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Original Research Article

A STUDY OF CLINICAL AND HEMATOLOGICAL PROFILE IN CHILDREN AFFECTED WITH SICKLE CELL DISEASE IN TERTIARY LEVEL HOSPITAL

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SCD- sickle cell disease, SCA- sickle cell anemia, ACS- Acute Chest Syndrome VOC- Vaso-occlusive Crisis, PICU- paediatric intensive care unit, HbF- fetal hemoglobin, HbS- sickle hemoglobin, Hb- hemoglobin, KGH- King George Hospital, AP- Andhra Pradesh, CBP- complete blood picture, MCV- Mean Corpuscular Volume, MCHC- Mean Corpuscular Hemoglobin Concentration, TLC- Total Leucocyte Count , NIS- National Immunization Schedule.

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Abstract

Background: Sickle cell anemia (SCD)is a hemoglobinopathy in which the red cells contain abnormal hemoglobin HbS causing myriad of manifestation ranging from decreased survival of RBC manifesting as anemia which may be asymptomatic to various crisis which are an emergency. The present study was undertaken to know the different clinical presentations and severity of disease in relation to their hematological profile in children admitted in PICU with SCD. The aim is to identify the clinical presentations and hematological profile patterns of SCD affected children. The objective is to study the patterns of sickness, clinical profile and hematological parameters of SCD affected children presenting to PICU of Tertiary care hospital. **Materials and Methods:** 50 children of age 6months to 12 yrs who were admitted to PICU with SCD (homozygous and compound heterozygous) were enrolled in the study. Complete history and clinical findings were noted and appropriate blood investigations like complete blood picture and Hemoglobin electrophoresis in all children and Chest Xray and USG abdomen in relevant cases were done. **Result:** Among 50 children in study group, maximum were between 7-9 years age (36%) with male predominance (1.7: 1). 92% of children were homozygous form of SCD and 8% were having sickle-thalassemia. Anemia was the most common (76%) presenting feature, followed by vaso-occlusive crisis (60%), splenomegaly, jaundice and febrile illness. There was significant difference in height, weight, number of transfusions, HbF levels and the number of episodes of painful crisis among SCD children using hydroxyurea. Data entered in strucued proforma and statistical analysis done using SPSS version 21. **Conclusion:** Children with Sickle cell disease suffer from chronic ill health requiring frequent hospital admission with high morbidity and mortality. Parental counselling and antenatal screening are essential to prevent occurrence of the disease in families with an already affected child. Mass screening of marriageable youth for SCD and premarital counselling should be done in the tribal population. Hydroxyurea should be initiated early in the disease process as there was significant difference in height, weight, number of crises, transfusions and HbF levels between children using and not using hydroxyurea.

INTRODUCTION

Sickle cell hemoglobinopathy is a group of hereditary disorders in which the red cells contain an abnormal hemoglobin i.e. HbS. Sickle cell disease is the commonest genetic disease worldwide. It is an autosomal recessive disease due to substitution of valine for glutamic acid in the Beta chain due to which red cells are rapidly hemolysed with a lifespan of 10 to 12 days. SCA occurs in India with a gene

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frequency of 4.3% and is relatively common in multiple states including Odisha, Maharashtra, MP, Jharkhand, Gujarat and in the tribal districts of AP. This disorder may manifest as Sickle cell trait (heterozygous state), Sickle cell disease (homozygous state) or as compound heterozygous state in combination with another abnormal Hb or thalassemia.

Clinical manifestations of sickle cell anemia begin early in life and they are extremely varied. Some patients are entirely asymptomatic whereas some are constantly troubled by painful episodes or vaso-occlusive crises. Icterus, pallor and mild Splenomegaly are the usual presentations in a young child. SCD may also manifest as febrile illness or vaso-occlusive crisis affecting microcirculation resulting in acute complications and chronic organ damage with high morbidity and mortality.

Children with homozygous inheritance and compound heterozygous inheritance present earlier in their life with growth retardation and require multiple transfusions.

This study is a hospital based observational study and is taken up to know the different clinical presentations and severities of SCD in relation to their hematological profile in children suffering from SCD and are admitted to PICU of a Tertiary care hospital.

