ORIGINAL RESEARCH ARTICLE

Ocular Manifestations of Sickle Cell Hemoglobinopathy: A Study in Tertiary Eye Care Centre of North Maharashtra (India)

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Abstract:

Background:

Sickle cell disease (SCD) is the most common genetic disease worldwide. The increase in life expectancy of SCD patients in recent years has led to the emergence of more complications of the disease, including ocular changes, which were uncommon in the past. SCD can affect virtually every vascular bed in the eye and can cause blindness in the advanced stages.

Purpose:

The present study was carried out to assess the incidence and prevalence of all ocular manifestations in SCD and to correlate with age and demographical parameters.

Materials & Methods:

The present prospective study was conducted at tertiary care center from June 2018 to June2019 and included 146 SCD patients including Sickle cell carriers/traits (SCT). A detailed comprehensive eye examination was performed to know the status of any ocular findings.

Results:

Most common peripheral retinal change seen was venous dilatation and tortuosity in 55.23% SCD and 29.5% of the SCT patients. The conjunctival signs were observed in 77.55% SCD and 27.2% of the SCT patients. Other complications such as iris atrophy, temporal disc pallor, chronic maculopathy, neovascularisation, retinal detachment were rare and none of the patients had anterior chamber signs.

Conclusion:

In summary, present study documents higher prevalence of retinopathy along with some conjunctival signs in Indian SCD patients. In general, overall peripheral retinal changes are more common in SCD patients than in SCT subjects. Further, this study demonstrates that retinopathy contributes to the susceptibility for development of vision loss in SCD cases. It is therefore recommended that all patients must undergo ophthalmological examination at the diagnosis of SCD and follow-ups at regular intervals to prevent visual loss.

Keywords:

Ocular changes, retinopathy, sickle cell disease, sickle cell trait

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Introduction:

Sickle cell disorder (SCD) is most common hemoglobinopathy affecting humans. Due to its associated significant morbidity and mortality, SCD remains a major public health concern affecting millions of people around the world. In India it is more common in the tribal population who live in remote hilly places[1].

SCD patients are at high risk for developing multi-organ, acute and chronic complications linked with significant morbidity and mortality[2]. Organs commonly involved in SCD are the kidneys, skeleton, lungs, liver, eyes and skin. Some of the ophthalmological complications of SCD include retinal changes, refractive errors, vitreous hemorrhage, and abnormalities of the cornea[2,3,4]. The ocular manifestations in SCD result from vascular occlusion (5). All ocular and orbital structures can

be affected by microvascular occlusions in SCD including conjunctiva, iris, retina, and choroid[2]. Vaso-occlusive changes can lead to several anterior segment complications, such as conjunctival sickling, which are characterized by capillary vessel segmentation[2,5]. Iris changes manifest as atrophy with or without posterior synechiae. The development of the iris neovascularization could lead to secondary glaucoma, and severe pain and vision loss. Posterior segment findings include optic neuropathies, retinopathies, maculopathies, retinal hemorrhages, choroidopathy, vascular changes associated with tortuosity, "silver-wire" arterioles, angioid streaks, and arterial and vein occlusions [2, 4, 6,7].

The clinical manifestations of SCD involve several complex chemical, molecular processes and pathways such as endothelial activation, inflammation, blood cells adhesiveness, and oxidative stress[5]. However, the major cause of vision loss is proliferative sickle cell retinopathy (PSR)[5,8]. The most significant ocular changes are those which occur in the fundus, which can be grouped into PSR, and non-proliferative retinal changes based on the presence of vascular proliferation[2,9]. This distinction is important because the formation of new vessels is the single most important precursor of potentially blinding complications[5]. Although various systemic complications of SCD are known to be more common in patients with the HbSS genotype, visual impairment secondary to PSR is more common in patients with the HbSC genotype[6,9].The retinopathy associated with the different types of sickle disease has been well documented in various parts of the world[6,7,10]. Ocular manifestations occurred in 69.15% of SCD the patients in Zambia[11]. It is reported that incidence increases with age in both genotypes, with crude annual incidence rates of 0.5 % cases SS subjects and 2.5 % cases SC subjects, while prevalence was greater in SCD[12]. 46 to 49% of proliferative retinopathy reported was due to sickle cell disease[7,13]. A cohort study performed on Jamaican children found peripheral retinal vessel closure in approximately 50% of SS and SC genotypes at the age of 6 years and this increased to affect 90% of children by the age of 12 years[14].

