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Original Research Article

Evaluation of correlation between clinical profile and amount of abnormal hemoglobin in sickle cell hemoglobinopathy

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Abstract

Aim and objectives: The present research was undertaken to study the clinical presentation of sickle cell haemoglobinopathy cases and correlates its severity with the subtypes of hemoglobin quantified on high performance liquid chromatography (HPLC).
Method: Total 54 sickle cell anemia (SCA) cases of age >12 years were included in the study. A detailed history, complete clinical examination and hematological investigation were done. From each patient 3 ml of venous blood was withdrawn and mixed with EDTA and sent to pathology laboratory for HPLC. The correlation between clinical profile and quantity of abnormal Hb was determined.
Results: The common presenting symptom was vaso-occlusive crisis (VOC) (30; 55.55%) followed by severe anaemia (22; 40.74%), a vascular necrosis (15; 27.77%) and infections (11; 20.37%). HbF had statistically significant positive correlation with Hb% and mean age of onset of symptoms while had negative correlation with WBC count and frequency of VOC. We found negative correlation between Hb% and HbS level but it was not statistically significant, (p=0.231). Also negative correlation found between mean age of onset of symptoms and HbS level, (p<0.001). There was statistically significant positive correlation between WBC count, frequency of VOC and HbS level (p=0.0067).
Conclusion: Clinical profile of sickle cell anemia is observed to be moderate i.e. less severe in this region as compared to reported in African Countries. HbF levels are higher in SCA patients and high level of HbF has a definitive role in ameliorating the severity of sickle cell anemia. These results point strongly to the recommendation of the therapy to raise the HbF level in patients wherever it is low.
Keywords: Haemoglobinopathy, Sickle cell anemia, Hemoglobin, Chromatography, EDTA, Vaso-occlusive crisis, Necrosis.

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1. Introduction

Hemoglobinopathies are common genetic disorders resulting from formation of one of the abnormal globin chain of the haemoglobin molecule. It is one of the major public health problems in the state of Maharashtra, India. Hemoglobinopathies can be either quantitative or qualitative[1] WHO figures estimate that 5% of the world population is a carrier for hemoglobinopathies [2] and of these, sickle cell anemia (SCA) alone is the most common heritable hematologic disease affecting humans [3], was first described in early 20th century. Sickle cell disease (SCD) is a widespread genetic problem limited to certain communities and geographical localities. This is exemplified by the fact that SCD has highest prevalence in Central India, in certain localities of Vidharbha Region of Maharashtra [4].

SCA is found to manifest as early as around 3 months of age or may remain asymptomatic till the development of severe anemia, vaso-occlusive crises, splenic sequestration, crippling avascular bone necrosis, osteomyelitis or epistaxis. These are challenging clinical events deserving competent and urgent medical management [5]. However, most of the patients with SCD suffer from hemolytic anaemia, intermittent episode of vaso-occlusive crises in connective and musculoskeletal structures; produce painful ischaemia manifested by acute pain and tenderness, fever, tachycardia and anxiety. These recurrent episodes, called painful crisis, are the most

common clinical manifestation. Despite the unicity of the genetic mutation i.e. responsible, clinical presentation of the SCD was found to be different according to regions and patients. Phenotypic heterogenicity of patients with SCD was linked to the difference between haplotypes of beta-globin gene. Five haplotypes were identified in the world-Benin, Senegal, Bantu, Cameroon and Arabian-Indian. Senegal and Arabian-Indian Haplotype are associated with moderate form of SCD [6].

Several biological and environmental factors are presumed to account for the morbidity pattern in patients with SCD; e.g. fetal hemoglobin is one of the biological factors thought to decrease morbidity in these patients. Senegal and Arabian-Indian haplotypes are associated with higher haemoglobin F levels than Benin and Cameroon haplotypes [7]. Haemoglobin F level has been a useful criterion in predicting the clinical severity of SCD. Many studies had shown the relationship between haemoglobin F value and clinical severity in SCA patients [8].

In the present study, we used frequency of vaso-occlusive crisis, mean age of onset of symptom, degree of anaemia, avascular necrosis, white blood cell count and leg ulcer as measures of clinical severity assessment. The clinical severity then correlated with quantity of abnormal haemoglobin i.e. HbF and HbS, determined by high performance liquid chromatography.

