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STUDY OF CLINICAL PROFILE OF CHILDREN WITH SICKLE CELL ANEMIA AND EVALUATION OF CARDIAC FUNCTION IN THEM USING 2D ECHOCARDIOGRAPHY

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ABSTRACT **Introduction:** Sickle-cell anemia (SCA), a severe form of sickle-cell disease, is a global hemoglobinopathy with a significant on affected individuals. The disease is characterized by a single point mutation in the β-globin gene, leading to the synthesis of unstable sickle haemoglobin (HbS). This results in HbS polymerization, oxidative stress, inflammation, and endothelial activation. Despite advancements in treatment strategies, mortality remains high in this population. Cardiac complications, although recognized, are not well-explored. This study aims to investigate the clinical profile of children with SCA and assess cardiac function using 2D echocardiography.

Aims & Objectives:

1.To assess clinical profile of children with sickle cell anemia

2.Evaluation of cardiac function in them using 2D Echocardiography.

Materials and Methods:

This prospective observational study was conducted at a Government General Hospital, enrolling children aged 5 to 12 years with SCA.Detailed demographic information, family history, and clinical data were collected. All enrolled children underwent investigations, including complete blood count (CBC) and 2D Echocardiography was performed by a cardiologist. Data was analysed with appropriate statistical methods. **Results:** The study included 100 children with SCA, with a mean age of 8.7 years. Clinical presentations revealed a prevalence of vascular occlusion (73%), splenomegaly (14%), infections (7%), and hepatomegaly (6%). Electrocardiographic parameters indicated sinus bradycardia (24%), left atrial enlargement (19%) and diastolic dysfunction (84%). Mean values of echocardiographic parameters were also reported. Hydroxyurea therapy showed statically significant improvement in haemoglobin levels, number of blood transfusions, hospital admissions and other clinical parameters. **Conclusions:** This study provides valuable insights into the clinical profile especially cardiac abnormalities among children with SCA.All SCA childrens should be routinely screened for cardiac abnormalities and counselled appropriately. The clinical benifits of hydroxyurea therapy highlights the importance of early initiation of this drug in all childrens with SCA.

KEYWORDS : Sickle cell disease, Cardiac abnormalities, Vaso-occlusive crisis, Hydroxyurea

INTRODUCTION:

Sickle cell disease is a hemoglobinopathy affecting millions worldwide. A single point mutation in the 6th codon (GAG instead of GTG; valine replacing glutamic acid) of the β globin gene results in the synthesis of the unstable sickle hemoglobin (HbS) which causes HbS polymerization, production of reactive oxygen species (ROS) and triggering a cascade of inflammation and endothelial activation.

Sickle cell anemia (SCA) is the more severe genotype of sickle cell disease (SCD). It represents the homozygous condition of the beta S (βS) globin allele Sickle cell trait(SCT) prevalence in India ranges from 5% to 7 % and that of SCA from 0.4% to 1 %. The prevalence of sickle cell carriers varies from 0.8 % to 35.1 % in different tribal populations Clinical characterization of SCA includes hemolysis, chronic and acute inflammation, vaso-occlusive complications, multiple organ damage, and reduced patient survival. Even with improved treatment, including the early usage of prophylactic antibiotic regimens, judicious blood transfusions, and the administration of hydroxyurea in selected patients, mortality remains high for this population

The symptoms and complications of sickle cell disease (SCD) arise mainly from the crises (clinical and subclinical). Activation and damage of endothelial cells with activation of adhesion molecules lead to inflammation, release of C-reactive protein (CRP) and other inflammatory mediators and subsequent enhancement of ischemia.