It is observed and reported that there is an increase in the incidence and prevalence rates of all ocular complications of SCD with age[7,12]. PSR had occurred in 43% subjects with SCD and in 14% subjects by the ages of 24 to 26 years[7]. Therefore, the present study was undertaken to assess the incidence and prevalence of all ocular manifestations in SCD and SCT and to correlate these with age and demographical parameters in our area which contributes the population of the Tribal area. This study was also done to explore measures to reduce the complications, morbidity and mortality in SCD.

Materials and Methods:

It is a prospective observational study of diagnosed patients of SCD for ocular manifestations. This study was done during period of June 2018 to June 2019. The patients who attended out-patient department at SBH Govt Medical College, Dhule were included in the study. The centre is a recognized tertiary health care centre equipped with latest medical technology in ophthalmology department. Informed consent was taken from the patients selected for the study and it was initiated on approval of institutional ethical committee.

Inclusion criteria:

All the cases of sickle cell disorder diagnosed on history, clinical examination and confirmed by hemoglobin electrophoresis. Those who gave consent to participate in study, patients in steady state and age ranged from 1 to 60.

Exclusion criteria:

Patients having diabetes mellitus, hypertension and those patients having diseases other than SCD which may cause ocular manifestations, were excluded from the study.

A total of 146 patients who qualified the inclusion criteria were the final subjects of the present study. 85 were SCD and 61 were sickle cell carriers / trait (SCT). Evaluation of the patients was done by recording detailed clinical history and systemic examination along with visual acuity on Snellen's chart. Local and slit lamp examination along with direct and indirect opthalmoscopy was done in each patient. Tonometry using Goldmann applanation tonometer was done to record intra-ocular pressure.

Investigations included laboratory tests such as Haemogram (blood hemoglobin, Total and Differntial leucocyte counts, Reticulocyte counts), ESR and peripheral smear, Random blood sugar. Sickling test was done to screen for sickle cell anemia. Quantification of haemoglobin varients was carried out by automated high performance liquid chromatography (HPLC) using VARIANT™ II Hemoglobin Testing System (BIO-RAD, Hercules, California, USA). X-ray skull and long bones in selected patients were done to exclude patients for confounding factors. Ultrasound B-scan was done in selected patients where media was hazy and any pathology in vitreous or retina was suspected. Fundus fluorecein angiography was also done in selected patients.

Result and Observations:

In the present study, 146 cases of SCD were examined which included 85 cases of Sickle cell anemia (HbSS) and 61 were of sickle cell trait (HbAS). 116 out of total 146 study subjects (79.45% cases) have shown ocular changes (Fig-1). Highest numbers of male SCD and SCT patients were in the age group of 21-30 followed by 11-20 yrs group (Fig-2). The peak for female SCD patients was in 11-20 yrs while for SCT females it was 21-20 yrs (Table-1, Fig-2). The Mean age of the subjects with ocular changes was 20.37 years. It was also observed that, of the 80 patients who had veno-occlusive crisis, 73 patients (91.25%) had shown ocular changes (Table-2, Fig-3).

Table-1 : Distribution of patients according to age, gender and sickle cell anemia genotype

Age group	SCD		SCT		Total
	M	F	M	F	
00 – 10	4	6	2	3	15
11 – 20	15	13	8	4	40
21 – 30	16	7	14	15	52
31 – 40	5	8	5	3	21
41 – 50	2	4	3	1	10
51 – 60	3	2	1	2	8
Total	45	40	33	28	146

Table 2: Ocular changes in sickle cell patients

Vaso-occlusive crisis	Ocular changes		Total
	Positive	Negative	
Present	73	8	81
Absent	43	22	65
Total	116	30	146

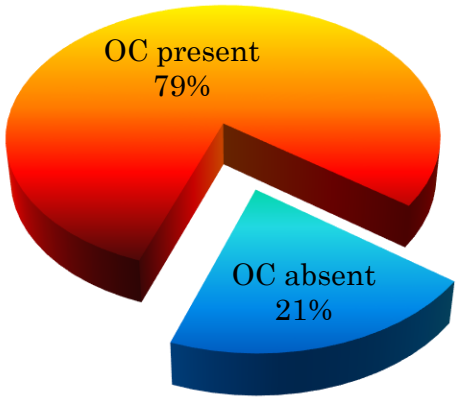

Fig 1. Chart showing ocular changes (OC) in Sickle cell patients.

