www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i6.44

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Original Research Article

Clinico- haematological Profile of Sickle Cell Disease and Sickle Cell Beta-Thalassaemia in the State of Odisha

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Abstract
Background: *Hemoglobinopathy is a group of inherited disorders characterized by structural variations of the hemoglobin molecule. Sickle cell disease, beta thalassemia and sickle beta thalassemia constitute the major genetic blood disorders in Odisha. The aim of this study was to determine the clinico-haematological patterns of patients with sickle cell haemoglobinopathies.*
Methods: *Blood samples are collected from 88 subjects diagnosed as sickle cell disease and sickle β+ thalassemia after taking informed consent as well as appropriate ethical clearance. Screening is done by sickling test and capillary electrophoresis.*
Results: *Out of 88 patients 43 patients (48.9%) are Sickle Cell Disease (28 males and 15 females) and 45 patients (51.1%) are S/ß Thalassaemia (37 males and 08 females) included in the present comparative study. Results are statistically analysed and tested using student's t-test for significance. Since there is no statistically significant sex differences observed for different haematological indices in the studied diagnostic categories, their mean values are pooled together for comparison purposes. Statistically significant higher mean values were observed in sickle beta thalassemia patients i.e. HbA mean 3.69±2.94 P value <0.0027, HbA2 mean 4.12 P value <0.017 than in the sickle cell Disease. In Sickle Cell Disease the mean height is 145.69±31.08 P value <0.001, serum ferritin level 737.8±772.6 P value <0.0003 and HbS levels72.8±8.03 P value <0.01, which is significantly higher than Sickle Cell Beta Thalassemia. Hydroxyurea was administered orally at doses between 10 and 20 mg/kg per day. There are overall increases in HbF in most of the cases with reductions in the frequency of recurrent blood transfusion, vasoocclusive crisis and avascular necrosis.*
Conclusion: *Molecular diagnosis of Hb D, HbE or Hb S gene is required along with characterization of β-thalassemia mutations in this region.*
Abbreviations: *HbS –Sickle cell Haemoglobin, HbF :foetal Haemoglobin and S/ßThalassaemia: Sickle beta Thalassemia*
Keywords: *Hemoglobinopathy, sickle cell disease, S/ßThalassaemia,*

Introduction

The combination of the sickle cell mutation and beta-thalassemia (β-Thal) mutation gives rise to a compound heterozygous condition known as Hb S/β thalassemia (Hb S/β-Thal), which was first described in 1944 by Silvestroni and Bianco [(1)]. Sickle β thalassemia is a major haemoglobin disorder responsible for most of the symptoms and

complications of sickle cell disease. Patient's heterozygous Sickle cell Haemoglobin (HbS) and beta Thalassemia (β-Thal) may suffer sickle cell disease but their symptoms are less severe than the homozygous sickle cell disease, which is known as Sickle cell beta thalassemia (Hb S/β-Thal) [(2)]. Hb S/β-Thal is classified according to severity as sickle cell β° thalassemia in which β Globin production is zero, Sickle cell β⁺ thalassemia where β globin is produced is less than normal and the milder form is designated as Sickle cell β⁺⁺ thalassemia with high Hb A (20-30%) Increased Hb A2 is the diagnosed feature of β thalassemia is found both in β° & β⁺ thalassemia [(2)]. The symptoms of Sickle cell disease and Sickle cell β° thalassemia is almost similar involving irreversible sickle cell, severe anaemia and frequent vaso occlusive crisis[(3)]. In HbS/β-thalassaemia, the β-thalassaemia gene interacts with the HbS-gene to increase the level of HbF (usually>15%) and HbS from above 50% to a level near that observed in sickle cell disease (HbSS) individuals [(5)]. Relative higher level of HbF in this double heterozygous condition may be beneficial by decreasing HbS polymerization while adding a new detrimental effect by aggravating the mild haemolytic components of HbS gene. The net phenotypic expression of the interaction of two genes is remarkably variable i.e. completely asymptomatic condition at one end while at the other end of the spectrum, the severity can be that of SCD or β+-Thalassaemia [(6,7)]. Changes in haematological parameters include microcytic red cell, target cell, 60-90%of HbS, 0-30% of HbA, 1-20% of HbF [(8)]. The type of β-thalassaemia gene that is co-inherited with HbS gene may partly explain such variations which need to be corroborated by further study. Moreover, the high incidence of iron deficiency and α-thalassaemia gene in our population may alter the picture significantly which is relevant to their management. Few published study regarding vascular phenotypes of SCD (HbSS) and genotype-phenotype expression of HbS –β-thalassaemia are available from Orissa as well as from the whole country. Orissa is a state where there is higher percentage of HbF in SCD (HbSS) and high prevalence of both HbS and β-thalassaemia genes and thus HbS-β-thalassaemia. The study of these haemoglobinopathies has a tremendous importance in our state.