MATERIALS AND METHODS

Study design: This study was a hospital based observational study done in children presenting to PAEDIATRIC INTENSIVE CARE UNIT AND WARD, King George Hospital, Tertiary care hospital, Visakhapatnam, for a period of 1 year from August 2021 to July 2022.

Inclusion criteria

All Children with age group between 6 months to 12 years, who were admitted to PICU with sickle cell disease (Homozygous and compound heterozygous forms): 41 Children who were diagnosed with homozygous form of sickle cell disease and 9 children with Sickle Thalassemia were included in the study.

Exclusion criteria

Children who were diagnosed with heterozygous form of sickle cell disease and hemoglobinopathies other than Sickle Thalassemia

Children, whose parents have not given consent for their child's participation in the study.

Methodology: Institute Ethics committee approval and informed consent from parents or care takers of the children enrolled was taken prior to the study. 50 children of age 6 months to 12 years who were admitted to PICU and ward of KGH with complications and those who meet the inclusion criteria were enrolled in the study. To know the clinical features and hematological parameters, thorough history taking and clinical examination was done. CBP and HPLC was done in all children and in relevant cases other investigations like Chest Xray and Ultrasound abdomen were done.

Statistical analysis:

Data entry was done in Microsoft EXCEL spreadsheet and the final statistical analysis was done with the use of Statistical Package for Social Sciences (SPSS) software version 21.0.

For statistical significance, P value of less than 0.05 was considered as significant.

RESULTS

In the present study, 50 children in the age group of 6 months to 12 years with sickle cell disease were enrolled in the study. Mean age of these children was 5.6±2.4 years.

46% of the total children in this study were from tribal villages near Visakhapatnam,20% from urban areas and 34% from rural areas.

In the present study, consanguinity was present in parents of 25(50%) children and remaining 25 children, there was no history of consanguinity. History of consanguineous marriages was more among the parents of children belonging to tribal areas.

In the study population, 88 % of children were immunized completely with NIS vaccines, and 12 % were inadequately immunized. 90% were not given special vaccines and only 10% were immunized with pneumococcal and meningococcal vaccines. None of them received vaccines for influenza or typhoid infections.

Among the study population, 16% weighed <10kgs, 70% weighed 10 to 20 kgs & 14% weighed 21 to 30 kgs. Mean weight of the children in the study population was 15.4 ± 4.6 kgs. Among the children in the study, Height of 24% children was ≤90 cms, 4% children between 91 to 100 cms, 66 % children was between 101 to 125 cms and 6% children was between 125 to 150cms. Mean height of the study population was 103.5±15cms.

Table 1: Demographic details of study population

Demographic details	Total (n=50)
Age distribution	
6m to 3y	12 (24%)
4y to 6y	15 (30%)
7y to 9y	18 (36%)
10y to 12y	5 (10%)
Mean age	5.6±2.4
Gender distribution	
Males	32 (64%)
Females	18 (36%)

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Age at diagnosis	
6-12 mnths	10 (20%)
1-2 yrs	13 (26%)
>2yrs	27 (54%)
Immunization status	
Immunized adequately (as per nis)	44
Immunized inadequately	6
Immunized with special vaccines pneumococcal, meningococcal & hib vaccine	5
Other vaccines (influenza, typhoid vaccines etc;)	Nil
Distribution according to locality	
Tribal	23
Non-tribal	27
Consanguinity among parents	
Yes	25
No	25

Table 2: Mean height and weight of study population according to different values of hemoglobin

Hb(gm%)	Frequency	Mean height(cms)	Mean weight(kgs)
4-6	7	108.14±18.9	16.7±4.8
6-8	40	102.15±15.5	15±4.5
>8	3	111.6±8.01	17.3±3.2

Table 3: Distribution according to the clinical presentation/findings

Feature	Frequency	Percentage
Anemia	38	76
Vasoocclusive crisis	30	60
Splenomegaly	25	50
Jaundice	22	44
Febrile illness	20	40
Hepatomegaly	10	20
Acute chest syndrome	4	8
Hepatosplenomegaly	3	6
Stroke	2	4

Among the study population, most common presentation was anaemia (76%), followed by vaso-occlusive crisis (60%), splenomegaly (50%), jaundice (44%), febrile illness (40%), hepatomegaly (20%), acute chest syndrome (8%) and stroke (2%).