Heart disease represents an important cause of mortality and morbidity in SCD. However, the knowledge on the involvement of cardiac function is scarce. Cardiac abnormalities in patients with SCA are due to anemia, volume overload, myocardial fibrosis and pulmonary HTN. Compared with controls, left ventricle end-systolic diameter (LVESD), end-diastolic diameter(EDD), early-diastolic mitral flow velocity (EDMFV)and late-diastolic mitral flow velocity (LDMFV) were significantly more in the patients with SCA[10]. Although, the left ventricular ejection fraction (LVEF)s were in the normal ranges in patients and controls, both LV and RV MPI(myocardial performance index)were significantly more in patients than those in normal children[5].MPI may be a useful non-invasive and sensitive tool for the assessment of the sub-clinical cardiac LV and RV dysfunctions in patients having SCA. The current study aimed at evaluating cardiac function in children with SCA using 2D ECHO.

MATERIALS AND METHODS:

Study design: prospective observational study

Study population: All SCA children in the age group of 5 to 12 years admitted in paediatric wards and ICU in Government general hospital, KAKINADA

Study duration: June 2021 to November 2022(18 months duration of study)

Inclusion criteria: Childrens diagnosed with sickle cell anemia by HB electrophoresis

Exclusion criteria: Childrens with SCA associated with congenital heart disease or acquired heart disease

Methodology:

Prior permission from institutional ethics committee was taken. Informed consent was taken from the care givers of children. Detailed history regarding demography details, family history of SCA/SCT, hospital admissions, number of blood transfusions, compliance with drugs like Hydroxyurea and Folic acid and relevant physical examination was done in all enrolled children. Investigations including CBP and 2D-ECHO was done for all children. Other investigations were done whenever required. The data collected in a

predesigned proforma and the results were tabulated and statistically analysed using SPSS 21 software

2D-ECHO wss done by Cardiologist on admission and was repeated after 3 months.

RESULTS:

In the present study, children of 5 -7 years age group constituted 26%,8-10 years age group were 34% and 11-12 years were 40%. The mean age of the study subjects was 8.7 years ± 2.47 SD, 48% were boys and 52% were girls,72% were illiterate and 28% were literate ,26% of study participants resided in urban areas, 43% in tribal areas and 31% in rural areas, 12% of study participants belonged to upper class, 30% to middle class and 58% to lower class. Out of 100 children with SCA , 89% had undergone blood transfusion and 11% had no blood transfusions.

Table:1 Demographic details of study population

Demographic details	Total (n=100)	Percentage
Age distribution		
5 to 7 yrs	26	26%
8 to 10yrs	34	34%
11 to 12 yrs	40	40%
Mean age	8.7+/- 2.47 SD	
Gender distribution		
Male	48	48%
Female	52	52%
Literacy status of parents		
Literate	28	28%
Illiterate	72	72%
Residence		
Urban	26	26%
Rural	43	43%
Tribal	31	31%
Socioeconomic status		
Upper class	12	12%
Middle class	30	30%
Lower class	58	58%
History of blood transfusion		
Yes	89	89%
No	11	11%

In the present study, 73% of subjects had Vascular occlusion,14% had Splenomegaly , 7% had infections and 6% had hepatomegaly

Table:2 Distribution according to clinical presentation/findings

Feature	Frequency	Percentage
Vascular occlusion	73	73%
Splenomegaly	14	14%
Infection	7	7%
Hepatomegaly	6	6%

In the present study, only 24% of study subjects had sinus bradycardia, 4% had sinus tachycardia. 19% had Left Atrial Enlargement.Out of100 study subjects 22% had Prolonged QTC, 6% had Premature Ventricular Complex,9% had Wandering Pacemaker,16% had Systolic Dysfunction. 84% of study subjects had Diastolic Dysfunction

Table:3 Distribution according to ECG parameters

ECG parameters	Frequency	Percentage
Sinus bradycardia	24	24%
Sinus tachycardia	4	4%
Left atrial enlargement	19	19%
S.dysfuntion	16	16%
D.dysfuntion	84	84%
Prolonged QTC	22	22%
Premature ventricular complex	6	6%
Wandering pacemaker	9	9%

