ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 7, Issue – 6, November - 2024, Page No. : 80 – 88

Clinical Profile of Subjects with Sickle Cell Trait

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How to citation this article: Dr. Shruti Shetty, Dr. Madhuri Pandharipande, "Clinical Profile of Subjects with Sickle Cell Trait", IJMACR- November - 2024, Volume – 7, Issue - 6, P. No. 80 – 88.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Introduction: Sickle cell anemia is highly prevalent in sub-Saharan and equatorial Africa with lesser but significant prevalence in the Middle East and India. Sickle cell trait (SCT) is a relatively benign condition, and affected individuals are at no increased risk of morbidity or mortality. Fetal hemoglobin (HbF) is a major genetic modulator of the hematologic and clinical features of sickle cell disease. The present study is done to assess the clinical manifestation, hematological, biochemical, radiological parameters and prevalence of complications in cases of sickle cell trait.

Methodology: The present Hospital based, Observational Cross-sectional study was conducted on 50 patients HPLC proven cases of sickle cell trait, attending general medicine or sickle cell OPD and cases admitted in wards of department of medicine. All subjects were evaluated for any symptoms, signs and complications of sickle cell syndrome. Hematological, Renal function tests, Urine examination, USG of abdomen and pelvis, MRI hip and MRI venography were performed. The severity of vaso-occlusive crises was determined using Visual Analogue Scale (VAS). The clinical severity score was calculated in all patients, using the scoring system.

Results: The mean age was 33.46 ± 11.4 years. Highest number of cases, (30%) were from 20-29 years age group. Male-to-female ratio was 1:1.3. 50% were asymptomatic, the most common Symptom was history of bone pains (24%), Fatigue (16%) and pallor (10%). In 75% patients had moderate VOC vaso-occlusive crisis, severe in 16.67% patients. 96% patients had a clinical severity score between 7-10. Mean Hb, mean corpuscular volume (fL), red cell distribution width (%) and hematocrit (%) was 11.51±2.3, 77.63±7.09, 14.52±1.05 and 37.35±4.45 respectively. Mean value of total bilirubin (mg%), direct bilirubin (mg%), AST(IU/L), ALT(IU/L), ALP(IU/L) and

blood urea (mg%) was 1.57±1.97, 0.49±1.04, 48.16± 45.58, 45.26±39.8, 84.44±12.7 and 31.46±8.47 respectively. Isosthenuria (specific gravity of 1.010) was present in 6% patients. USG showed splenomegaly in 20% patients, 12% had massive splenomegaly(>16cm). MRI revealed ischemic stroke, cortical venous sinus thrombosis and avascular necrosis of the hip in 1 patient each. Mean HbF was 10.69±5.05%.

Conclusion: Complications like vaso-occlusive crisis, sickle hepatopathy, nephropathy, stroke, cortical venous sinus thrombosis and avascular necrosis, usually documented in homozygous sickle cell disease also occur in patients with heterozygous sickle cell trait. Vaso-occlusive crisis of moderate, as well as severe intensity is observed in patients with sickle cell trait.

Keywords: Sickle Cell Trait, Clinical profile, Hematological parameters, Bbiochemical parameters, Complications

Introduction

Sickle cell disease, a term familiar to physicians is actually a misnomer since it refers not to a single disease, but rather a collection of inherited blood disorders with the propensity for erythrocytes to change into a crescent or 'sickle' shape. The World Health Organization estimated in 2006 that 5 percent of the world population carries a gene for a hemoglobinopathy. Sickle cell anemia is highly prevalent in sub-Saharan and equatorial Africa with lesser but significant prevalence in the Middle East, India, and the Mediterranean region. [1,2]

Inheritance of both HbS alleles is termed as sickle cell disease (HbSS) while only one allele is termed sickle cell trait (HbAS). Individuals who are homozygous for the sickle cell gene are mostly affected and manifest a protean of symptoms and complications. Sickle cell trait (SCT), defined as the heterozygous inheritance for sickle hemoglobin, has evolutionarily persisted throughout the world because of its strong protective effects against severe and cerebral malaria. As many as one in three Africans living in areas where malaria is endemic and approximately one in twelve Americans with African ancestry have sickle cell trait. [1,3]