Table 4: Distribution according to no. of transfusion in 1 year

No. of transfusions in 1yr	frequency	Percentage
<5	19	38
5-10	21	42
>10	10	20

Majority of children (42%) in this study received 5-10 transfusions per year. Among the children included in this study, 38% required < 5 transfusions in a year, 42% received 5-10 transfusion per year and 20% received > 10 transfusion per year.

Table 5: Hematological Profile after performing complete blood picture and HPLC, mean values of the hematological parameters were as follows

Parameter	Male (mean)	Female (Mean)	Total	P value
Hb %	7.07±0.7	7.2±1.02	7.09±0.88	0.822
RBC	3.4±0.3	3.4±0.38	3.4±0.3	0.90
Plt count	2.74±1.17	2.9±1.44	2.8±1.24	0.63
MCV	66.1±3.66	65.4±3.58	65.8±3.6	0.75
MCH	21.9±2.6	22.3±2.2	22.5±2.5	0.29
Hb S	56±4.5	53.7±2.6	55.5±4.2	0.022
Hb F	11.8±2.9	12.7±3.9	12.1±3.3	0.34
TLC	12.6±2.4	11.8±3.04	12.3±2.7	0.29
Hb A2	2.07±0.4	2.28±0.7	2.14±0.54	0.24

Among the study population, no. of children with their Hb % of 4-6 gm%, 6-8gms% and >8gms % was 7, 40 and 3 respectively with their mean height and weight of 108.14±18.9cms, 102.15±15.5cms , 111.6±8.01cms and 16.7±4.8kgs , 15±4.5kgs , 17.3±3.2kgs respectively.

In HPLC (High Performance Liquid Chromatography), 92% of study population showed presence of HbSS+A and 8% showed HbSβ thalassemia.

Table 6: Efficacy of hydroxyurea

	In cases using hydroxyurea	Cases not using hydroxyurea	P value
No. of painful crises in 1 year	5.2±3.9	4.6±5	0.64
Total no. of transfusions in 1 year	2.91±0.99	3.77±1.73	0.04

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Height	109.2±14.4	98.7±15.9	0.018
weight	17.1±4.8	13.9±3.9	0.013
HbF	14.4±2.6	10.2±2.5	<0.00001

Out of 50 children in the study, 28(62%) were using hydroxyurea, 4(10%) were using deferasirox, 1 child was using both hydroxyurea and deferasirox and17(37%) were using neither of the drugs. The mean age of children using hydroxyurea was 6.8±1.8 years.

There is statistically significant difference in height ($P < 0.01$), weight ($P < 0.01$), no. of transfusions ($P < 0.04$) and HbF levels (P value < 0.00001) between the cases using and not using Hydroxyurea.

DISCUSSION

Sickle cell disease is one of the common inherited hemoglobinopathies known and is one of common causes of anemia in children. Prevalence of sickle cell disease in India is 5.7%.

In the present study, a total of 50 children of 6 months to 12 years were studied for a period of 1 year. Out of which 16% were diagnosed between 6 months to 12 months, 22 % at 1 yr to 2 yrs and 64% at age more than 2years. The lowest age at presentation was 6 months and highest age was 6.5 years. Imoudu A Iragbogie et al,[1] in their study on pediatric sickle cell disease reported 13% diagnosed at age 0 to 5 months, 64 % at 6 months to 12 months, 13% at 13 months to 2 years and 10% at more than 2 years. This is in contrast to the present study, because majority of the cases in the present study were diagnosed after 2 years of age.[2,3] Mustafa et al,[4] reported that 80% were diagnosed at age less than 5 years. Snehamayee naik et al,[3] reported mean age at diagnosis 2.79 years with lowest age at 6 months and highest at 12 years. Variation in the age at which sickle cell disease is diagnosed is due to the variation in the genotype of sickle cell disease. There are several genotypes of sickle cell disease. Most common are African, Arab etc. In Arab genotype, child usually is diagnosed at later age.[5-10]

In this study, 32 (64%) were male and 18 (36%) were female. Imoudu A et al,[1] reported males 61% and female 39%. Viviane Feza Bianga et al,[2] in their study reported that, out of 55 cases, 31 (54.4%) were males and 24 (43.6%) were females. In the study by Snehamayee et al,[3] 43 (71.6%) were male and 17 (28.3%) were females and Varsha shah et al,+[9] reported. 4% male and 37.6% females. Male predominance in the present study could be due the tendency of parents to seek for medical attention for male children compared to female children.