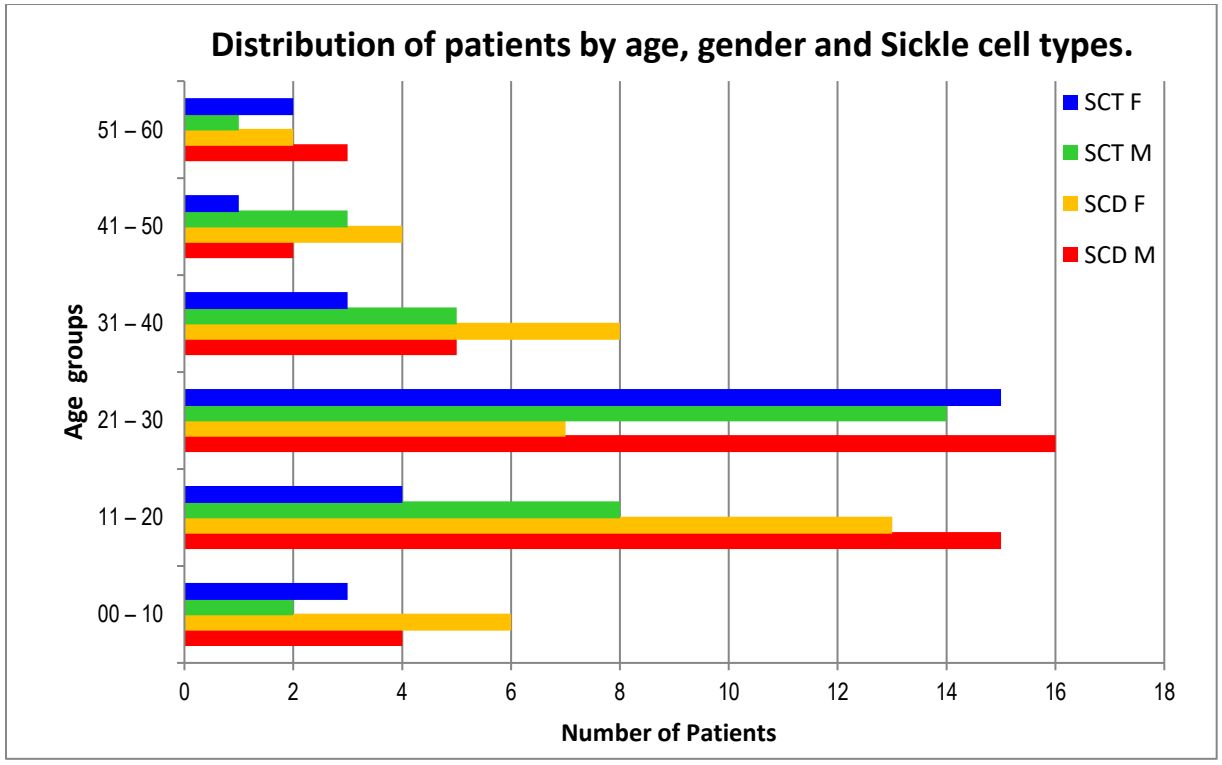

Fig 2. Chart showing distribution of sickle cell patients as per gender and age groups. (SCD = Sickle cell disease; SCT = Sickle cell Trait or carrier; M = Males; F = females)