2. Materials and Methods

In this cross sectional analytical study, total 54 sickle cell anemia cases attending general medicine OPD, sickle cell OPD and Indoor wards of Department of Medicine, with age >12 years, irrespective of their gender, origin, caste and ethnic background, were included. Patients who had received blood transfusion within three months prior to the day of inclusion and patient who were and/or are on hydroxyurea therapy were excluded from the study.

After screening consecutive cases of sickle cell anemia, as per inclusion and exclusion criteria, a detailed history and complete clinical examination (steady state or crisis) was done. All the patients were subjected to hematological investigation like automated CBC, basic investigations. 3 ml of venous blood was withdrawn from the case after taking their written informed consent. This 3 ml of blood was mixed with EDTA and sent to pathology laboratory for HPLC. Other laboratory and radiological investigations were also done. The correlation between clinical profile and quantity of abnormal Hb was determined.

2.1 Statistical Analysis

Statistical analysis was done with the help of Microsoft excel 2003 version software using Student's' test. Probability value of $p<0.05$ were considered significant while $p<0.01$ taken as highly significant.

3. Observations and Results

Total 54 sickle cell anemia cases of age >12 years were enrolled in the study, among them 30 (55.55%) were males and 24 (44.44%) were females. The maximum numbers of patients were in the age group of 13-19 years (33; 61.11%) as shown in table 1. Mean age of patients was 20.86± 6.24 years, ranging from 13-50 years.

Table 1: Age and sex distribution of patients

Age (years)	Male (%)	Female (%)	Total
13-19	19 (63.33%)	14 (58.33%)	33 (61.11%)
20-29	08 (26.66%)	07 (29.16%)	15 (27.77%)
30-39	02 (6.66%)	03 (12.50%)	05 (9.25%)
≥40	01 (3.33%)	00 (00%)	01 (1.85%)
Total	30 (55.55%)	24 (44.44%)	54 (100%)

The common presenting symptom was vaso-occlusive crisis (VOC) (30; 55.55%) followed by generalized weakness due to severe anaemia (22; 40.74%). Other symptoms are shown in table 2. None of the cases had symptoms of stroke. The average age of onset of first symptom was 7.89 years. Maximum number of patients (31; 57.40%) became symptomatic between 5-10 years age group. 15 (27.77%) patients had first symptom before the age of 5 years and 13 (24.07%) patients had first symptom after the age of 10 years. 25 (46.29%) patients had frequency of VOC less than equal to one episode per year, while 24 (44.44%) had greater than one episode of VOC per year. Out of 54 patients, 5 (9.25%) patients never had an episode of VOC.

Table 2: Distribution of patients according to symptoms

Symptoms	No. of cases % (out of 54)
VOC (Joint pains etc.)	30 (55.55%)
Severe anemia	22 (40.74%)
Avascular necrosis AVN (Head of femur)	15 (27.77%)
Infections	11 (20.37%)
Acute chest syndrome (ACS)	05 (9.25%)
Leg ulcer	02 (3.70%)
Stroke	00 (0.00%)
Asymptomatic	24 (44.44%)

Note- Total percentage exceeds 100% because many cases had more than one symptom.

Total 30 (55.55%) patients presented as VOC, among them limbs were the most common site of pain (20; 66.66%) followed by hands (18; 60%) and knees (16; 53.33%), (Figure 1).Among 30 (55.55%) VOC cases, fever was found as precipitating factor in 11 (36.66%) patients, next common precipitating factor of VOC were exposure to cold (7; 23.33%), exhaustion and severe physical activity (6; 20%) and dehydration (2; 6.66%). In 4 (13.33%) patients no precipitating cause was identified.