In present study, 44 children (88%) were immunized adequately with all vaccines in NIS and 6 children (12%) were not immunized as per age with vaccines of NIS. Imoudu et al,[1] in their study reported that 58.5% were immunized adequately and 41.5% were inadequately immunized. Infection is the most common cause of morbidity and mortality in children with sickle cell disease. Major risk factor for increased vulnerability to infection is splenic dysfunction. Organisms most commonly involved are streptococcus and H.influenza. Osteomyelitis is most often caused by Salmonella. All sickle cell disease affected children should be given prophylaxis with oral antibiotics upto 5 yrs of age and Pneumococcal vaccine is advised. As spleen is non-functional in these patients, to prevent infections, they should be vaccinated adequately and vaccination with pneumococcal, meningococcal vaccines should also be done as risk for life threatening infection with capsulated organisms is very high in these children.

Among 50 children in this study, mean weight was 15.4±4.6 kgs. With mean weight in male children15.7±5.02kgs and that of female children 14.9±3.65kgs. Mean height was ranging between 125 to 150 cms. Mean height was 104±16.7 in male children and 102±14.9 cms in female children. Imoudu et al,[1] reported Mean weight of male children as 19.08±8.4 kgs and that of female children was 18.14±6.5 kgs and mean heights in male and female children was reported as 113.6±22.5 cms and 113.21±18.8cms respectively.

Growth retardation in SCD children can begin as early as 1-2 yrs. There are multiple reasons for growth retardation. Most common cause is, these children suffer chronic ill health, which can be frequent episodes of crisis due to VOC, splenic sequestration crisis in addition to increased predisposition to infections. All these factors have adverse influence on growth and development of these children in addition to high prevalence of malnutrition as majority of children belong to low socio-economic background.

Children with sickle cell disease can present with varied clinical manifestations. VOC is the major manifestation of SCD and presents mostly as acute painful episodes. Usual presentations in young child are icterus, pallor due to anemia and mild splenomegaly. Disease may manifest as febrile illness since these children are more prone to infections. ACS is a type of VOC affecting lungs. 10-20% can have acute onset or silent stroke before 18 years age. Spleen undergoes auto-splenectomy and is often not palpable beyond 6years of age. Hence these patients should be brought for follow up regularly. Patients and their family should be educated about nature of the disease, its outcome. In the present study, anemia was the most common presentation (76%), followed by vaso-occlusive crisis (60%), splenomegaly (50%), jaundice (44%), fever (40%), hepatonegaly (20%), acute chest syndrome (8%) and stroke (2%). 3 children (6%) had Hepatosplenomegaly. Out of 25 children who had palpable spleen, 4 (16%) had grade 3 splenomegaly, 10 (20%) of them has grade 2 splenomegaly and 11 (22%) children had grade 1 splenomegaly. Kinjal Patel et al,[10] reported vaso-occlusive crisis as the

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most common presentation, followed by anemia, febrile illness, splenomegaly, jaundice, acute chest syndrome and stroke. Viviane Feza et al,[2] (45.5,%) and Snehamayee et al3 (90%) reported anemia as the most common presentation, which is similar to the present study.

The mean Hb in this study was 7.09±0.88 gm%. The lowest value of Hb at the time of diagnosis was 4.5 gm % and highest was 8.3 gm %. The hematological parameters of the present study are similar to the results of the study done by varsha shah et al.[9]

In this study, out of 50 children 28 (56%) children were using hydroxyurea.