The general consensus of the scientific community and of the public is that SCT is a relatively benign condition, and affected individuals are at no increased risk of morbidity or mortality. However, sickle cell trait is not completely benign. Fetal hemoglobin (Hb F) is one of the major genetic modulators of the hematologic and clinical features of sickle cell disease. The pathophysiology of sickle cell disease is dependent on the polymerization of deoxy sickle hemoglobin. [4,5] As HbF is excluded from polymer formation, increased levels of fetal hemoglobin have proven to confer a protective effect. Phenotypic heterogenicity of patients with sickle cell disease were linked to the difference between haplotypes of beta-globin gene. Five haplotypes were identified in the world – Benin, Senegal, Bantu, Cameroon and Arabian- Indian. The Arab-Indian and Senegal haplotypes of sickle cell disease are associated with higher levels of fetal hemoglobin and have moderate forms of the disease.[6]

The scarce literature on sickle cell trait and their complications is inconsistent to our clinical experience, working in endemic area for the sickle cell mutation. Hence the following study was undertaken to document the clinical profile of patients with sickle cell trait. Parameters including frequency of vaso-occlusive crisis and preceding hospitalizations, antecedent blood transfusion, splenic size, stroke and avascular necrosis were used as measures of clinical severity assessment.

The clinical severity was then correlated with quantity of fetal hemoglobin, determined by high performance liquid chromatography.

Objectives

1. To assess the clinical manifestation, hematological, biochemical and radiological parameters in cases of sickle cell trait.
2. To assess the prevalence of complications like vaso-occlusive crises, sickle hepatopathy, stroke, avascular necrosis, nephropathy and gallstones in cases of sickle cell trait.

Materials and Methods

The present Hospital based, Observational Cross-sectional study was conducted on 50 patients HPLC proven cases of sickle cell trait, attending general medicine or sickle cell OPD and cases admitted in wards of department of medicine between January 2020 to October 2021. Patients with age <12 years, not willing to give written informed consent, with other hemoglobinopathies like HbS-Thal, HbSF, HbC, Hb D, HbE, pre-existing hematological malignancies or history of blood transfusion in the past 3 months, as in them HPLC cannot be performed or Patients who were and/or are on Hydroxyurea therapy, were excluded.

Only those subjects with High performance liquid chromatography (HPLC) proven sickle cell trait, willing to give written informed consent were selected for the study. All subjects were clinically evaluated for any symptoms, signs and complications of sickle cell syndrome. Hematological indices hemoglobin levels, total leucocyte count, differential leucocyte count, platelet count, red cell distribution width, MCV, MCH, MCHC were tested. Renal function tests, Urine examination for specific gravity, casts, crystals and organismswere done. Ultrasound of abdomen and pelvis, MRI hip and MRI venography were performed when further evaluation was needed. The complete data was collected in a specially designed Case Record Form.

The severity of vaso-occlusive crises was determined using Visual Analogue Scale (VAS). The pain VAS is a continuous scale comprised of a horizontal (HVAS) or vertical (VVAS) line, usually 10 centimeters (100 mm) in length, anchored by 2 verbal descriptors, one for each symptom **extreme.**[7] The clinical severity score was calculated in all patients, using the scoring **system.** [8]

Statistical Analysis

The presentation of the Categorical variables was done in the form of number and percentage (%). Quantitative data were presented as the means ± SD and as median with 25th and 75th percentiles (interquartile range). The comparison/association of the variables which were quantitative in nature were analysed using independent t test (for two groups) and ANOVA test (for more than two groups). The association of the variables which were qualitative in nature wereanalysed using Chi-Square test. Univariate logistic regression was used to find out odds ratio with 95% CI of HbF for predicting outcomes. Spearman rank correlation coefficient was used for correlation of HbF and clinical severity score. Analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, ver 21.0. For statistical significance. p value of less than 0.05 was considered statistically significant.

Results and Observations

The present study was conducted from January 2020 to October 2021. 50 patients aged >12 years who were HPLC proven cases of sickle cell trait were included in the study. All subjects were clinically evaluated, hematological indices and renal function test parameters were assessed, Urine and fundus examination was done,

other investigations were performed and results are as follows.