Table: 4 Mean values of 2D ECHO Parameters in the study population

Parameters	Values(Mean ±SD)
Mean of AOD(aortic dissection)	26.6±2.7
Mean of LAD(left anterior descending)	38.0±4
Mean of LVM (left ventricular mass)	206.2±44.3
Mean of LVMI(left ventricular mass index)	135.0±25.8
Mean of IVSD(interventricular septum thickness in diastolic)	10.5±1.9
Mean of LVPWD(left ventricular posterior wall thickness in diastole)	11.0±1.7
Mean of LVIDD(left ventricular internal diameter in diastole)	55.6±1.4
Mean of LVIDS(left ventricular internal dimensions at end systole)	35.2±3.1
Mean of LVEDV(left ventricular end diastolic volume)	118.2±16.7
Mean of LVESD(left ventricular end systolic diameter)	48.9±9.7
Mean of RWT(relative wall thickness)	0.4±0.08

Table:5 Distribution of study subjects based on Impact of hydroxyurea therapy– before treatment and after treatment.

VARIBLE	BEFORE GIVING .HU		AFTER GIVING HU		P-value
	Mean	SD	Mean	SD	
HAEMOGLOBIN	8.584	.8532	9.259	.7952	<0.001
TLC	8868.13	1667.387	6298.63	652.631	<0.001
PLATELET COUNT	235890.38	48468.842	249977.85	80191.207	0.116
VASOOCCLUSIVE CRISIS	5.06	.789	1.46	.501	<0.001
BLOOD TRANSFUSIONS	2.55	1.029	.91	.830	<0.001
HOSPITAL ADMISSIONS	2.05	1.431	.53	.502	<0.001

In the present study, all the subjects were given hydroxyurea therapy and after the therapy all of them were evaluated. The mean hemoglobin of them before giving hydroxyurea was 8.584± 0.85SD which increased to 9.259± 0.795SD after use of hydroxyurea which was statically significant (P value <0.001).There was statically significant difference between mean total leukocyte count, platelet count, vasooclussive crisis, blood transfusions and hospital admissions before and after giving hydroxyurea in the study. The mean total leukocyte was 8868.13± 1667.387SD which decreased after treatment to 6298.63 ± 652.6SD ,mean platelet count before was 235890.38± 48468.842 SD which increased after treatment to 249977.85 ± 80191.207 SD. Mean Vaso-occlusive Crisis before was 5.06± 0.7 SD which has decreased after treatment to 1.46±0.5 SD, mean blood transfusion before treatment was 2.55± 1.02 SD which has decreased after treatment to 0.91 ±0.8 SD,mean hospital admissions before treatment was 2.05± 1.4 SD which decreased after treatment to 0.53 ±0.5 SD .

DISCUSSION:

Age:

In present study, children with SCA in the age group of 5 to 12 were included. The mean age of the children was 8.7 years ± 2.47 SD. Most of the subjects belonged to age group of 11 to 12 (40%) years. In the study by, Ahmed et al [1]., among 5-15 years old sickle cell anaemia cases, mean age of cases was 8.95 years ± 3.2 SD. Iragbogie et al [2]study, in Nigeria among sickle cell disease children of age 2- 16 years,mean age of children was 6.97 ± 3.63 years. Bianga et al [7], in republic of Congo and reported that mean age of cases was 8.4 years. Shrivastava et al [4]study , in Raipur among 8 to 18 years old sickle cell anaemia cases reported that the age distribution among sickle cell patients below 13 years was 40% and above 13 years was 60%. Ribera et al [3] study, in Brazil among under 20 years age reported that mean age of cases was 8 years.

Gender:

The incidence of Sickle cell disease is not gender related since it is transmitted as an autosomal recessive disorder ,In the present study there was slightly female predominance with male to female ratio of 0.92:1. In a study by Iragbogie et al [2]., it was reported as 1.6: 1. It was reported by Swarnkar K et al as 0.37: 1 by Ahmed et al [1] as , 1.2: 1 by Biang et al [7]as , 1.1: 1 by Srivastava et al [4] as, 1.2: 1 and by Ribera et al [3] and Blanc et al [5] as 1.3:1

Anthropometry:
Sickle cell anemia is a chronic disease it affect the physical growth of the SCA children .In the present study, mean weight of study subjects was 25.8±7.2 kgs in the present study and mean height was 124.68±12.4 cm.The mean height of the subjects was lower than the reference standards, However this was not statically significant .Ribera et al [3]study, reported mean weight average as 24.6 kg for weight and mean-height as 120.1 cms in the sickle cell patients.

