulitis was seen in 2% cases, and fever with leg ulcers was seen in 2% cases. Wound culture was positive in 2 cases which presented as foot ulcer in age group of 21-25 years and 26-30 years. The organism isolated was Staphylococcus aureus. Both wound culture positive cases were seen in males.

Leg ulcers: However in present study, we found two cases of leg ulcer (2%) and all patients were males. Prevalence of leg ulcers was very low as compared to above studies and only males had leg ulcers. This can be explained by more outdoor activities in males causes them more prone for trauma and frequency of vaso-occlusive crisis was also higher in males as compared to females. Kar B C, et al. (1986) [21] reported that leg ulcers are rare in Indian patients.

In the present study, fever with convulsions was seen in 1% case. Febrile convulsions are the commonest cause of seizures in early childhood between 6 months to 5 years of age in the absence of neuroinfection. The convulsions are not related to the degree of temperature rise but

are frequent if temperature rises rapidly [22]. Several genetic associations had been identified [23].

Urinary tract infection: In the present study, fever with burning micturition was seen in 2% cases. Patients with sickle cell anemia have increased susceptibility to develop UTI because of altered blood flow in the renal vasculature which causes papillary necrosis and loss of urinary concentrating and acidifying ability of the nephrons with the consequent formation of abnormally dilute and alkaline urine which favours bacterial proliferation [24]. This predisposes them to recurrent UTI and subsequent renal damage.

Malaria: In the present study, incidence of Malaria was seen in 9% cases, which was lower than the other studies [25-29]. Malaria is endemic in tropical Africa and some individuals including pregnant women, children and sickle-cell disease (SCD) patients have an increased susceptibility to its infection [30-32] Malaria is the most common precipitating cause of crises in sickle cell disease in countries where malaria is endemic [33]. Maharajan, et al. reported that malaria parasites were the commonest infecting organism in people with homozygous sickle cell disease requiring hospitalizations in Nigeria [34].

Hepatitis:

In the present study, Hepatitis was seen in 3% cases and Hepatic encephalopathy in 1% case .The incidence was more in males. A study in a Saudi Arabian population (1986) found a prevalence of HBsAg (4.4% and 4.8%) in females and males. It had been inferred from this Saudi study that the infection was acquired early in life, a pattern characteristic of areas of high prevalence of the infection. The cause of the infection was ascribed to serum-sharing, associated with close personal contact and oozing dermatologic lesions that occur early in childhood [35]. Yohannan, et al. (1990) found that 2 of 3 patients developing fulminant hepatic failure over the course of a year were sickle cell anemia patients with acute hepatitis A infection.

They propose that the underlying sickle cell disease may have predisposed to the severity of the presentation. All patients with sickle cell anemia and chronic liver disease should be tested for hepatitis A virus antibodies and if negative be vaccinated against hepatitis A [36].

In present study, the only serological marker measured was the surface antigen (HBsAg). HBsAg appears before the onset of symptoms, and concentration reaches a peak during acute disease and then usually declines to undetectable levels in three to six months. The persistence of HBsAg beyond six months is indicative of chronic infection.

The lower prevalence of the surface antigenemia (3% cases of hepatitis) in present study, could be attributed to a better education of the sickle cell patients, and caregivers on the general upkeep of these patients, in hospital, home, school or work place.

Blood culture: In present study, Klebsiella Pneumoniae was isolated in 51.85% cases which are comparable with other study as per **Table - 3**. It could be argued that the predominance of Klebsiella sp, Staphylococcus aureus, and Salmonella sp simply reflects high levels of carriage of these organisms in the environment [37, 38].

Table - 3: Bacterial isolate in blood culture in present study and other studies.

Bacterial isolate	Serjeant, et al. (2001) [38]	Present study
Streptococcus pneumoniae	30%	3.70%
E.coli	10%	14.81%
Klebsiella Pneumoniae	-	51.85%
Salmonella	20%	7.40%
Staphylococcus Aureus	-	7.14%
Enterococcus	-	7.40%
Acinetobacter	10%	3.70%

Conclusion

- The incidence of infection was more common in age group 0-5 years.
- The incidence of infection was more common in males as compared to females.
- Respiratory tract infection was the most common infection.
- Gram negative organism- Klebsiella pneumoniae was the most common organism isolated followed by E. coli, Salmonella and Acinetobacter.
- Among Gram positive organism - staphylococcus aureus, enterococcus, Streptococcus pneumoniae were common bacterial isolates.
- Among non-bacterial causes - Malaria was common infection.

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