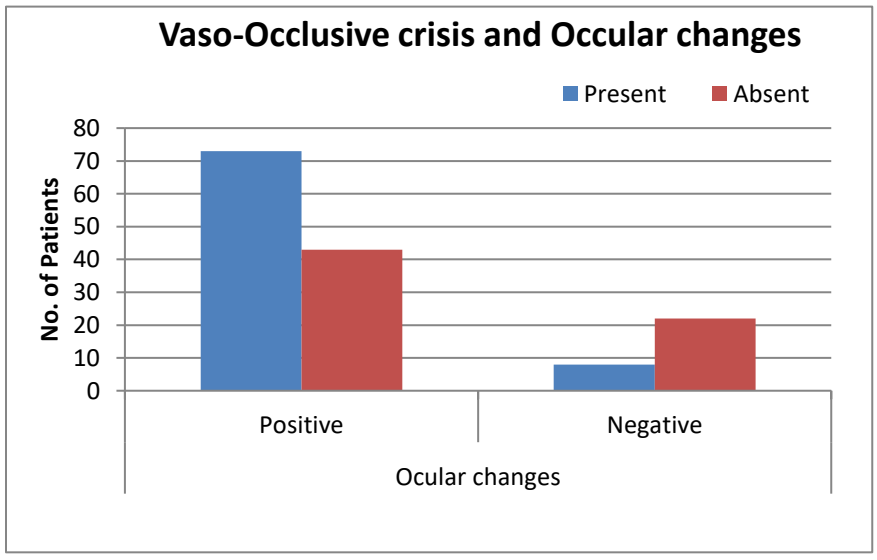

Fig 3: Chart showing frequency of ocular changes in relation to vaso-occlusive crisis in sickle cell patients.

In the present study, 146 cases of SCD were examined which included 85 cases of Sickle cell anemia (HbSS) and 61 were of sickle cell trait (HbAS). 116 out of total 146 study subjects (79.45% cases) have shown ocular changes (Fig-1). Highest numbers of male SCD and SCT patients were in the age group of 21-30 followed by 11-20 yrs group (Fig-2). The peak for female SCD patients was in 11-20 yrs while for SCT females it was 21-20 yrs (Table-1, Fig-2). The Mean age of the subjects with ocular changes was 20.37 years. It was also observed that, of the 80 patients who had veno-occlusive crisis, 73 patients (91.25%) had shown ocular changes (Table-2, Fig-3).

The conjunctival signs were observed in 62 (77.55%) patients with SCD and 18 (34 %) patients with SCT (Table-3, Fig-4). There were only 2 (2.35%) cases of SCD showing iris atrophy. None of the patients had anterior chamber signs. Out of 85 cases of SCD only 3 (3.52%) cases had temporal disc pallor apart from which no other disc abnormality was observed. Chronic maculopathy was found in 2 (2.35%) patients of SCD and 7(10.6%) patients of SCT (Table-4, Fig-5).

Most common peripheral retinal change seen was venous dilatation and tortuosity in 47 (55.23%) patients of SCD and 18 (29.5%) patients of SCT (Fig-6). Retinal hemorrhages were found in 18 (22.5%) SCD and 4 (6.06%) SCT. Neovascularisation was found in 3 (3.52%) patients with SCD while retinal detachment was present in 2 (2.5%) patients with SCD leading to potential blindness (Table-5). In general, overall peripheral retinal changes are more common in sickle cell disease patients than in sickle cell carrier subjects.

Table 3: Conjunctival signs in sickle cell anemia.

	Hb genotype	n	Conjunctival signs present.	**No** conjunctival signs observed	Percentage of total
1	HbSS	80	62	18	77.50
2	HbAS	53	18	35	34.00
3	HbF	13	0	13	00.00
	Total	146	80	66	54.79

Table 4: Macular changes according to sickle cell type.						
	No change	Maculopathy	Macular hole	ARMD	Dull FR	Total
SC Disease	79	2	0	3	1	85
SC Trait	48	7	0	2	4	61
Total	127	9	0	5	5	146

Table 5: Peripheral Retinal changes in sickle cell patients.				
Retinal Changes	**SCA (n=85)**	**%**	**SCT (n=61)**	**%**
Pallor (P)	2	2.35	3	4.91
Exudates (E)	5	5.88	1	1.6
Venous dilatation & tortuosity (VD)	47	55.23	18	29.5
Haemorrhages (Hae)	18	22.35	4	6.56
Iridescent spots (IS)	10	11.76	1	1.6
Schisis cavity (SC)	9	10.5	0	0
Neovascularisation (NV)	3	3.52	0	0
Mottled brown areas (MbA)	2	2.35	1	1.6
Arteriolar attenuation (ArA)	0	0	1	1.6
Retinal detachment (RD)	2	2.35	0	0
No changes (NC)	24	28.23	37	60.65