Education Status Of The Parents:
In the present study, 72% were illiterate and 28% were literate. Bianga et al [7]., had r eported that 54.5% of children had a primary education level, and 34.5%had no education level.

Socioeoconomic Status:
children with low socioeconomic status have worse nutritional status and who are undernourished report higher disease severity and low health related quality of life.In the present study, 12% of study subjects belonged to upper class, 30% to middle class and 58% to lower class. Majority of the subjects belong to lower SES(58%). 26% of study subjects in present study were from urban areas, 43% from tribal areas and 31% from rural areas. Most of the children in present study were from tribal area (43%).In a study by Iragbogie et al [2], 38% of the subjects belonged to lower socioeconomic status which is lesser than the current study.In a study by Ahmed et al [1], 82% were from low socioeconomic status, 10% moderate and 8% high socioeconomic status.Swarnkar K et a [6] , reported that 67.5% of cases were of lower socio-economic status.

Blood Transfusion:
In the present study, 89% of study subjects had undergone blood transfusion which is similar to study by Ribera et al [3],who reported that 86.7% of cases had blood transfusions. Bianga et al [7]study , reported that 76.4% children received blood transfusions

Cardiac Activity And Ecg Changes:
Cardiac abnormalities in patients with SCA are due to chronic anaemia, volume overload, myocardial fibrosis, pulmonary HTN and deposition of iron in cardiac tissue due to iron overload secondary to multiple blood transfusions. In the present study, only 24% of study subjects had sinus bradycardia, 4% had sinus tachycardia. 19% had Left Atrial Enlargement.Out of100 study subjects 22% had Prolonged QTC, 6% had Premature Ventricular Complex,9% had Wandering Pacemaker,16% had Systolic Dysfunction. 84% of study subjects had Diastolic Dysfunction. Shrivastava et al [4] , reported that electrocardiogram was abnormal in 90% of sickle cell patients. In the electrocardiographic study, tachycardia was seen in 14% cases, sinus arrhythmia in 44% cases, left axis deviation in 42% cases and right ventricular hypertrophy in 20% cases. There was a significant change observed in PR interval in 44% cases, QTc interval in 20% cases, left ventricular hypertrophy in 44% cases and biventricular hypertrophy in 10% cases. Ribera et al [3], reported that in comparison to the non-sickle cell anaemia group, the mean left ventricle z-score in the sickle cell anaemia group was 13 times higher and it was around 5 times higher in either the posterior wall or the right ventricle. Comparing the sickle cell anaemia group to the non-sickle cell anaemia group, the number of echocardiographic alterations in the left atrium, right ventricle, septum, and left ventricle was 19 times,4.1 times , 3.4 times , and 24.6 times greater respectively. Only the sickle cell anaemia group (44.4%) showed changes to the posterior

Sickle Cell Features:
In present study, 73% of study subjects had Vascular occlusion ,14% had Splenomegaly, 7% had infections and 6% had hepatomegaly (HP). Majority of the study subjects had Vascular occlusion(73%).In a study by Iragbogie et al [2], 22% had steady state hepatomegaly, and 27% had steady state splenomegaly. 10% had experienced an episode of ACS within the 12-months preceding recruitment, while 40% had atleast 1 acute bacterial infection, which is higher than that reported in the present study.In a study by Ahmed et al., 83% experienced painful crisis, 70% with head foot swelling, 7% with hepatomegaly, 2% with splenomegaly and 2% with hepatosplenomegaly. Swarnkar K et al., reported that among vaso-occlusive crisis ,the most frequently experienced was hand-foot syndrome(51.7%) which was followed by splenic sequestration (20.69%) and the most frequent infection reported was septicemia (15.51%). Bianga et al [7] , reported that anemia was found in 45.5%, followed by vaso-occlusive crises in 20%. However, other circumstances such as jaundice, respiratory difficulty and splenomegaly were found only in 3.6%. Blanc et al [5] reported thoracic vaso-occlusive events in 14% patients.

