AETIOPATHOGENESIS OF FEVER IN HOSPITALISED SICKLE CELL DISEASE CHILDREN REVISITED WITH SPECIAL REFERENCE TO BLOOD CULTURE

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ABSTRACT

BACKGROUND

Sickle Cell Disease (SCD) poses a considerable health burden in India. The sickle gene is widespread among many tribal population groups in India with prevalence of heterozygotes varying from 1-40 percent). The disease has multiple acute and chronic complications, including haemolytic crises, severe pain, renal complications, thromboembolic phenomenon and overwhelming infections; some complications of SCD generate high mortality.

MATERIALS AND METHODS

This is a cross-sectional, hospital inpatient based, observational study. Convenience sampling technique was used to include 74 consecutively diagnosed cases of sickle cell disease children less than 14 years of age and suffering from fever. A blood culture was performed in each case prior to starting of antibiotics.

RESULTS

The present study comprised of 74 children with confirmed sickle cell disease admitted to ward with fever. The largest numbers of cases were between 1 to 3 years age group. Febrile episodes decreased as the age advanced. Around 30% of febrile patients presented with cough followed by 24% with pain in limbs. Anaemia was the most common physical finding (92%) followed by splenomegaly in 86% cases. URTI being most common aetiology. Most common organism isolated by blood culture was Staph. aureus in 8 samples.

CONCLUSION

As because fever is a consistent finding in severe bacterial infections, extensive evaluation, early intervention in febrile SCD children may reduce the morbidity and mortality rates. Although, the greatest concern has traditionally been S. pneumoniae, effective vaccination has reduced its incidence. It is probably wise to treat all highly febrile children with sickle cell disease with antibiotics pending the results of blood culture. Strengthening of routine immunisation programme is needed.

KEYWORDS

Febrile, Sickle Cell, Blood Culture.

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BACKGROUND

Sickle Cell Disease (SCD) poses a considerable health burden in India. Sickle cell disease is a most common haematologic disease in this part of southern Odisha documenting high rates of admission of 70% for febrile episodes.[1,2] SCD is characterised by abnormal red blood cell shape (sickling). This abnormal shape decreases the cell's flexibility and results in multiple complications. This abnormality is due to a mutation in the haemoglobin gene that results in an amino acid substitution of valine for glutamine in the beta chain. The mutation can occur in a heterozygous (SCD trait) or homozygous form. The sickle gene is widespread among many tribal population groups in India with prevalence of heterozygotes varying from 1-40 percent.[1] The coincidence of large tribal populations with the 'sickle cell belt' of Central India and northern Kerala, Tamil Nadu and western Odisha has given rise to the assumption that tribal people are more prone to the HbS gene, although this seems widely distributed among tribal and nontribal people.[3] The disease has multiple acute and chronic complications, including haemolytic crisis, severe pain, renal complications, thromboembolic phenomenon and overwhelming infections. Some complications of SCD like bacteraemia and sepsis generate high mortality. High fever is a cause of concern in children with homozygous sickle cell disease. The well-known susceptibility to blood-borne infections results in a high awareness of septicaemia, although its frequency as a cause of high fever is unknown.[4]

Patients with SCD have compromised splenic function, defect in alternate pathway of complement activation, defect in opsonisation and defect in granulocyte function that

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increases both the rate of bacteraemia among these children and the subsequent risk of a rapid progression to sepsis, septic shock and death.[1,5] For the management of febrile episodes among children with SCD, these recommendations state that temperatures 38.5°C should be considered an emergency and patients should seek immediate medical attention for laboratory evaluation and empirical antimicrobial therapy.[4] RTI, pneumonia, septicaemia, UTI, skin and soft tissue infection, osteomyelitis above all malaria infections are seen as per endemicity.[5] SCD patients are prone to invasive infections with encapsulated bacteria. These patients should be assumed to be functionally asplenic. Bacteraemia carries significant risk of morbidity and mortality in this group of patients' lists below severe anaemia, which is the most common complication.[6]

Previous studies have indicated that febrile children with Sickle Cell Disease (SCD) had a 13% to 30% risk of being bacteraemic due to compromised immune function.[2] Increased awareness and sensitisation may help in diagnosing many cases of SCD such that proper antibiotic therapy as per organism isolated can be planned. With this background, the present study was carried out with the primary objectives to determine the bacteraemia in febrile episodes among SCD patients presenting to the Department of Paediatrics of a tertiary care teaching hospital.

MATERIALS AND METHODS

This was a cross-sectional, hospital inpatient based observational study carried out in the Paediatrics Department of M.K.C.G. Medical College from January to June, 2017. Convenience sampling technique was used to include 74 consecutively diagnosed cases of sickle cell disease children less than 14 years of age and suffering from fever. The cases were included in the study only after being confirmed by HB electrophoresis. A blood culture was performed in each case prior to starting of antibiotics. Patients were subjected to thorough clinical examination to find out any focus of infection attributed to fever. Using universal precautions (spirit-iodine-spirit), about 2 mL of venous blood was collected and inoculated to 20 mL of liquid medium and sent to laboratory. Utmost care was taken to avoid contamination. Routine blood investigations and slide for malaria parasite were done in each case. Other tests like urine culture (if UTI was suspected), chest x-ray in cases of respiratory tract infection and pneumonia were advised. Lumbar puncture also carried out in cases where meningitis was suspected. Those cases that had antibiotics therapy prior to blood culture were excluded. The data was collected in a predesigned case record form. Descriptive statistics was used to report the study findings. A 'p' value of <0.05 was considered statistically significant in Z-test for proportions. This study was approved by the Institutional Ethics Committee of the medical college. Written informed consent was obtained from the patient or his attendants or parents.