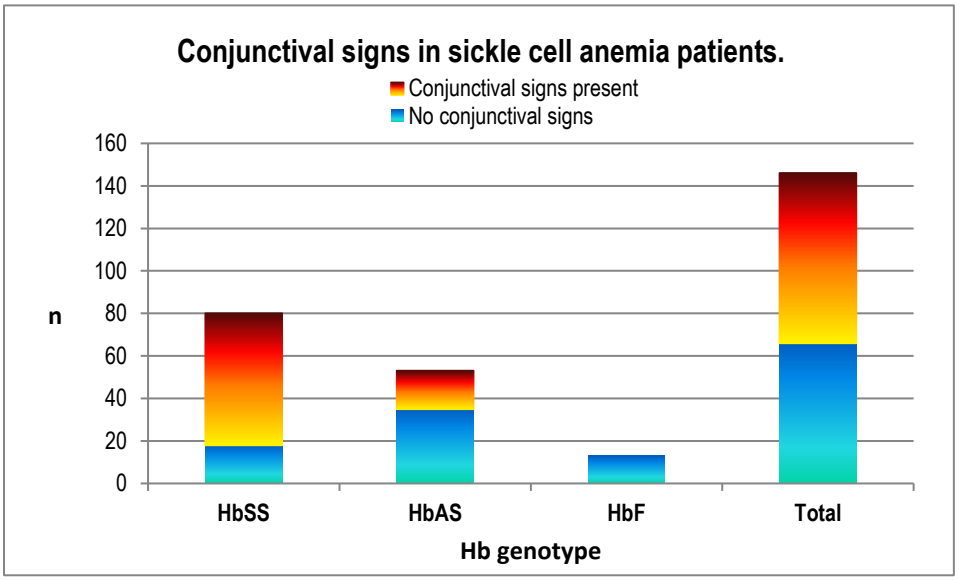

Fig 4. Chart showing conjunctival signs in sickle cell patients as per Hb genotype groups. (HbSS = Sickle cell disease; HbAS = Sickle cell Trait or carrier; HbF = Fetal Haemoglobin)

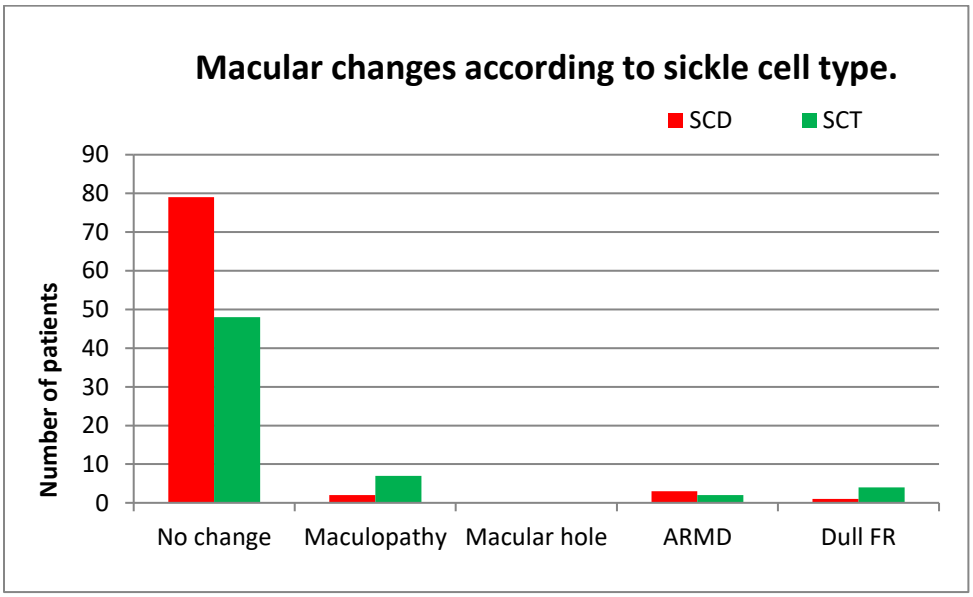

Fig 5. Chart showing macular changes in sickle cell patients.
(SCD = Sickle cell disease; SCT = Sickle cell Trait or carrier; ARMD = Age related macular degeneration; FR = Foveal reflex)