Material & Method

Study Design: Cohort Study (Prospective Observational study) with asking research questionnaire developed for this purpose,

Study Location:- This study is based on 43 cases sickle cell disease and 45 cases of sickle beta thalassemia selected from the Out Patient Department (OPD) cases in the clinical haematology, S.C.B. Medical Collage Hospital, Cuttack from 20013 to 2016. Their family history, name, age, sex, caste, native place, pedigree chart and clinical sign symptoms were rerecorded after taking written consent. About 3-4 ml IV blood samples were collected using EDTA as anti coagulant by disposable syringe from each patient. Clinical sign and symptoms related to haemoglobinopathy and laboratory investigations were done by automated blood cell counter and haemoglobin electrophoresis. Sickling test was done by sodium matabisulphite solution as a reducing agent for the presence of sickle cell haemoglobin.

Inclusion Criteria: All patients who diagnosed or suspecting to have a sickle cell haemoglobin-opathies and confirmed by positive sicklling test.

Exclusion criteria: Healthy people who suspected to have sickle cell haemoglobinopathies with negative sickling test.

Ethical issues

This study confirms to the ethical principles of medical research developed by the World Medical Association Declaration of Helsinki. Ethical clearance was given by the Institunal Ethics Committee S.C.B Medical College Cuttack, 753007 [Orissa] IEC/IRB No:94/24.02.2011.

Data Analysis

All data obtained with questionnaire and biochemical analysis were analyzed using the

Graph Pad program for Windows (Graph Pad Software). Statistical significance was accepted when P value is ≤ 0.05

Results

There were in all 88 cases, out of which 43 (28 males and 15 females) were sickle cell Disease and 45 cases (37 males and 08 females) were sickle cell β+ thalassemia included in the present comparative study. We observed 28 male (65.11%) and 15 female (34.88%) patients in Sickle Cell Disease, M:F was being 2:1 approximately. There were 45 cases of Sickle beta Thalassemia with 37 male and 08 female the M: F ratio was being 4.6:1.

Table No 1: Sex Distribution of Sickle Cell Disease and Sickle B+ Thalassemia
SCD: sickle cell disease, SBTβ+: sickle beta+ thalassemia

Disease	SCD			SBTβ+		
Sex	Male	Female	Total	Male	Female	Total
Number	28	15	43	37	08	45
Percentage	65.11%	34.89%		82.22%	17.78%	

Table No 2: Mean Age and Standard Deviation
SCD: sickle cell disease, SBTβ+ sickle beta thalassemia

Disorder	Minimum	Maximum	Median	Total	Mean ±S/D
SCD	02	62	18	43	20.14±13.16
SBT	04	34	17	45	17.16±8.7

Table No 2: Out of 45 cases of Sickle Beta Thalassemia between the ages of 4 to 34 years, the median age was being 17 years and 43 cases of Sickle Cell Disease between the ages 02 to 62 years, the median age was being and 18 years. The mean age and Standard Deviation was being 17.16± 8.7 and 20.14±13.16 in both the observed groups. The P value (<0.2), which was statically insignificant. There were 41cases (91%) has been seen below 30 years of age in Sickle beta Thalassemia and 37(86%) in Sickle Cell Disease.