RESULTS

Total of 123 cases of SCD diagnosed and of that 79 cases were presented with fever (62%). Of that 79 cases, the present study comprised of 74 children, and in 5 children, blood culture could not be sent (Table 1). Maximum number of febrile episodes were found upto 6 yrs. age group (64%) and 27% were belonging to 6-14 years (Table 2). Main presenting symptom was cough in 30% cases, 24% children had pain in limbs, 22% had abdominal pain (Table 3). Anaemia was seen in 92% (68), splenomegaly in 86% (64), hepatomegaly in 82% (61) and jaundice in 47% (35) cases (Table 4). Respiratory aetiology (URTI and pneumonia) was identified in 40% (22% + 18%), sepsis in 8% and enteric fever in 5% cases (Table 5).

Routine immunisation coverage was 68% (51). Additional vaccinations like pneumococcal 4% (3) and typhoid 12% (9) were seen (Table 4). Of 74 blood cultures sent, culture positivity was 23% (17), most common organism grown was Staph. aureus 11% (8). Gram-negative organism E. coli cultured in 5% (4) and pneumococci in 1 blood sample only (Table 7). Association of poor outcome seen in 9% (7) septicaemia cases (3) being most common cause of mortality (Table 8).

Total No. of SCD Cases Admitted	No. of SCD Cases with Fever	%	p value
123	79	60.16%	<0.001

Table 1. Incidence of Febrile Cases in Sickle Cell Disease (SCD)

Age (yrs.)	Male	Female	Total	%	p value
<1 year	8	5	13	18	0.03
1-3 yrs.	8	7	15	20	0.003
3-6 yrs.	11	8	19	26	<0.001
6-14 yrs.	17	10	27	36	<0.001
		Total	**74**		

Table 2. Age and Gender Distribution of Cases of Sickle Cell Disease with Fever (n=74)

Symptoms	No. of Cases	%	p value
Cough	22	30	<0.001
Respiratory distress	13	17	0.03
Chest pain	8	11	0.816
Pain in limbs	18	24	<0.001
Pain abdomen	16	22	<0.001
Joint pain	7	9	0.874
Convulsion/unconsciousness	6	8	0.585
Weakness	5	7	0.351

Table 3. Different Symptoms of Sickle Cell Disease with Fever (n=74)

Symptoms	No. of Cases	%	p value
Cough	22	30	<0.001
Respiratory distress	13	17	0.03
Chest pain	8	11	0.816
Pain in limbs	18	24	<0.001
Pain abdomen	16	22	<0.001
Joint pain	7	9	0.874
Convulsion/unconsciousness	6	8	0.585
Weakness	5	7	0.351

Table 4. Different Physical Findings in Patients of Sickle Cell Disease with Fever (n=74)

Infections	No. of Cases	%	p value
URTI	16	22	<0.001
Pneumonia	13	18	0.03
Sepsis	6	8	0.585
Meningitis	3	4	0.088
UTI	3	4	0.088
Cellulitis	3	4	0.088
Enteric fever	4	5	0.351
Osteomyelitis	1	1	0.013
Malaria	5	7	0.351
Fever without focus	10	14	0.314
Vaso-occlusive syndrome	10	14	0.314
Total	**74**		

Table 5. Sickle Cell Disease with Fever According to Aetiology (n=74)

Routine immunisation	51	68%
Pneumococcal vaccine	3	4%
Typhoid	9	12%
H. influenzae	28	38%

Table 6. Immunisation Status in Cases of Sickle Cell Disease with Fever (n=74)

E. coli	4	5%
S. pneumoniae	1	1%
Staph. aureus	8	11%
Acinetobacter	2	3%
Others	2	3%
Total	**17**	**23%**

Table 7. Organism Isolated by Blood Culture (n=74)

Septicaemia	3
Meningitis	1
Pneumonia	1
Severe anaemia with CCF	2
Total	**7 (9%)**

Table 8. Mortality Pattern in Cases of Sickle Cell Disease with Fever (n=74)

DISCUSSION

This study showed that SCD patients are recurrently admitted to hospitals at a significant rate (62%),[5,6] which can put them at a high risk of developing a hospital-acquired infection. Maximum number of febrile episodes were found upto six years age group, upto three years accounting 37% and 3 to 6 years, 26% cases.[7] This disease predominated in males, 59%. Though, there is no sex predilection in SCD, the higher incidence in male detected could be due to more outdoor activity and less degree of immunity in them.[6] Anaemia was the most common physical finding in 92% of cases and next was splenomegaly and hepatomegaly. Jaundice was present in 47% of cases.[8]