Table 1: Age distribution of study subjects

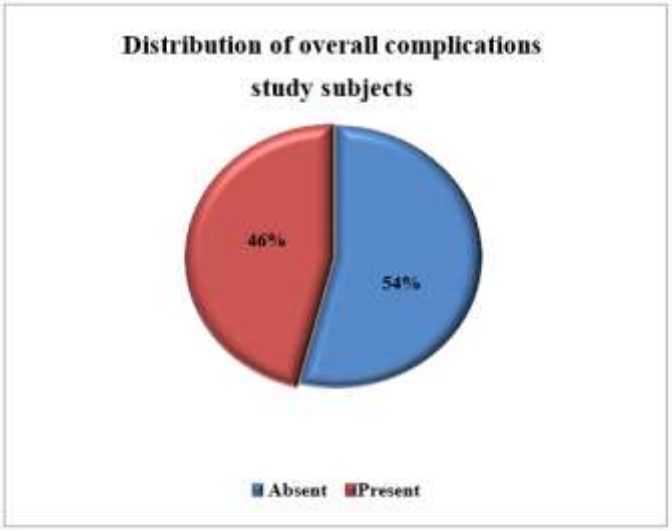
Demographic characteristics		Frequency (n=50)	Percentage
Age(years)	10-19	6	12.00%
	20-29	15	30.00%
	30-39	14	28.00%
	40-49	11	22.00%
	50-59	4	8.00%
Gender	Male	21	42.00%
	Female	29	58.00%
Total		50	100.00%

In present study, 30.00% of patients belonged to age group 20-29 years followed by 30-39 years (28.00%), 40-49 years (22.00%) and 10-19 years (12.00%). Age group was 50-59 years of only 4 out of 50 patients (8.00%). Mean value of age(years) of study subjects was 33.46 ± 11.4 with median (25th-75th percentile) of 32(26-42.75). 58.% of patients were females and 42.00% of patients were males. Sex ratio (M : F) was 1:1.3.

Clinical parameters in cases of sickle cell trait:

In present study, 50.00% of patients were asymptomatic. History of bone pains was present in 24.00% of patients followed by fatigue (16.00%), pallor (10.00%), hemolytic facies (6.00%) and Icterus (4.00%). Breathlessness, palpitations, chest pain, edema feet, raised JVP and leg ulcers was seen in none of the patient.

Graph 1: Frequency distribution of overall complications in study subjects



In present study, 23 out of 50 patients (46.00%) had presence of one or more complications. 27 patients (54.00%), had no evidence of the presence of any complications.

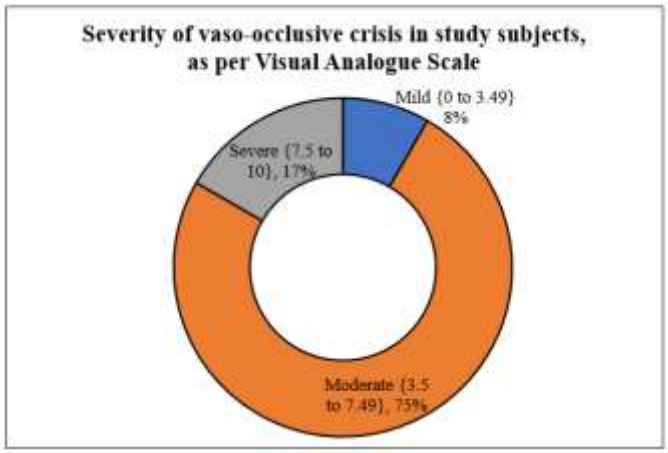
Table 2: Frequency distribution of complications in study subjects:

Complications		Frequency (n=23)	Percentage
Sickle Hepatopathy		2	4.00%
Stroke	Ischaemic Stroke	1	2.00%
	CVST	1	2.00%
Avascular necrosis		1	2.00%
Gallstones	Gallstones	10	20.00%
	Gallstones with cholecystitis	4	8.00%
	Gallstones without cholecystitis	6	12.00%
Nephropathy		3	6.00%
More than 1 complications		7	4.00%

In present study, in 24.00% of patients, vaso-occlusive crisis was present. Acute chest syndrome, hemolytic and

aplastic was seen in none of the patient. 4.00% of patients had sickle Hepatopathy, 2% of patients had ischaemic stroke and avascular necrosis each. 20.00% of patients had gallstones. 12% of patients had gallstones without cholecystitis and 8% of patients had gallstones with cholecystitis. 6% of patients had nephropathy. More than 1 complication were present in 14% of patients.