Table No:3 Clinical Finding
R-VOC: recurrent vaso occlusive crisis, AVN: avascular necrosis and BT: blood transfusion

Findings	Sickle Cell Disease (n=43)	Sickle B+Thalassemia(n=45)
Spleen	20	23
Liver	15	10
R-VOC	29	14
B T Required	14.45±1.84(n=22)	5.44±1.97(n=18)
AVN	01	00
Hypertension	01	00
Cholilithiasis	00	01

At the time of diagnosis Splenomegally was invariably present 20 out of 43 cases (64.44) and 23 out of 45 cases in both the phenotypes. Splenic enlargement was found 2-4 cms below the left costal margin in an average and only in two cases >12cm were observed. Hepatomegally was also observed in 15 and 10 cases in the present study. Out of 43 cases of SCD recurrent blood transfusion was required in 22 cases (14.45± 1.84) and 18 cases (5.44±1.97) in SB+ Thalassemia having P value< 0.001 which is statistically very significant. Avascular necrosis, Hypertension and Cholelithiasis were showed insignificant association in our study. Table No 3

Table No 4: Sickle Cell Disease (n=43) Mean value of hematological indices.				
	Mean	S/D	P Value	S/E
Age yrs	20.14	13.16	<0.0001	2.0
Height	145.69	31.08	<0.0001	4.74
Weight	42.14	14.22	<0.0001	2.17
Hb%	9.64	1.43	<0.0001	0.22
TLC K	9372.1	1157.3	<0.0001	240.5
TPC L	186.11	17.78	<0.0001	2.7
FERRITINng	737.8	772.6	<0.0001	117.8
MCV fl	62.11	2.11	<0.0001	0.322
MCH pg	19.02	2.07	<0.0001	0.316
MCHC	26.91	1.42	<0.0001	0.217
HbA%	2.27	0.7	<0.0001	0.122
HbF%	19.8	8.7	<0.0001	1.33
HbA2%	3.40	1.71	<0.0001	0.261
HbS%	72.8	8.03	<0.0001	1.23

Table No 4: The mean height in centimeters is145.69 cms(± 31.08) range 53 to 170 centimeters and weight in kilograms is 42.14 kg (±14.22) range 10 to 60 kilograms which indicates growth retardation. The mean Hemoglobin percentage 9.6 gm% with standard deviation (±1.43) range 6.8 to13 gm%, TLC 9372(±1157) K range 6K to 11K,TPC 186 (+18) Lakhs range 165 to 240 L, Serum Ferritin ng 737.8 (±772.6)ng range 23.9 to3349ng , MCV fl 62.11(±2.11) range 58.9 to 67 fl , MCH pg 19.02 (±2.07) range 14.8 to 22.4fl , MCHC g% 26.91(±1.42) range 23 to 29.8g% were observed in the present study. The Electrophoresis data of HbA%,HbF%,Hba2% and HbS% were seen as 2.27(±0.7)% range 1.4 to 4.4% ,19.8(±8.7)% range 7.2 to 45.4%,3.4(±1.71)% range 1.3 to 7.8 %and 72.8(±8.03)% range 53.6 to 83.2% respectively.

Table No 5: Sickle Beta Thalassemia(n=45) Mean value of hematological indices. S/E : standard error				
	Mean	S/D	P Value	S/E
Age yrs	17.16	8.7	<0.0001	1.3
Height	134.44	34.67	<0.0001	5.168
Weight	38.48	16.00	<0.0001	2.385
Hb%	10.2	±1.9	<0.0001	0.283
TLC K	9815	1649.6	<0.0001	245.9
TPC L	184.3 L	20.76	<0.0001	3.095
FERRITIN	297.94	99.62	<0.0001	27.630
MCV fl	63.06	2.63	<0.0001	0.392
MCH pg	19.35	2.16	<0.0001	0.322
MCHC	27.14	1.73	<0.0001	0.258
HbA%	3.69	2.94	<0.0001	0.438
HbF%	21.63	5.24	<0.0001	0.781
HbA2%	4.12	1.00	<0.0001	0.194
HbS%	69.45	4.35	<0.0001	0.648

Table No 5: The mean height in centimeters was 134.44 cms(± 34.67) range 73 to 176 centimeters and weight in kilograms is 38.48 kg (±16.00) 16 to 80 kilograms which indicates growth retardation. All the 45 cases are sickling positive with mean haemoglobin percentage is 10.2(SD

