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Evaluation and Documentation of Ophthalmic Lesions in Children Having Homozygous Sickle Cell Disease

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Abstract

Background: Homozygous sickle cell disease is prevalent in tribal population of South Gujarat. *Aim:* To determine prevalence of different ocular manifestations in pediatric patients with homozygous sickle cell disease in South Gujarat. *Setting and Design:* Cross sectional study at tertiary level government hospital and primary health centers. *Methods:* 125 children with homozygous sickle cell disease, who fulfilled the criteria were enrolled, were enrolled in the study during a period from *December 2015* to *June 2017*. We collected data on demography, ocular history, hospitalization history and complete eye examination. We calculated systemic severity index. *Statistical analysis used:* We used SPSS version 20. *p* value ≤ 0.05 was considered to be statistically significant. *Results:* Majority of children were from age group *11–18 years* (68.8%) and belonged to schedule tribe with almost equal gender distribution; M: F = 1:1.08. Ocular abnormalities were observed in 43 (34.4%) patients. Anterior segment presentations were: Conjuctival sign-21 (16.8%), Iris atrophy-1 (0.8%). Posterior segment signs were: Retinal venous tortuosity-25 (20%), High cup: Disc ratio-3 (2.4%), Vitreous hemorrhage (Grade 4 Proliferative Central Retinopathy) -4 patients (3.2%), Salmon patch hemorrhage-2 (1.6%), Angioid streaks-2 (1.6%), Drusen-1 (0.8%), Central retinal artery occlusion-1 (0.8%). Ocular manifestations were found to be statistically significant in patients with systemic severity index between 0.8-1. Blindness was found in 4% cases. *Conclusion:* Mild ocular morbidities are found in children having homozygous sickle cell disease in most vulnerable communities of South Gujarat. Regular eye check-up is recommended in children having high systemic severity index for early diagnosis and treatment of potential blinding conditions.

Keywords: Homozygous sickle cell disease; Systemic severity index; Venous tortuosity; Conjuctival sickling sign; Vitreous hemorrhage.

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Introduction

Hemoglobinopathies are a group of genetic disorders of hemoglobin. They affect about 4.5% of the world population.[1] In India too, they have been considered responsible for the largest number of genetic disorders, contributing to imbalance in health profile.[2] It is estimated that incidence of major Hemoglobinopathies traits in Gujarat is about 12%.[3] Sickle Cell Disease (SCD) is one such severe hematological disorder. The prevalence of sickle cell in India varies between 1 and 44% because of consanguinity, caste issues and area endogamy.

Sickling disorders include: (1) heterozygous (HbAS) sickle cell trait (2) homozygous (HbSS) sickle cell disease (3) compound heterozygous states for HbS with hemoglobin C (HbSC), D (HbSD), E (HbSE) or other structural variants and (4) the combination of the sickle cell gene with different

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forms of thalassemia (HbSThal). Out the various genotypes which are known to cause SCD, the three predominate types identified in most populations are HbSS [often called Sickle Cell Anemia (SCA)], HbSC and HbS/-thalassemia.[5]

The polymerization of deoxygenated HbS results in premature destruction of red blood cells (hemolysis) and blockage of blood flow (vaso-occlusion). Micro-vascular occlusions is the most common cause of visual loss, especially those who suffered repeated episodes of vaso-occlusion are vulnerable to blindness. Sickle cell disease can affect every part of the eye.

According to Indian Council of Medical Research, sickle cell disease is most common in tribal populations. Gujarat has 89.12 lakhs tribal population (10–15% of the total tribal population of India). It is expected to have 70,000 Sickle Cell Disease patients and prevalence of Sickle Cell Trait (SCT) varies from 0 to 31.4% among different tribes.[6,7] Due to the high prevalence in some communities, the screening program is arranged by the government for control of sickle cell anemia in South Gujarat which has created disease awareness in the population. The improvement in the medical care of children with Sickle cell Disease has increased their survival.[8,9] This has raised the possibility of increased number of blind years in children surviving with sickle cell disease, if the potential blinding ophthalmic problems are not timely identified.