Graph 2: Severity of vaso-occlusive crisis in study subjects, as per Visual Analogue Scale



In the present study, in 9 out of the total 12 patients with vaso-occlusive crisis (75.00%) of patients, severity of VOC was moderate {3.5 to 7.49} followed by severe {7.5 to 10} in 2 patients (16.67%). Severity of VOC was mild {0 to 3.49} in only 1 out of 12 patients (8.33%). Mean value of VAS of study subjects was 5.74 ± 1.75 with median (25th-75th percentile) of 5.5(4.5-6.875).

Clinical severity score of study subjects:

The clinical severity score has a minimum score of 7 and maximum score of 22. In present study, in 48 patients (96.00%), clinical severity score was 7-10. Clinical severity score was 11-14 in only 2 out of 50 patients (4.00%). Mean value of clinical severity score of study subjects was 7.76 ± 1.08 with median (25th-75th percentile) of 7(7-8).

Hematological and Biochemical parameters and Urine Analysis:

Mean value of Hemoglobin(g/dL), mean corpuscular volume (fL), red cell distribution width (%), platelet count (1000/µL), total leucocyte count (1000/µL) and hematocrit (%) of study subjects was 11.51 ± 2.3, 77.63 ± 7.09, 14.52 ± 1.05, 2.95 ± 0.62, 6.26 ± 1.46 and 37.35 ± 4.45 with median(25th-75th percentile) of 11.7(10.425-13.025), 79.2(73.325-82.45), 14.6(13.825-15.275), 2.95(2.6-3.2), 6.2(5.425-7.05) and 37.8(34.725-40.175) respectively.

Table 3: Hematological and Biochemical parameters and Urine Analysis:

Parameters		**Mean ± SD**	**Median (25th- 75th percentile)**	**Range**
Hematological Parameters	Hemoglobin(g/dL)	11.51 ± 2.3	11.7(10.425- 13.025)	3.3-15.8
	Mean corpuscular volume (fL)	77.63 ± 7.09	79.2(73.325- 82.45)	55.4-90.3
	Red cell distribution width (%)	14.52 ± 1.05	14.6(13.825- 15.275)	12.4-16.3
	Platelet count(1000/µL)	2.95 ± 0.62	2.95(2.6-3.2)	1.7-4.4
	Total leucocytecount (1000/µL)	6.26 ± 1.46	6.2(5.425-7.05)	3.8-12.8
	Hematocrit (%)	37.35 ± 4.45	37.8(34.725- 40.175)	26.7-44.1
Biochemical Parameters	Total bilirubin (mg%)	1.57 ± 1.97	1.25(0.8-1.6)	0.4-12.1
	Direct bilirubin (mg%)	0.49 ± 1.04	0.3(0.125-0.4)	0.1-6.4
	AST(IU/L)	48.16 ± 45.58	38(36-42)	28-312
	ALT(IU/L)	45.26 ± 39.8	37(35-41)	20-254

	ALP(IU/L)	84.44 ± 12.7	85.5(78-93)	57-110
	Blood urea (mg%)	31.46 ± 8.47	30.5(25.25-37.75)	19-50
	Serum creatinine (mg%)	0.82 ± 0.28	0.8(0.6-0.975)	0.4-1.6

Mean value of total bilirubin (mg%), direct bilirubin (mg%), AST(IU/L), ALT(IU/L), ALP(IU/L), blood urea (mg%) and serum creatinine(mg%) of study subjects was 1.57±1.97, 0.49±1.04, 48.16±45.58, 45.26±39.8, 84.44±12.7, 31.46±8.47 and 0.82±0.28 with median (25th -75th percentile) of 1.25 (0.8-1.6), 0.3 (0.125-0.4), 38 (36-42), 37 (35-41), 85.5 (78-93), 30.5(25.25- 37.75) and 0.8(0.6-0.975) respectively.

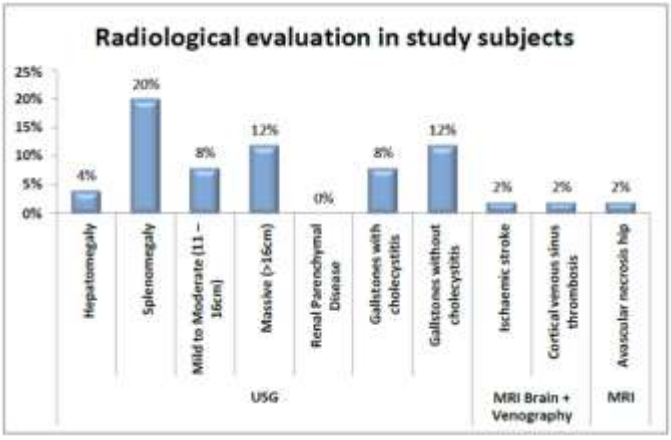
Urine analysis in study subjects

In present study, in 47 patients (94.00%), urine analysis was normal followed by isosthenuria in 3 patients (6.00%). Urine analysis showed no evidence of albuminuria (>20mg/dL), hematuria and casts or crystals in any of the cases.