Figure 1: Presentation of vaso-occlusive crisis

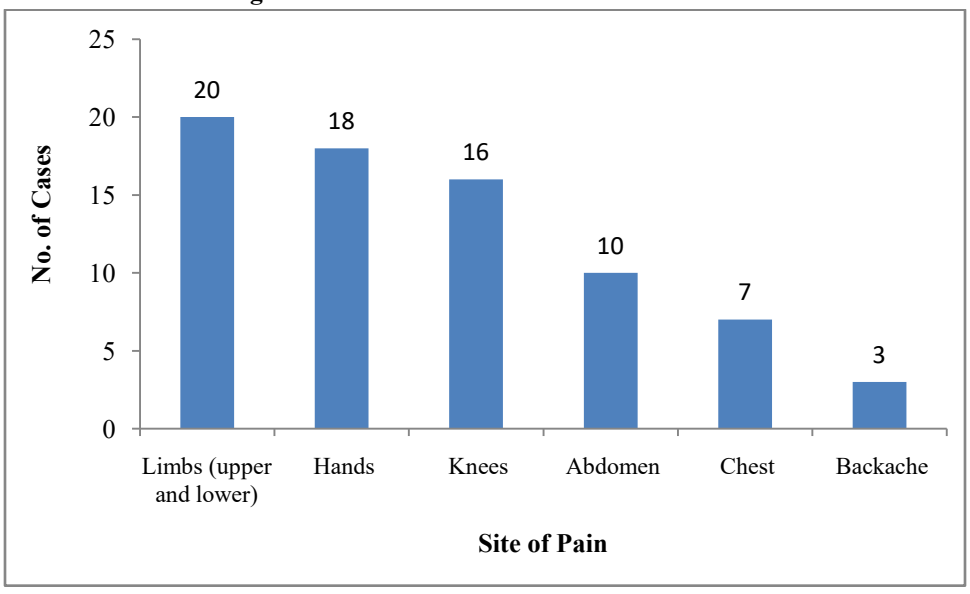

Table 3 show the comparison of clinical parameters (Hemoglobin, WBC count, Mean age of onset of first symptoms and Frequency of VOC) with the HbF and HbS levels

Table 3: Clinical parameters compared with HbF and HbS level

Clinical Parameters		HbF	HbS
Hemoglobin (gm %)	≤6 gm%(N=22) Range:3.3-5.9 gm%	19.02±7.12	72.91±8.02
	>6 gm% (N=32) Range: 6.2-11.5 gm%	24.13±3.24	70.03±4.13
	P Value	0.01*	0.15
WBC Count	≤10000/mm^3(N=40) Range: 2900-9000/mm^3	25.43±3.24	67.73±4.13
	>10000/mm^3 (N=14) Range: 10300-17000/mm^3	17.22±5.12	77.41±7.53
	P value	<0.0001*	<0.0001*
Mean age of onset of first symptoms (years)	<5 years (N=15) Range: 3.5-4.9 years	15.13±4.23	75.52±4.87
	5-10 years (N=26) Range: 5-10 years	20.05±7.06	72.12±5.21
	P value	0.0234*	0.0621
	5-10 years (N=26) Range: 5-10 years	20.05±7.06	72.12±5.21
	>10 years (N=15) Range: 10.5-26 years	29.81±4.53	63.54±9.21
	P value	<0.0001*	<0.0001*
Frequency of VOC (Average number of episode per year)	No VOC (N=5)	26.24±8.21	68.42±58
	≤1 VOC (N=25) Range 0.3-1	26.35±7.23	68.24±4.25
	P value	0.92	0.88
	≤1 VOC (N=25) Range 0.3-1	26.35±7.23	68.24±4.25
	>VOC (N=24) Range: 1.2-3	17.03±4.35	74.36±7.39
	P value	<0.0001*	<0.001*

Note: - * Indicate statistically significant difference

HbF had statistically significant positive correlation with Hb% and mean age of onset of symptoms and had negative correlation with WBC count and frequency of VOC, (Table 4).We found negative correlation between Hb% and HbS level but it was not statistically significant, (p=0.231). Also negative correlation found between mean age of onset of symptoms and HbS level, (p<0.001). There was statistically significant positive correlation between WBC count, frequency of VOC and HbS level (p=0.0067), (Table 4).

Table 4: Correlation between clinical parameters and HbF and HbS levels

Clinical parameters	Correlation (r) with HbF	Significance (p)
Hemoglobin gm%	0.343	0.009
WBC count	-0.423	<0.001
Mean age of onset of symptoms	0.514	<0.001
Frequency of VOC	-0.462	<0.001
Clinical parameters	**Correlation (r) with HbS**	**Significance (p)**
Hemoglobin gm%	-0.152	0.231
WBC count	0.512	<0.001
Mean age of onset of symptoms	-0.465	<0.001
Frequency of VOC	0.3432	0.0067