The knowledge about the magnitude of ocular manifestations in homozygous sickle cell disease patients of South Gujarat will be helpful to plan strategies for early diagnosis and intervention of blinding eye conditions in such debilitated patients.

Materials and Methods

The study was conducted in a tertiary care Government hospital and few primary health centers in South Gujarat. We took patient's assent and informed consent of their parents. The research was conducted in accordance to the tenets of Declaration of Helsinki. The study was approved by the Human Ethics Research Committee of our institute.

The present study is a cross sectional hospital and community based study of ocular manifestations in diagnosed cases of homozygous sickle cell disease in children. 125 children between *2* and *18 years* of age from *December 2015* to *June 2017* were recruited in the study. Pediatricians in our hospital were requested to send diagnosed cases of homozygous sickle cell disease patients to outdoor patient department of Ophthalmology for detailed ophthalmic examination. We also approached to health centers in South Gujarat where many cases of homozygous sickle cell disease are registered and who come for regular follow up. The Medical Officer of the peripheral health centers were requested to organize camps for registered cases of homozygous sickle cell disease patients for ophthalmic examination. When camp was organized, patients and their parents were explained about the disease and importance of eye examination in it. We excluded patients who had ocular comorbidities like developmental cataract, developmental glaucoma, retinopathy of prematurity; patients having other hemoglobinopathies like leukemia, thalassemia, etc.

We documented detailed ocular history, past history, family history and sibling history of the patients. History regarding hospitalization, purpose of hospitalization, duration and number of hospitalization till date was recorded.

Sickle cell disease is a systemic disease, the more severe the disease, higher are the chances of end organ damage one would expect including damage to ocular structures. To study this association, we calculated systemic severity index by dividing number of hospitalizations since birth, by age of the patient.[10]

We did detailed anterior and posterior segment examination of all patients. Visual acuity assessment was done by Snellen's chart. Anterior segment examination for conjuctival sickling sign, iris depigmentation or atrophy was done on slit lamp when patients were examined at a tertiary care center or on a torch light when patients were examined at peripheral health centers. We carried out indirect and direct ophthalmoscopy to identify lesions in posterior segment after dilating pupils with Tropicamide and Phenylephrine combination eyedrops. Patients with ocular manifestation were explained about their eye condition, the warning signs and further management depending on the severity of involvement.

Statistical analysis

Data entry was done and descriptive statistics was used to express values of parameters as mean and standard deviation. Analysis of result was done by MS Excel and Statistical Package for Social Scientists (SPSS) software version 20. Any p value less than or equal to 0.05 was considered to be statistically significant.

Results

Total 125 pediatric patients were recruited in the study. Nearly two third of them were above *11 years* of age; mean age being *11.96 years* (SD: 4). The gender distribution was nearly equal (M:F = 1.08). Ocular manifestations were found in only one third (34.4%) of the total cases. Posterior segment manifestations, either in isolation or in association with anterior segment changes, were found in majority of sickle cell cases who had ocular changes. Blindness was present in only 4% cases and there were no cases of low vision. (**Table 1**)

The major anterior segment manifestation was conjunctival sickling sign in 21 patients (16.8 %). Iris atrophy was present only in one patient (0.8 %). The major posterior segment finding was venous tortuosity (20%). The high cup disc ratio (2.4%) was not associated with raised IOP in any of the cases. The prevalence of Proliferative Sickle Cell Retinopathy (PSCR) in form of Vitreous hemorrhage (Stage 4 PSCR) was 3.2% in our study. Angiod streak and Salmon patch hemorrhage was found in 1.6% cases. (**Table 2**)

Table 1: Profile of cases examined

Parameter		Number of cases (%)	
Age-Sex Distribution			
Age group (*Years*)	Male	Female	Total (%)
2–5	8	5	13 (10.4)
6–10	15	11	26 (20.8)
11–18	42	44	86 (68.8)
	65 (52%)	60 (48%)	125 (100)
Ocular Manifestations			
Anterior segment		8 (6.4)	
Posterior segment		21 (16.8)	
Both		14 (11.2)	
Total cases with ocular manifestation		43 (34.4)	
Visual Acuity at time of examination			
Vision > 6/18		110 (88)	
Low vision Category 1 (< 6/18 to 6/60)		0	
Low vision Category 2 (< 6/60 to 3/60)		0	
Blindness Category 3 (< 3/60 to 1/60)		2 (1.6)	
Blindness Category 4 (< 1/60 to perception of light)		3 (2.4)	
Blindness Category 5 (No perception of light)		0	
Vision not assessed*		10 (8)	

