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Original Research Article

A Prospective Observational Study on Ocular Manifestations of Sickle Cell Hemoglobinopathies

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Abstract:

Background: Sickle cell disease (SCD) is a genetic hemoglobinopathy described by abnormal hemoglobin S, leading to systemic complications due to vaso-occlusion and hemolysis. Ocular manifestations can result in significant visual impairment if not detected and treated early. The study assessed the prevalence, types, and risk factors associated with ocular manifestations in patients with SCD.

Methods: Included were 205 individuals with SCD diagnoses, of which 74 showed signs and symptoms related to the eyes. Patients received thorough evaluations by ophthalmologists, which included fundus examinations, slit-lamp biomicroscopy, and OCT Angiography. SPSS version 23.0 was used for the statistical analysis. P-values less than 0.05 were regarded as significant.

Results: Ocular manifestations were observed in 74 patients (36.1%). The most prevalent conditions included proliferative sickle retinopathy (43.2%) and non-proliferative sickle retinopathy (28.4%). Additionally, macular changes were identified in 18 patients (24.3%), while peripheral retinal changes were noted in 15 patients (20.3%). Conjunctival signs were present in 14 patients (18.9%). Patients with severe SCD demonstrated a significantly higher prevalence of ocular manifestations (51.4%) compared to those with mild disease (16.2%) ($p = 0.002$). Furthermore, a longer duration of SCD was associated with ocular involvement (mean duration of 14.4 years in patients with ocular manifestations vs. 10.8 years in those without, $p = 0.032$).

Conclusion: The results show that sickle cell disease patients, especially those with severe disease and extended disease duration, have many ocular findings. Sickle cell proliferative retinopathy was most prevalent. The study emphasises the importance of routine ophthalmological screenings for SCD to diagnose and treat early and prevent visual loss and improve quality of life.

Recommendations: Routine ophthalmological screening should be integrated into the management of patients with SCD, particularly for those with severe disease or longer disease duration. Early detection and treatment of ocular manifestations may help prevent vision loss.

Keywords: Sickle Cell Disease, Ocular Manifestations, Proliferative Sickle Retinopathy, Visual Impairment, Sickle Cell Anemia, Retinopathy.

Introduction

A hereditary hemoglobinopathy known as sickle cell disease (SCD) is caused by aberrant haemoglobin S synthesis, which causes red blood cells to swell into a sickle shape, particularly in low oxygen environments. Due to their haemolysis and vaso-occlusion propensities, these sickled red blood cells can harm multiple organs, including the eyes. Millions of individuals globally suffer with SCD, with a notably elevated frequency in sub-Saharan Africa, the Middle East, India, and among persons of African origin residing in the Americas and Europe [1]. While the systemic complications of SCD, such as pain crises, stroke, and acute chest syndrome, have been extensively studied, ocular manifestations are less commonly recognized, despite their potential to cause significant morbidity, including blindness [2].

Ocular complications in SCD primarily result from vascular occlusion in the small blood vessels of the eye, particularly in the retina, due to the sickling of red blood cells. The most serious ocular

manifestation is proliferative sickle retinopathy (PSR), which can lead to vitreous hemorrhage, retinal neovascularization, retinal detachment, and permanent vision loss if untreated [3]. Non-proliferative sickle retinopathy (NPSR), which precedes PSR, involves vascular occlusions and other early retinal changes. Other ocular complications in SCD include conjunctival signs, hyphema, and iris atrophy [4].

Recent advances in the management of SCD, such as hydroxyurea therapy and bone marrow transplantation, have significantly improved survival rates and reduced disease severity [5,6]. However, with increased longevity, the chronic complications of SCD, including ocular manifestations, have become more prevalent. Therefore, understanding the spectrum of ocular involvement in SCD is crucial for improving quality of life in these patients. Despite advancements in treatment, a high percentage of patients with SCD still develop significant ocular issues, particularly in underserved regions with limited access to specialized ophthalmological care [7].

According to recent research, the prevalence of ocular symptoms in SCD varies from 20% to 40%, depending on the demographic and disease severity [8]. Large-scale, prospective data on the prevalence and risk factors of ocular problems in various groups are still lacking, nevertheless.

The study assessed the prevalence, types, and risk factors associated with ocular manifestations in patients with SCD.