±1.9) with minimum 4.6gm% to maxmum 13.6 gm% , the mean of TLC and TPC is 9815 (SD±1649.6) ranges from 6000 to 12300 & 184.3 lakhs (SD± 20.76) ranges from 162 to 245 L respectively . We measured serum ferritin in 13 cases and the mean is 297.94 ng/ml (SD±99.62) ranges from 116.3 to 434ng. Analysis of electrophoresis shows the mean value of HbA is 3.69(SD± 2.94) ranges from 1to 27.9 ,HbF 21.63 (SD± 5.24) ranges from 11 to 22.7 ,HbA2 4.12 (SD±1.00) ranges from 1.6 to 5.7 and HbS 69.45 (SD±4.35) ranges from 45.9 to 82.3. In our observation the fetal hemoglobin was raised to 21.63, ranging from 11% to 32.7% and Hb A2 was also raised with mean value 4.12 which is >3.5%, suggestive of sickle cell-β-thalassemia .We observed high percentage of HbS ranging from 45.9 to 82.3 the mean was being 69.45.Patients having high levels HbA2 (>3.5%) as well as HbS (67%) are determinant for Sickle cell beta thalassemia (Weatherall).(2)

Table No: 6 Mean value of hematological indices in Sickle Cell Phenotypes Odisha.

Disease	Sickle Cell Disease (n=43)				Sickle Beta Thalassemia(n=45)			
	Mean	S/D	S/E	P.Value	Mean	S/D	S/E	
Age yrs	20.14	13.16	2.0	0.2116	17.16	8.7	1.3	
Height	145.69	31.08	4.74	0.001	134.44	34.67	5.168	
Weight	42.14	14.22	2.17	0.26	38.48	16.00	2.385	
Hb%	9.64	1.43	0.22	0.123	10.2	±1.9	0.283	
TLC K	9372.1	1157.3	240.5	0.15	9815	1649.6	245.9	
TPC L	186.11	17.78	2.7	0.66	184.3 L	20.76	3.095	
FERRITIN	737.8	772.6	117.8	0.0003	297.94	99.62	27.630	
MCV fl	62.11	2.11	0.322	0.658	63.06	2.63	0.392	
MCH pg	19.02	2.07	0.316	0.99	19.35	2.16	0.322	
MCHC	26.91	1.42	0.217	0.49	27.14	1.73	0.258	
HbA%	2.27	0.7	0.122	0.0027	3.69	2.94	0.438	
HbF%	19.8	8.7	1.33	0.232	21.63	5.24	0.781	
HbA2%	3.40	1.71	0.261	0.017	4.12	1.00	0.194	
HbS%	72.8	8.03	1.23	0.01	69.45	4.35	0.648	

The mean haemoglobin concentration of both the cases is 10.2 gm% SD ± 1.9 and 9.64±1.34 which shows moderate anaemia in our observation and similar to the study done by Maria Stella Figueiredoet.al 2015. Results were statistically analysed and tested using student's t-test for significance, if any, between the different diagnostic groups. Since there was no statistically significant sex differences observed for different haematological indices in the studied diagnostic categories, their mean values were pooled together for comparison purposes (Table No 6). Statistically significant higher mean values were observed in sickle beta thalassemia patients i.e. HbA mean 3.69±2.94 P value <0.0027, HbA2 mean 4.12 P value <0.017 than in the sickle cell Disease. The mean height 145.69±31.08 P value <0.001, serum ferritin level 737.8±772.6 P value <0.0003 and HbS levels72.8±8.03 P value <0.01 in Sickle Cell Disease were significantly higher in Sickle Cell Disease in comparison with Sickle Beta Thalassemia.

Table No. 7: After Hydroxyurea treatment.

Observation	Before Hydoxyurea Treatment		After Hydoxyurea Treatment	
	S C D	SB+T	SCD	SB+T
HbF%	19.8±8.7	21.63 ± 5.24	29.33±4.56	33.99±6.81
B.T.Requird	14.45±1.84	5.44±1.97	4.76±2.34	2.58 ± 2.09
R- VOC	29	14	3 cases	2 cases

Table No. 7: Hydroxyurea was administered orally at doses between 10 and 20 mg/kg per day. There were overall increases in HbF in most of the cases with reductions in the frequency of VOC & AVN. There was marked reduction in requirement of blood transfusion from 14.45 ± 1.84 units' to4.76±2.34 units in SCD and 5.44±1.97 to 2.58 ± 2.09 in SBT. There was statistically significant increase in HbF from 19.8±8.7 to 29.33 ±5.03 (P value <0.0001) in SCD and from 21.63 ± 5.24 to33.99±6.81 (P Value< 0.0001) in SBT. Vasoocclusive crisis was also reduced from 29 to 03 and 14 to 02 before and after Hydroxyurea treatment in both the groups respectively. The overall incidence of avascular necrosis was reduced to normal in the present study.