*These kids were < *5 years* and were unco-operative for vision assessment with available charts. They gave finger counting positive at various distances

Table 2: Various Posterior segment manifestations (*n* = 35) in children with homozygous sickle cell disease

Posterior segment manifestations	Numbers	Percentages
Venous Tortuosity	25	20
Non-significant Cup: Disc Ratio	3	2.4
Vitreous hemorrhage	3	2.4
Salmon patch hemorrhage + Vitreous hemorrhage	1	0.8
Salmon patch hemorrhage + Central retinal artery occlusion	1	0.8
Angioid Streaks	1	0.8
Angioid Streaks + Drusen	1	0.8
Total	**35**	**28**

The causes for blindness in our study were Vitreous Hemorrhage (3.2%) and Central retinal artery occlusion (0.8%). In current study, all the patients enrolled belonged to schedule tribe. Gamit, Chaudhari Kotwadiya & Dhodia were the major tribes constituting about two third (72.8%)

Table 3: Distribution of ocular manifestations in different communities

Community	Number of patients of homozygous SCD examined (%)*	Number of patients of HbSS with ocular manifestations (%)*
Gamit	54 (43.2)	16 (37.2)
Chaudhari	18 (14.4)	5 (11.62)
Kotwadiya	11 (8.8)	3 (6.9)
Vasava	5 (4)	2 (4.6)
Dhodia	8 (6.4)	4 (9.3)
Nayka	2 (1.6)	1 (2.3)
Halpati	4 (3.2)	2 (4.6)
Valvi	1 (0.8)	1 (2.3)
Gavli	2 (1.6)	0
Ozariya	3 (2.4)	1 (2.3)
Bhanvar	4 (3.2)	3 (6.9)
Dikar	3 (2.4)	1 (2.3)
Shingada	2 (1.6)	0
Bhisana	2 (1.6)	1 (2.3)
Pawar	1 (0.8)	1 (2.3)
Mathur	1 (0.8)	0
Saidanve	1 (0.8)	0
Dipalde	1 (0.8)	1 (2.3)
Kokri	1 (0.8)	0
Chauhan	1 (0.8)	1 (2.3)
Total	125	43

*Column Percentages

of the total HbSS patient examined and 65% of the total cases with ocular manifestations. The number of cases with ocular morbidity was proportionate to the number of cases included in the study for all the major tribes. (**Table 3**)

Table 4: Univariate analysis of ocular manifestation with various variables in the patients

Factor	Ocular manifestation (n = 125)					
	Yes	No	Total	Odds Ratio	χ^2 Test	p value
Gender						
Male	24	41	65	1.2635	χ^2 = 0.382	0.5365
Female	19	41	60	0.7917		
Age groups						
2–5	2	11	13	0.3173	χ^2 =1.4794	0.1349
6–10	10	16	26	1.25	χ^2 = 0.24	0.6242
11–18	31	55	86	1.2682	χ^2 = 0.3311	0.5650
Systemic severity index*						
0–0.3	14	47	61	0.3625	χ^2 = 6.921	0.008521
0.4–0.7	17	32	49	1.0216	χ^2 = 0.00308	0.9557
0.8–1	8	1	9	18.09	χ^2 = 10.2906	0.0008
Above 1	4	2	6	4.052	χ^2 = 1.5998	0.1236

*Systemic severity index = number of hospitalization from birth/age of patient in *years*

Mean of systemic severity is 0.38 with range of 0–1.66. (SD = 0.31). The univariate analysis shows that only systemic severity has statistically significant association with ocular findings. When systemic severity is between 0.8–1, more ocular manifestations are found (p value -0.0008). (**Table 4**)