The mean number of vaso-occlusive crises were 4.8 ± 3.18 in cases using hydroxyurea and 4.1±15.9 in cases not using hydroxyurea. In study done by Dipti Jain et al5, the mean number of vaso-occlusive crises before and after 24 months of starting hydroxyurea were 4.27±1.99 and 0.15±0.47 and Sunil K. Pondugula et al,[6] it was 5±1.44 in placebo group and 0.57±0.68 in hydroxyurea group after 12 months of the study. Hydroxyurea is the only effective drug proved to reduce painful episodes and ameliorate the severity of SCD. It also decreases hemolysis and need for blood transfusion. In the present study, there was no significant difference between the mean number of vaso-occlusive crises in those using and not using hydroxyurea which might be due to lack of compliance and also due to poor follow up visits. Children using hydroxyurea might need dose adjustment of hydroxyurea during follow up visits every 8 weeks after assessing the efficacy of drug and by finding any adverse effects of the drug as it is a myelosuppressive agent.

Clinical picture of SCD is heterogenous with wide variations in clinical severity. Children from India belong to Arab. Indian haplotype has mild disease due to structural changes in β globin gene which increase HbF level. HbF decrease polymerization of HbS molecule there by decreasing the severity of clinical picture. This may be the reason that in the present study Blood transfusion requirement is not the same. In the present study, mean number of transfusions were 2.91±0.99 and 3.77±1.73 in cases using and not using hydroxyurea respectively, which is significant (P value 0.04). Dipti Jain et al,[5] reported mean number of transfusions 0.77±1.33 and 0.15±0.5 before and 24 months after starting hydroxyurea and it was reported as 1.90±1.45 and 0.30±0.47 in placebo and hydroxyurea groups after 12 months by Sunil K et al.[6]

Serum ferritin should be checked in cases receiving repeated transfusions, so that iron chelating therapy can be initiated in order to prevent the features of iron overload. In the present study only 1 child, whose transfusion requirement is >10 per year was started on deferasirox to prevent iron overload.

In present study mean heights in those using and not using hydroxyurea were 109.2±14.4 and 98.7±15.9 respectively (P 0.01), and the difference is significant. Sunil K. et al,[6] reported mean heights in hydroxyurea group and placebo group as 111.67±17.19 and 104.27±19.76 respectively.

In present study mean weights in those using and not using hydroxyurea were 17.1±4.8 and 13.9±3.9 respectively (P 0.01), and the difference is significant and sunil K. et al6 reported mean weights in hydroxyurea group and placebo group as 21.77±7.64 and 19.67±6.75 respectively. In present study mean Hb F% in those using and not using hydroxyurea were 14.4±2.6 and 10.2±2.5 respectively (P< 0.0001), and the difference is significant. This increase in HbF in patients using hydroxyurea has protective effect and hence these patients required less number of transfusions, when compared to those not using hydroxyurea. According to recent guidelines, hydroxyurea should be started as early as 1 year of age, to prevent the occurrence and frequency of painful crises, to decrease the frequency of transfusions and also to prevent serious manifestations like stroke. In study done by Sunil K. et al6 mean HbF in hydroxyurea group and placebo group were 39.77±8.92 and 24.91±5.28 respectively.

History of consanguineous marriages is more among the parents of children belonging to tribal areas. Hence parents should be counselled about the disease which can be inherited by other children in their family i.e; siblings of the patients, and should get those children screened for sickle cell disease, so that early detection can be done which helps in preventing serious manifestations like stroke.

CONCLUSION

Sickle cell disease is an autosomal recessive chronic hematological disorder of varied clinical presentation requiring frequent hospital admission with high morbidity and mortality. Parental counselling and antenatal screening are essential to prevent occurrence of the disease in families with an already affected child.

Multipronged community awareness approach is needed. Mass screening of marriageable youth for SCD and premarital counselling should be done in the tribal population. Acute clinical events in sickle cell disease can have significant morbidity and mortality in paediatric age group. Nutritional status of the child should be maintained in optimal state to prevent complications associated with the disease process.

There was significant difference in height, weight, number of crises, transfusions and HbF levels between children using and not using hydroxyurea hence hydroxyurea should be initiated early in the disease process as it greatly decreases the morbidity associated with the disease process and improves the living of the individuals affected by the disease.

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