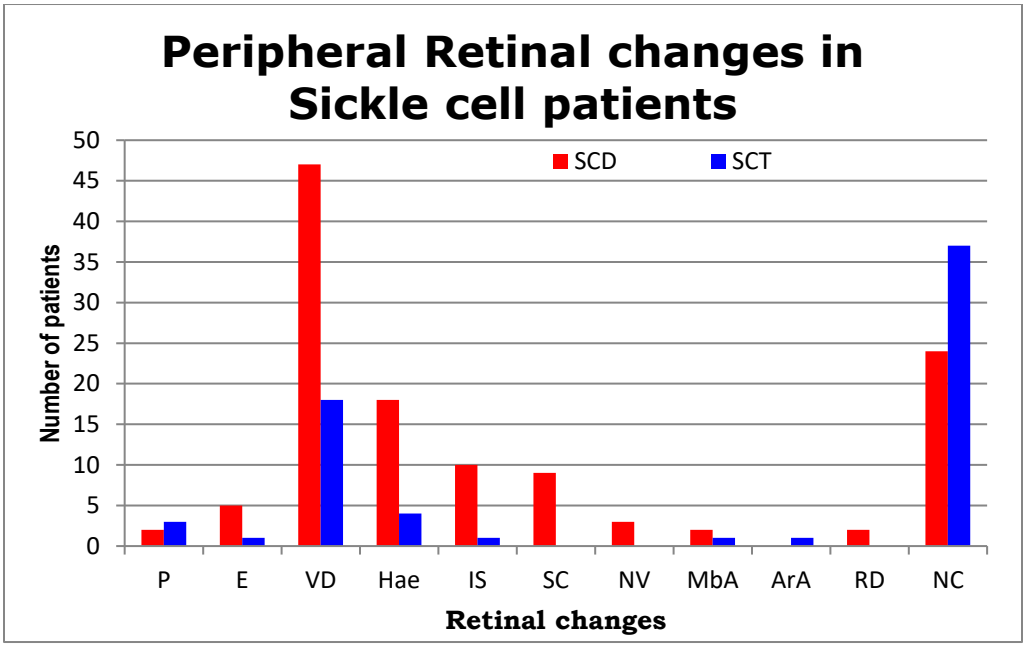

Fig 6. Chart showing distribution of peripheral retinal changes in sickle cell patients.
(SCD = Sickle cell disease; SCT = Sickle cell Trait or carrier; P = Pallor; E = Exudates; VD = Venous dilatation & tortuosity; Hae = Hemorrhages; IS = Iridescent spots; SC = Schisis cavity; NV = Neovascularisation; MbA = Mottled brown areas; ArA = Arteriolar attenuation; RD = Retinal detachment; NC = No changes)

Discussion:

Sickle cell anemia leading to microvascular abnormality can affect most of ocular structures. Though most ocular associations are harmless, few of them can lead to potentially blinding eye disease. Pathogenesis of ocular manifestations in sickle cell anemia is embedded in the abnormal hemoglobin variant HbS.

It is well established that sickle cell hemoglobin (HbS) is the result of a point mutation in the gene coding for β globin, when the amino acid valine is substituted for glutamic acid at the sixth position of the β chain. This single amino acid substitution has far-reaching effects on hemoglobin interactions, erythrocyte morphology, and hemodynamics. The HbS has an unusual property to bind with other HbS molecules within the erythrocyte in deoxygenated state. The basic structural unit that results is a twisted, ropelike structure composed primarily of hemoglobin molecules with binding through the β chains. This process is referred to as polymerization. The result is a strand of relatively

rigid, polymerized hemoglobin molecules. Onto this basic polymer, other hemoglobin molecules may also polymerize, leading to large polymer strands. These rigid strands distort the erythrocyte into a variety of elongated shapes and decrease its deformability. This sets the stage for vascular obstruction and hemolysis.