Radiological evaluation in study subjects:

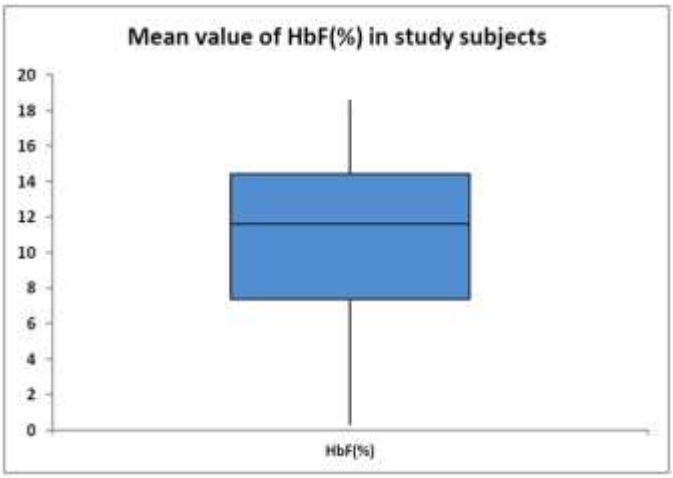
In the present study, 10 patients (20%) had splenomegaly of which 6 patients (12%) had massive splenomegaly (>16cm) followed by mild to moderate (11–16cm) splenomegaly in 4 patients (8%). 2 patients (4%) had evidence of hepatomegaly. Gallstones with cholecystitis in 4 patients (8%) and gallstones without cholecystitis in 6 patients (12%) was present. No evidence of renal parenchymal disease in any patient. 1 patient each (2%) had ischaemic stroke, cortical venous sinus thrombosis and avascular necrosis hip.

Graph 3: Radiological evaluation in study subjects



Mean value of HbF (%) in study subjects: Mean value of HbF (%) of study subjects was 10.69±5.05 with median (25th- 75th percentile) of 11.6(7.35-14.425).

Graph 4: Descriptive statistics of HbF (%) of study subjects.



Discussion

The present study was undertaken in 50 cases of sickle cell trait visiting the outpatient department or those admitted in wards of a tertiary care centre, since levels of fetal hemoglobin are known to influence the morbidity in cases of sickle cell disease, further evaluation of correlation of the prevalence of complications, clinical severity score and severity of

vaso-occlusive crises with the levels of HbF levels were carried out. An attempt was also made to determine a protective threshold of fetal hemoglobin.

Demographic characteristics of study population:

50 patients aged >12 years who were HPLC proven cases of sickle cell trait were included in the study. The mean age of study subjects was 33.46 ± 11.4 years. 21 males and 29 females were included, with a male: female ratio of 0.72. **Kar BC et al[9]** conducted a cross-sectional study in 200 sickle cell trait patients with 150 age and gender-matched controls. The mean age of the study population in this study was 30.24 ± 6 years. The age-wise distribution of subjects is comparable to the present study.

Symptoms and signs in subjects with sickle cell trait:

While 50% of the study population was asymptomatic, the commonest symptom was bone pain present in 24% of the subjects. This was followed by fatigue (16%). None of the subjects complained of breathlessness, palpitations or chest pain. The present study revealed that clinical manifestations which are known to occur in patients of sickle cell disease, can also occur in patients of sickle cell trait.

In a study conducted by **Gaikwad et al[10],** among 97 patients of sickle cell trait, the chief complaints were weakness and fatiguability in 44 patients (45.36%), painful and swollen digits of hands and feet in 8 patients (8.24%). In the study of **Chikhlikar et al[11],** 23% of patients with sickle cell trait of a total study population of 100 complained of recurrent fever with cough. 15% of the patients had abdominal pain and 8% presented with bone pains. 68% of the subjects were anaemic and 10% had history of recurrent jaundice.