Discussion

In the present study, 70% of the patients with HbSS disease were above 11 years. This may be due to less awareness about the health problem in the community. Disease is diagnosed only when there

is a complication or observed in a routine checkup. Ocular manifestations were found in 34.4 % cases which are comparable to similar such study done in Nigeria.[11]

Conjuctival signs were the major anterior segment finding. It is considered as a pathognomonic sign for sickle cell disease.[12] However, in our study the rate is lower as compared to study done in past where 70% of SS disease patient had conjuctival sign. It was also reported that the frequency is higher for homozygous variety of patients as compared to sickle cell heterozygous variety or sickle thalassemia.[13] The reason of lower rate in our study could be the study population, whereby only pediatric patients were studied. It suggests that development of conjuctival finding may be related to the age of the patient. The major posterior segment finding was venous tortuosity similar to other studies.[14,15] Though 2.4% case had sickle disc sign none had glaucoma. The prevalence study reported it to be 12% in SS patient but none of HbSC or HbSthal patient had sickle disc sign.[13] There are documented case reports of sickle cell patient developing neovascular glaucoma.[16]

Proliferative Sickle Cell retinopathy prevalence of 3.2% in our study was contradictory to study in Nigerian children where no cases of Sickle cell retinopathy were reported.[11] Sickle Cell Retinopathy is also an age dependent process.[17] Earlier studies have reported lesser prevalence rate of PSCR in HbSS patient than HbSC patients in pediatric population similar to the findings in adults.[13,15,18–20]

The prevalence of angiod streak in our study was 0.8 % and was not associated with vision loss. It is studied that angiod streak in sickle cell patients are paripapillary and rarely affects vision.[21] In the natural course study, it was reported that majority of the patient with angiod streak were above *50 years* of age and no eye had clinical evidence of neo-vascularization.[13]

Majority of our patients had normal vision. Proliferative Sickle Cell retinopathy manifesting as vitreous hemorrhage was the major cause of blindness in our study. Another study in Jamaican population also reported vitreous hemorrhage as the most frequent cause of moderate and severe vision loss. PSCR contributes to vision loss by predisposing an eye due to vitreous hemorrhage, vitreous traction, retinal detachment and epiretinal membrane formation.[23] However, the natural course of PSCR is determined by the phenomenon of auto infarction or development of atrophic lesions which results in spontaneous regression of lesions as studied by various researchers.[24,25] The lower frequency of vision loss in Sickle Cell Disease patient, as in our study, can be attributed partly to this phenomenon occurring in about 20–60% cases.[26] The treatment of PSCR with laser has shown to reduce the incidence of vision loss.[27,28] This is of particular importance in pediatric population as it will reduce the number of blind years.

All patients in our study belonged to tribal castes. According to Indian Council of Medical Research, sickle cell disease is most common in tribal populations. There are study reports of higher prevalence of sickle cell trait in Gamit, Chaudhari and Vasava communities and prevalence of 0.03 % SCD in few sub castes of Gujarati Patel like Dhodia and Koli.[29] Because of consanguineous marriage, there is more chance of offspring's born with with SS disease. Our study shows similar findings of higher number of patients with SCD examined and also those with ocular manifestation belonging to Gamit and Chaudhary community followed by kotwadiya and Dhodia.

The univariate analysis showed that only systemic severity has statistically significant association with ocular findings. This is in contradiction to another study where age and not systemic severity of sickle cell disease, had significant association with ocular manifestations.[14] This may be because the researcher studied a population with homozygous sickle cell disease where nearly 50% cases were above *16 years*. We can say that in pediatric population, systemic severity can be used to predict ocular changes in SS patient.

Conclusion

Present study reveals a low prevalence of ocular morbidities in children having homozygous sickle cell disease in most vulnerable communities of South Gujarat. It emphasizes the need of regular eye check-up only in children having high systemic severity index for early diagnosis and treatment of potential blinding conditions. The disease requires monitoring of patient diagnosed with proliferative lesion to timely decide the therapeutic options as it has a variable course of progression.

Key Message

Ophthalmic referral is recommended to screen children with homozygous sickle cell disease for early detection of potential blinding conditions like proliferative sickle retinopathy.

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