Out of infectious causes of fever, the prominent causes were URTI and pneumonia. Cough was common presenting feature in 30% of cases.[5] High-grade fever was usually seen in cases of sepsis, cellulitis and meningitis. Convulsions or unconsciousness were the presenting signs in 8% of cases pointing intracranial infections and malaria infection diagnosed in 5 cases. One case having high-grade fever diagnosed as osteomyelitis.[2] Ten cases reviewed here developed a fever with no clear cause even after extensive diagnostic evaluation; thus, those fevers may have been of a noninfectious aetiology in this population.[2,7] This study shows that fever was a frequent reason for outpatient consultation and hospitalisation of sickle cell children.[1] Routine immunisation coverage in our study was 69%. Few patients were also received typhoid and pneumococcal vaccination.[4]

In our study, blood culture positivity was only 23%. Most common organism isolated was Staphylococcus aureus. Gram-negative organism like E. coli isolated from blood in 4 number of cases. Two numbers of febrile SCD patients were positive blood culture for Acinetobacter. In our study, rate of bacteraemia among febrile children with SCD was higher in contrast to previous study.[2] Salmonella infection commonly seen in sickle cell patients. But, in our study, only 4 cases diagnosed of enteric fever and none was culture positive. The immunological features that contribute to the occurrence of these infections among sickle cell patients should be explored. S. pneumoniae was rarely encountered and only one culture was positive for this bacterial infection that was most commonly expected to occur in SCD patients.[4] Pneumococcal and H. influenzae B vaccination may attribute to reduced number of bacterial isolation. Similar results were also seen in two other studies.[4,5,9] The apparent lack of pneumococcal septicaemia in Indian sickle cell disease may reflect persisting splenic function and vaccine coverage. A high incidence of staphylococcal organism with SCD was noted in our study.[2] Possibility of bacterial contamination during sample collection should be taken care of to avoid false results.

In our present study, 7 cases out of 74 children died during the course of hospitalisation. Maximum number of deaths are due to septicaemia and seen in under 6 years of age. Serious bacterial infections like meningitis and pneumonia accounted for 2 death cases. Mortality pattern was quite similar to observations.[8] Other markers like high total leucocyte counts was seen in many febrile SCD patients. But, there was a little correlation between leucocytosis and major bacterial infections. Life-threatening infections could not be ruled out with normal leucocyte counts.[10]

CONCLUSION

Serious bacterial infections are a major threat to young children with sickle cell disease and they need to be considered as a special high-risk group. Blood culture must be advised in all cases to know bacteraemia and antibiotic sensitivity pattern, thereby reducing antibiotic overuse and resistance. As because, fever is a consistent finding in severe bacterial infections, extensive evaluation, early intervention in febrile SCD children may reduce the morbidity and mortality rates. More strengthening of routine immunisation and other vaccines will help to reduce S. pneumonia, S. typhi and H. influenza infections. Urinary tract infection is common in children with SCD. Routine screening is therefore recommended during fever. Additionally, it is recommended that a patient with sickle cell disease be protected from a nosocomial or community-acquired infectious disease adhering to handwashing and other infection control

measures. Analysis of large number of febrile sickle cell cases is needed for better understanding of pathogenesis of infections and better management of these children.

REFERENCES

[1] Colah RB, Mukherjee MB, Martin S, et al. Sickle cell disease in tribal populations in India. Indian J Med Res 2015;141(5):509-515.
[2] Al Salman J, Al Agha RA, Al Taitoon S, et al. Fever in sickle cell disease patients in the kingdom of Bahrain. Journal Infection and Public Health 2014;7(4):333-338.
[3] Serjeant GR, Ghosh K, Patel J. Sickle cell disease in India: a perspective. Indian J Med Res 2016;143(1):21-24.
[4] Baskin MN, Goh XL, Heeney MM, et al. Bacteremia risk and outpatient management of febrile patients with sickle cell disease. Pediatrics 2013;131(6):1035-1041.
[5] Wierenga KJ, Hambleton IR, Wilson RM, et al. Significance of fever in Jamaican patients with homozygous sickle cell disease. Arch Dis Child 2001;84(2):156-159.
[6] Samal GC, Naik KN. Incidence of sickle cell disease in school children of western Orissa. Ind J Hematol 1983;1:51-54.
[7] Shihabuddin BS, Scarfi CA. Fever in children with sickle cell disease: are all fevers equal? J Emerg Med 2014;47(4):395-400.
[8] Zarkowsky HS, Gallagher D, Gill FM, et al. Bacteremia in sickle hemoglobinopathies. J Pediatr 1986;109(4):579-585.
[9] Morrissey BJ, Bycroft TP, Almossawi O, et al. Incidence and predictors of bacterial infection in febrile children with sickle cell disease. Hemoglobin 2015;39(5):316-319.
[10] Narang S, Fernandez ID, Chin N, et al. Bacteremia in children with sickle hemoglobinopathies. J Pediatr Hematol Oncol 2012;34(1):13-16.