Discussion

The present study shows that maximum 41cases (91%) has been seen below 30 years of age in Sickle beta Thalassemia and 37(86%) in Sickle Cell Disease [9] Male patients are more than female which may be due to the fact that male child gets more attention as compared to female child [10]. The median age is being 17 years in sickle beta thalassemia and 18 years in Sickle Cell Disease. The mean age and standard deviation is being 17.16± 8.7 and 20.14±13.16 in both the observed groups. The P value (<0.2), which is statically insignificant [4]. The persistence of splenomegaly is higher in the present study probably due to the raised HbF level found in Indians[11]. In general examination hepato-splenomegally, low grade fever and bone pain are invariably present. recurrent blood transfusion is required in 22 cases (14.45± 1.84) in sickle cell disease and 18 cases (5.44±1.97) in Sβ+ Thalassemia having P value< 0.001 which is statistically very significant.[5]. Avascular necrosis, Hypertension and Cholelithiasis are insignificant association in our study. In Sickle Cell Disease (Table No 4) we observed growth retardation, anaemia, leucocytosis, increased Serum Ferritin and decreased levels of MCV, MCH and MCHC. The Electrophoresis data showed normal level of HbA% and increased level of HbF%, HbA2% and HbS% [12,13]. In sickle beta thalassemia (Table No 5) we observed the decrease of mean height and weight compared with the disabled world, which indicates growth retardation. All the 45 cases are sickling positive with mild anemia, leucocytosis, increased Serum Ferritin and decreased levels of MCV, MCH and MCHC. In our observation the mean fetal hemoglobin is raised to 21.63 and Hb A2 to 4.12%, which is >3.5%, and high percentage of HbS range (45.9 to 82.3) the mean is being 69.45 suggestive of sickle cell-β-thalassemia [1,5,14]. We compared Sickle Cell Disease with Sickle β+ Thalassemia in (Table No 6). The mean haemoglobin concentration of both the groups shows moderate anaemia [13]. Statistically significant higher mean values of. HbA, HbA2 are observed in sickle beta thalassemia than in the sickle cell Disease. The mean height, serum ferritin and HbS levels in are significantly higher in Sickle Cell Disease than Sickle Beta Thalassemia. [14] It is apparent from (Table No 6) that the majority of the Sickle Cell Disease and sickle cell-β -thalassemia cases showed reduced values of red cell indices like MCV, MCH and MCHC suggestive of hypochr-omic and microcytic anaemia[15]. Following Hydroxyurea treatment, there are overall increases in HbF in most of the cases with reductions in the frequency of vasoocclusive crisis & avascular necrosis as hydroxyurea increases the red cells containing an increased amount of fetal hemoglobin, which inhibits HbS polymerization, and decrease of leukocytes and platelets, which significantly limits their adherence to the vascular wall [16,17]. (Table7). There are marked reduction in requirement of blood transfusion due to increase in HbF level [16].

Conclusion

The high prevalence of sickle cell disease and beta thalassaemia in state of Odisha, India culminates the sickle beta thalassemia as major health

problem and has considerable morbidity and mortality. Differentiation of sickle cell anaemia and the sickle beta thalassemia syndromes has to be done carefully due to close similarity of symptoms and laboratory findings. The Hemoglobin Electrophoresis pattern of the Sickle Cell Disease and sickle-beta+ thalassemia consists of high HbS with a mild increase in HbF and HbA2 and low HbA value. Statistically significant higher mean values of HbA , HbA2 are observed in sickle beta thalassemia patients . Molecular diagnosis of Hb D, HbE or Hb S gene is required along with characterization of β-thalassemia mutations in this region. The prenatal diagnostic facilities, genetic/marriage counseling are the ultimate aims to be achieved in the state of Orissa.

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