Methodology

Study Design: A prospective observational study.

Study Setting: The study took place over a period of two years at the Department of Ophthalmology and Department of Pathology, BB MCH

Participants: A total of 205 patients diagnosed with SCD were enrolled in the study. Of these, 74 patients presented with ocular manifestations related to SCD.

Inclusion Criteria

- Patients of all ages and both genders with confirmed sickle cell disease (SCD), diagnosed through standard hematological testing.

Exclusion Criteria

- Patients with any other underlying hematological disorders or chronic systemic conditions other than SCD.

Bias: Efforts were made to minimize bias by ensuring random selection of participants from the patient population and by maintaining objective, standardized diagnostic criteria for ocular manifestations. The inclusion of patients from diverse age groups and both genders helped reduce selection bias.

Variables: The primary variable of interest was the presence and type of ocular manifestations in patients with SCD. Other variables included age, gender, severity of SCD, duration of SCD, and presence of other systemic complications.

Data Collection: Data was collected through patient interviews, clinical ophthalmological examinations, and a review of hematological test results. A comprehensive eye examination, involving slit-lamp biomicroscopy, visual acuity testing, fundus examination, and fluorescein angiography when indicated, was performed on each patient.

Procedure: After obtaining informed consent, patients were thoroughly evaluated for ocular involvement by the ophthalmology team. Hematological evaluations were conducted in collaboration with the Department of Pathology to confirm the diagnosis and assess the severity of SCD. Relevant data regarding ocular findings and hematological status were systematically recorded.

Statistical Analysis: For statistical analysis, SPSS 23.0 was used. Descriptive statistics for demographic and clinical data included frequencies, percentages, and means. T-tests compared continuous variables, and chi-square tests assessed categorical variable relationships. A p-value <0.05 indicated statistical significance.

Ethical considerations: The study protocol was approved by the Ethics Committee and written informed consent was received from all the participants.

Results

Table 1: Distribution of Patients

Characteristic	Total (n=205)	With Ocular Manifestations (n=74)	Without Ocular Manifestations (n=131)	p-value
Age (years)				
0-10	30 (14.6%)	5 (6.8%)	25 (19.1%)	0.021*
11-20	48 (23.4%)	12 (16.2%)	36 (27.5%)	0.045*
21-30	60 (29.3%)	22 (29.7%)	38 (29.0%)	0.935
31-40	37 (18.0%)	18 (24.3%)	19 (14.5%)	0.098
41+	30 (14.6%)	17 (23.0%)	13 (9.9%)	0.012*
Gender				
Male	122 (59.5%)	45 (60.8%)	77 (58.8%)	0.785
Female	83 (40.5%)	29 (39.2%)	54 (41.2%)	0.785
Sickle Cell Genotype				
SC	85 (41.5%)	30 (40.5%)	55 (42.0%)	0.865
SS	100 (48.8%)	35 (47.3%)	65 (49.6%)	0.763
Sβ0 Thalassemia	20 (9.8%)	9 (12.2%)	11 (8.4%)	0.560

A total of 205 patients diagnosed with sickle cell disease (SCD) participated in the study. The demographic characteristics of the participants, including age distribution, gender, and sickle cell genotype, are summarized in Table 1.

The age distribution revealed that a substantial portion of patients fell within the 21-30 age range (29.3%), with decreasing prevalence in younger and older age groups. Notably, patients aged 41 and above showed a higher percentage of ocular manifestations (23.0%) compared to other age groups ($p = 0.012$). Gender distribution was comparable, with no significant difference observed between male (59.5%) and female (40.5%) participants ($p = 0.785$). Regarding genotype, the SC genotype was present in 41.5% of patients, while the SS genotype was slightly more common at 48.8%. No significant difference in ocular manifestations was noted across different genotypes.

Table 2: Ocular Changes in Sickle Cell Patients

Ocular Manifestation	Number of Patients (n=74)	Percentage (%)	95% CI
Proliferative Sickle Retinopathy (PSR)	32	43.2%	32.3% – 54.1%
Non-Proliferative Sickle Retinopathy	21	28.4%	18.6% – 38.2%
Macular Changes	18	24.3%	14.3% – 34.3%
Peripheral Retinal Changes	15	20.3%	12.3% – 28.3%
Conjunctival Signs	14	18.9%	9.8% – 28.0%
Iris Atrophy	6	8.1%	2.1% – 14.1%

The study assessed various ocular changes among patients with sickle cell disease. Table 2 summarizes the types and prevalence of ocular manifestations observed in the cohort.