As a result of multiple episodes of polymerization (which is reversible) and dehydration (which is not fully reversible) is a dense, irreversibly sickled cell. When oxygenated, an irreversibly sickled cell may contain no polymer but is nonetheless distorted in shape and will contribute to vaso-occlusion. Thus majority of ocular complications in sickle cell anemia are the consequences of frequent vaso-occlusive crisis which cause → hypoxia, then → ischemia, which results in → infarction in ocular structures; this leads to → neovascularisation, then to → fibrovascularisation[2,5].

A prospective longitudinal study over 20 years has reported increased incidence of ocular complications with age in both sickle cell genotypes, with crude annual incidence rates of 0.5 cases% SS subjects and 2.5 cases% SC subjects[12]. Prevalence was reported to be higher in SC disease by the ages of 24 to 26 years. PSR had occurred in 43% subjects with SC disease and in 14% subjects with SS disease and spontaneous regression occurred in 32% of PSR-affected eyes[12]. Permanent visual loss was uncommon in subjects observed up to the age of 26 years[12]. In the present study, 5 patients were observed with severe vision loss. Highest numbers of male SCD and SCT patients in the present study were in the age group of 21-30 followed by 11-20 yrs group. The peak for female SCD patients was in 11-20 yrs while for SCT females it was 21-20 yrs. These findings agree with the earlier reports[11,12,15] that higher percentage of ocular complications in sickle cell subjects occur in the age group 11-30.

It has long been known that the macrovasculature of patients with sickle cell anemia may develop intimal hyperplasia. This creates irregular areas of endoluminal narrowing, which likely worsen vaso-occlusion by promoting thrombosis. This explains the present observations of highest percentage of ocular complications in sickle cell patients which is directly related to vaso-occlusion. Of the 80 patients who had veno-occlusive crisis, 73 patients (91.25%) had shown ocular changes. Similarly highest percentage of patients has shown venous dilatation and tortuosity as major clinical sign of non-proliferative retinopathy in both SCD and SCT patients. This finding confirms the earlier report that vascular tortuosity was the commonest ocular manifestation of sickle cell disease[11]. Our study documents higher prevalence of retinopathy along with some conjunctival signs in the SCD

patients who reported at our centre for specialized medical treatment. These SCD patients mostly came from tribal areas in hilly regions in northern region of Maharashtra state.

From the ophthalmologic perspective, the most important representative of this group of patients is sickle cell retinopathy, which presents a wide spectrum of fundus manifestations and may even lead to irreversible vision loss if not properly diagnosed and treated. Early-stage diagnosis of SCD patients with risk of retinopathy is recommended to prevent the progression of the disease through regular retinal examinations and adapted treatment modalities[2,5]. Retinal examination must be done in homozygous, double heterozygous patients or when the sickle trait is present with additional systemic vascular conditions. As the subjects of the this study mostly reside in remote hilly areas recognized as endemic zone, where specialized medical care is not available, great efforts have to be made for early diagnosis and detection of ophthalmic complications and to provide adequate treatment to these patients from the available modalities[4,5] to prevent subsequent vision loss.

The limitations of the present study are the lack of or control of confounding factors. Several factors, including environmental factors that might result in an ocular problem (such as light, drug and toxic substance exposure) were not considered. Also, the co-morbidity complex between SCD and other common hemoglobin disorder such as thalassemia is possible and the ocular problems in those cases are very complex [16]. In addition, inflammatory and ischemic biomarkers levels were not determined to correlate with the SCD retinopathy. Large scale association studies may provide a powerful tool for identifying alleles associated with complex phenotypes such as retinopathy in SCD. Periodic ophthalmologic examination starting at the age of 10 years is recommended for timely-identification of retinal lesions thus minimizing the risk of sight threatening retinopathy.