Laboratory parameters in subjects with sickle cell trait:

The mean value of hemoglobin in our study was 11.51 ± 2.3 g/dL, platelet count 2.95 ± 0.62 1000/µL and hematocrit (%) 37.35 ± 4.45. Mean corpuscular volume was 77.63 ± 7.09 fL, red cell distribution width (%) was 14.52 ± 1.05 and total leucocyte count 6.26 ± 1.46 1000/µL). **Jain et al[12]** noted similar observations with a lower mean hemoglobin value (10.2 g/dL). The mean hematocrit was 36%, platelet count 3.05 1000/ µL, mean corpuscular volume 76.9 fL. A study conducted by **Roberts GT et al[13]** found elevated mean RDW values in anemic patients, with the highest value seen in sickle cell anemia, sickle cell thalassemia, sickle cell trait, thalassemia trait, and iron deficiency anemia in decreasing order of magnitude. It was found that the RDW was proportional to the reticulocyte count, with the highest values in the patients with the highest reticulocyte count (sickle cell anemia). One clinical value of the RDW therefore may lie in its capacity for reflecting active erythropoiesis.

Complications in subjects with sickle cell trait:

In the present study, 27 patients had no evidence of any complication. Of the 23 patients with complications, vaso-occlusive crisis was the most frequently observed in 12 out of 50 patients (24%) in the present study. In 9 of 12 patients with vaso-occlusive crisis (75%), severity of VOC was moderate (35 to 74.9mm) followed by severe (75 to 100mm) in 16.67%. Avascular necrosis of the hip, ischaemic stroke and cortical venous thrombosis were confirmed by MRI in 1 patient each. 14% of the study population had more than one complication. The present study demonstrated that complications known to occur in patients of sickle cell disease, like sickle hepatopathy, acute chest syndrome,

gallstones, nephropathy, stroke, cortical venous sinus thrombosis can occur in patients with sickle cell trait. Vaso-occlusive crisis of moderate to severe intensity occurring in patients of sickle cell trait was also demonstrated.

The results of this study are comparable with that of a study conducted **by Kar BC**[9] in 200 cases of sickle cell trait with 150 age and gender-matched controls. 51% of sickle cell trait and 86% of control cases had mild to severe anaemia which improved with iron therapy in trait cases. There was one case of epilepsy with multiple small infarcts in the brain and another with focal fits with epileptogenic focus in the left cerebral hemisphere where no other cause could be found except sickle cell trait. **Jain et al**[12] observed that the most common cause of hospitalization in 41 patients with sickle cell trait was vaso- occlusive crisis (41.46%), followed by anemia in 32%. Incidence of vaso- occlusive crises was more in extremes of temperature in their study group, 41% in winters & 29% in summer months. The duration of hospital stay was less than 7 days in most of the patients (48.7%), 7-14 days in 36.5% and >14 days in 14.6%.

Levels of fetal hemoglobin in subjects with sickle cell trait:

In the present study, mean value of HbF (%) of study subjects was 10.69 ± 5.05 with median (25th-75th percentile) of 11.6(7.35-14.425). In a study conducted by **Ngo et al**[6]**,** adult HbS heterozygotes with the Arab-Indian (AI) haplotype have a mean baseline HbF of 17%. **Mashon et al**[14] reported a mean HbF level of 16.64 ± 8.73% in 436 cases of sickle cell disease. The Arab-Indian haplotype is linked to a novel variant in ANTXR1. ANTXR1, a type 1 transmembrane protein, is expressed at high levels in bone marrow. This variant explains 70% of HbF variability seen in the AI haplotype. **Chang Y et al**[15] conducted a study on 257 patients of sickle cell disease with age and gender matched sibling cohort group. This study proved a significant association of fetal hemoglobin levels with age (p-value 0.01), but not with gender (p-value 0.53). These results are comparable with those of the present study.

Conclusion

Complications like vaso-occlusive crisis, sickle hepatopathy, nephropathy, stroke, cortical venous sinus thrombosis and avascular necrosis, usually documented in homozygous sickle cell disease also occur in patients with heterozygous sickle cell trait. Vaso-occlusive crisis of moderate, as well as severe intensity is observed in patients with sickle cell trait.

Limitations

The present study was single centre based. A small number of patients were examined. It was a cross-sectional, analytical study with no long-term follow-up of thepatients.

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