Haemoglobin:
In present study, mean hemoglobin was 8.5 gm/dl with SD 0.8gm/dl.In a study by John et al., the mean hemoglobin was 6.5gm/dl SD 0.44gm/dl.

Bianga et al [7], reported the mean hemoglobin level as 6.425 g/dl with SD 1.59 and.Ribera et al., reported as 8.3mg/dl.Blanc et al [5], reported as 86.1 ± 16.5 g/L .

Mean values of 2D ECHO Parameters:
As shown in the table there were higher values observed in currents study when compared with Blanc et al [5], and lesser than Gustavo et al [10],

Impact of hydroxyurea therapy– before treatment and after treatment:
In the present study, there was statically significant difference in mean haemoglobin, leukocyte count, vasooclussive crisis,number of blood transfusions and hospital admission after giving hydroxyurea to the study subjects with P value <0.001. The mean hemoglobin of subjects before giving hydroxyurea was 8.584± 0.85SD which increased to 9.259± 0.79. Mean total leukocyte count before therapy was 8868.13± 1667.387SD which decreased after treatment to 6298.63 ± 652.6SD.Mean platelet count prior to treatment was 235890.38± 48468.842 SD which decreased after treatment to 249977.85± 80191.207SD after treatment. Mean Vaso-occlusive Crisis before treatment was 5.06± 0.7 SD which decreased after treatment to 1.46±0.5 SD .Mean blood transfusion before treatment was 2.55± 1.02 SD which decreased after treatment to 0.91 ±0.8 SD.In the present study Mean hospital admissions before treatment was 2.05± 1.4 SD which decreased after treatment to 0.53 ±0.5 SD . Karkosa K et al [9] , reported that the total number of SCA-related admissions during study period declined from 67 admissions/100 patient-years to 39 admissions/100 patient due to hydroxyurea therapy. Akinyenmi et al [8] , in the study reported that when compared to baseline values and values after 12 months of hydroxyurea treatment, there was a significant reduction in the frequency of vaso-occlusive crises, blood transfusions, hospitalizations, length of hospitalisation, and episodes of acute chest syndrome. .The median haematocrit level rose from 26 to 28% when the haematological parameters at baseline and 12 months after the start of hydroxyurea were compared (p 0.0001). The median white blood cell and platelet counts decreased from 11.1 to 6.2 10^9/l and 411 to 337 10^9/l, respectively, while the median percentage foetal haemoglobin level also increased from 7.8 to 14% (p 0.0001).

CONCLUSION:
Sickle cell anemia is a chronic hematological disorder of varied clinical presentation requiring frequent hospital admissions with high morbidity and mortality. The symptoms and complications of sickle cell disease arise mainly from crises. Most important crisis being vasooclussive crisis which can cause ischemic damage to various organs. Children with SCA suffer from chronic ill health due to these vasooclussive crises requiring frequent hospital admissions. Blood transfusionsare often administered in these children not only to treat anemia and vasooclussive crises but also reverse various other crises like aplastic crisis, splenic sequestration crisis, hyper hemolytic crisis,stroke , acute chest syndrome etc. Heart disease represents an important cause of mortality andmorbidity in SCD.Cardiac abnormalities in patients with SCA are due to chronic anaemia, volume overload, myocardial fibrosis, pulmonary HTN and deposition of iron in cardiac tissue due to iron overload secondary to multiple blood transfusions

There was significant difference in mean haemoglobin, number of blood transfusions, vasooclussive crises and hospital admissions between childrens using and not using hydroxyurea. Hence hydroxyurea should be initiated early in disease process, it greatly decrease the morbidity and mortality including the SCA related cardiac effects thereby greatly improving quality of life among children affected by this chronic hematological disorder

Limitations:
The main limitation of this study is that the evaluation of diastolic function by Doppler is not precise because Doppler Echocardiography permits only an indirect measure

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