4. Discussion

In the present study, age range of the patient was 13-50 years and majority of them were from 13-19 years (61.11%) which is comparable with the previous studies [9-11]. Male predominance was observed in this study, this finding is similar to the study done by Powars *et al* [12] and Shrikhande *et al* [13]. The highest number of males can be explained by the sex ratio in our region [14, 15] and male seek medical attention more than females. As similar to earlier study [4], in current study the caste incidence was found to be maximum in mahar community. The mean HbF was 22.86±7.35, it was slightly higher in females (22.42±6.23) as compared to males (21.98±5.64). These values are consistent with the findings observed by Shrikhande *et al* [13]. It is already quoted that HbF production was genetically determined and Arab-Indian haplotype is associated with higher HbF levels and moderate severity of sickle cell anemia as compared to Camroon haplotype. This explains the low value of HbF in Nigerian population in study by Kotila *et al* [9]. In the present study, mean HbS was 70.46±5.36 (It was 71.24±5.42 in males and 69.28±7.03 in females).

High HbF level in RBCs protects them from sickling, the phenomenon responsible for clinical manifestation of the hemoglobinopathy. So manifestations of sickle cell anemia are delayed due to high HbF levels [16]. The common presenting symptom was vaso-occlusive crisis (VOC) followed by generalized weakness due to severe anaemia and AVN. Diop *et al* [17] and Powars *et al* [12] observed VOC as the most common manifestation in sickle cell anemia patients, this finding is consistent with the present study. The incidence of ACS, leg ulcer was significantly lower in current study as compared to observed in Pawars *et al* [12]. None of the cases had symptoms of stroke, which is comparable with the study done by Diop *et al* [17]. The total percentage exceeds 100% because many patients had more than one symptom. The mean age of onset of first symptom was 7.89 years which is correlated with the other studies [9, 10, 17].

Moreover, VOC are the most common manifestation of sickle cell disease but its frequency varies from person to person depending on various environmental and genetic factors. Some cases with very low frequency of VOC or no VOC are commonly seen in regions associated with Senegal and Arab-Indian haplotype. In present study, 25 (46.29%) patients had frequency of VOC less than equal to one episode per year, while 24 (44.44%) had greater than one episode of VOC per year and 5 (9.25%) patients never had an episode of VOC. This result correlated well with the study done by Diop *et al* [17]. Out of 56 patients, 30 presented as VOC, among them limbs were the most common site of pain (37.03%) followed by hands (33.33%) and knees (29.62%), abdomen (18.51%) and chest (12.96%). Only three patients (5.55%) complained of backache. These observations are comparable with the Sheikha *et al* study [18].

Among the 30 VOC cases, fever was found as precipitating factor in 36.66% patients, next common precipitating factor of VOC were exposure to cold (23.33%), exhaustion and severe physical activity (620%) and dehydration (6.66%). In 4 (13.33%) patients no precipitating cause was identified. Sheikha *et al* [18] reported exposure to cold was the precipitating factor in 45% of VOC, fever in 35%, exhaustion and severe physical activity and dehydration in 35% and dehydration in 10% of VOC. The difference in above study and present study could be explained on the basis of environmental factors, as Sheikha *et al* [18] carried their study in Bahrain, a desert land.

HbF level varies significantly when compared with the frequency of VOC. We found average number of VOC was 0.7 per patient per year. The rate varied widely so that 5 out of 56 patients never had VOC, 25 patients had ≤1 VOC per year and 24 patients had > 1 VOC per year (range 1.3-3). These result correlated with the study done by Platt *et al* [10].There was statistically significant negative correlation between HbF and frequency of VOC, which is similar to the previous studies [19, 20]. We found statistically significant positive correlation between HbS and frequency of VOC.

5. Limitation of study

The study population in present study was small. Hence, large numbers of patients of sickle cell anemia are needed to confirm results of present study. It was a cross sectional analytical study and there was no follow up of cases of SCD. Prospective study is necessary to calculate the various incidence rates and for proper evaluation of clinical profile.

6. Conclusion

Clinical profile of sickle cell anemia is observed to be moderate i.e. less severe in this region as compared to reported in African Countries. Vaso-occlusive crisis is observed to be the most common presentation and Hb F levels are higher in SCA patients. HbF had statistically significant positive correlation with Hb% and mean age of onset of first symptom. While HbF had negative correlation with frequency of vaso-occlusive crisis and WBC count. HbS has statistically significant positive correlation with WBC count and frequency of vaso-occlusive crisis while statistically significant negative correlation with mean age of onset of symptom. Thus, high level of HbF has a definitive role in ameliorating the severity of sickle cell anemia. These results point strongly to the recommendation of the therapy to raise the HbF level in patients wherever it is low.

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