Conclusion:

In summary, present study documents higher prevalence of sickle cell retinopathy along with some conjunctival changes in SCD patients from northern region of Maharashtra state. In general, overall peripheral retinal changes are more common in SCD patients than in SCT subjects. Further, this study demonstrates that retinopathy contributes to the susceptibility for development of vision loss in SCD cases. Though most ocular associations are mild to moderate in severity but few of them can lead to potentially blinding eye disease therefore it is recommended that all patients with SCD must

undergo ophthalmological screening at the time of diagnosis and thereafter follow-up at regular intervals. Hence, it is essential to regularly follow sickle cell retinopathy cases to prevent any future visual catastrophe.

References:

1) Jadhav AJ, Vaidya SM, Bhagwat VR, Ranade AR, Vasaikar M. Haematological Profile of Adult Sickle Cell Disease Patients in North Maharashtra. Walawalkar International Medical Journal, 2016; 3 (1): 28-36.
2) Menaa F, Khan BA, Uzair B, Menaa A. Sickle cell retinopathy: improving care with a multidisciplinary approach. Journal of Multidisciplinary Healthcare 2017:10; 335-346.
3) Shukla P, Verma H, Patel S, Patra PK, Bhaskar LV. Ocular manifestations of sickle cell disease and genetic susceptibility for refractive errors.Taiwan J Ophthalmol. 2017; 7: 89-93.
4) Maria Teresa Brizzi Chizzotti Bonanomi, Marcelo Mendes Lavezzo. Sickle cell retinopathy: diagnosis and treatment. Arq Bras Oftalmol. 2013; 76(5): 320-327.
5) Abdalla Elsayed, MEA, Mura, M., Al Dhibi, H., Schellini S, Malik R, Kozak I, SchatzP.Sickle cell retinopathy. A focused review. Graefes Arch Clin Exp Ophthalmol. 2019; 257: 1353. https://doi.org/10.1007/s00417-019-04294-2
6) Clarkson JG. The ocular manifestations of sickle-cell disease: a prevalence and natural history study. Trans Am Ophthalmol Soc. 1992; 90: 481–504.
7) El-Ghamrawy MK, El Behairy HF, El Menshawy A, Awad SA, Ismail A, Gabal MS, et al. Ocular manifestations in Egyptian children and young adults with sickle cell disease. Indian J Hematol Blood Transfus. 2014; 30: 275-280.
8) Kent D, Arya R, Aclimandos WA, Bellingham AJ, Bird AC. Screening for Ophthalmic manifestations of Sickle Cell Disease in the United Kingdom. Eye 1994; 8: 618-622.
9) Fadugbagbe AO, Gurgel RQ, Mendonça CQ, Cipolotti R, dos Santos AM, Cuevas LE. Ocular manifestations of sickle cell disease. Ann Trop Paediatr. 2010; 30(1): 19-26.
10) Al-salem M. Benign ocular manifestations of sickle cell Anemia in Arabs. Indian J Ophthalmol. 1991; 39: 9-11.
11) Mumbi BW. Ocular manifestations of sickle cell disease at the university teaching hospital, Lusaka, Zambia. Masters in Medicine (Ophthalmology), Dissertation, University of Nairobi. 2014.

12) Downes SM, Hambleton IR, Elaine, Chuang L, Lois N, Serjeant GR,Bird AC. Incidence and Natural History of Proliferative Sickle Cell Retinopathy: Observations from a Cohort Study. Ophthalmology 2005; 112 (11): 1869-1875.
13) Bonamoni MT, Cunha SL, de-Aravjo JJ. Funduscopic alterations in SS and SC haemoglobinopathies: study of a Brazilian population. Ophthalmologica 1988; 197: 26-33.
14) Talbot JF, Bird AC, Maude GH, Acheson RW, Moriarty BJ, Sergeant GR. Sickle cell retinopathy in Jamaican children: further observations from a cohort study. Br J Ophthalmol. 1988; 72: 727-32.
15) Rautray K, Tidake P, Acharya S, Shukla S. Ocular Manifestations In Sickle Cell Disease –A Preventable Cause Of Blindness?. IOSR Journal of Dental and Medical Sciences, 2015; 14 (11): 11-16.
16) Joob B, Wiwanitkit V. Ocular manifestations of sickle cell disease. Taiwan J Ophthalmol. 2018; 8: 55.