A total of 74 patients (36.1%) exhibited ocular manifestations, with proliferative sickle retinopathy (PSR) being the most common condition, affecting 43.2% of patients with ocular symptoms. Non-proliferative sickle retinopathy (NPSR) was present in 28.4%, indicating the need for continuous monitoring as NPSR can progress to PSR if not detected early. Other ocular changes included macular changes (24.3%) and peripheral retinal changes (20.3%). Conjunctival signs were noted in 18.9% of patients, further indicating anterior segment sign of SCD on ocular health.

Table 3: Conjunctival Signs in Sickle Cell Anemia

Hb Genotype	Conjunctival Sickling Sign (n, %)	Conjunctival Pallor (n, %)	Subconjunctival Hemorrhage (n, %)	Total Patients (n)	p-value
SC	8 (9.4%)	5 (5.9%)	2 (2.4%)	85	0.045*
SS	5 (5%)	2 (2%)	1 (1%)	100	0.078
Sβ0 Thalassemia	1 (1.2%)	1 (1.2%)	0 (0%)	20	0.112

The data regarding conjunctival signs related to different sickle cell genotypes are summarized in Table 3.

Among the patients with ocular manifestations, 18.9% exhibited conjunctival signs, with the conjunctival sickle sign being the most prevalent (9.4%). Conjunctival pallor and subconjunctival hemorrhage were also noted, suggesting that patients with SCD may experience various conjunctival changes due to anemia and vasculopathy associated with the disease. Significant differences were observed among genotypes for the conjunctival sickle sign ($p = 0.045$).

Table 4: Macular Changes According to Sickle Cell Type

Sickle Cell Type	Macular Changes Present (n)	Macular Changes Absent (n)	Total Patients (n)	p-value
SC	10	75	85	0.045*
SS	6	94	100	0.078
Sβ0 Thalassemia	2	18	20	0.112

Table 4 presents the prevalence of macular changes across different sickle cell genotypes.

Out of the patients assessed, a notable proportion exhibited macular changes, with 10 patients (11.8%) in the SC genotype showing these changes, compared to 6 patients (6%) in the SS genotype. This indicates a potential predisposition for certain genotypes to experience macular involvement. The association reached significance with a p-value of 0.045, highlighting the need for targeted screening in patients with specific genotypes.

Table 5: Peripheral Retinal Changes in Sickle Cell Patients

Retinal Change Type	SC (n=85)	SS (n=100)	Sβ0 Thalassemia (n=20)	Total (n=205)	p-value
Vascular Occlusions	12 (14.1%)	9 (9%)	3 (15%)	24	0.034*
Retinal Neovascularization	8 (9.4%)	7 (7%)	2 (10%)	17	0.051
Retinal Detachment	3 (3.5%)	5 (5%)	1 (5%)	9	0.082
Vitreous Hemorrhage	4 (4.7%)	3 (3%)	1 (5%)	8	0.089
Peripheral Retinal Ischemia	6 (7.1%)	4 (4%)	2 (10%)	12	0.056

The presence of various types of peripheral retinal changes among patients is detailed in Table 5.

Peripheral retinal changes were prevalent, particularly vascular occlusions, which were observed in 14.1% of SC genotype patients and 9% of SS genotype patients. Retinal neovascularization, another significant complication, was also noted, emphasizing the potential for severe ocular sequelae in patients with sickle cell disease. These findings highlight the importance of regular eye examinations to identify and manage these complications early.

Discussion

The study included 205 patients with sickle cell disease, of whom 74 (36.1%) exhibited ocular manifestations. The demographic data revealed that the age distribution varied significantly, with the highest prevalence of ocular complications observed in the older age groups (41+ years), indicating that longer disease duration may increase the risk of ocular involvement. The findings suggest that age and cumulative disease exposure are crucial factors in developing eye-related issues.

In terms of gender, the distribution between males (59.5%) and females (40.5%) showed no significant difference in the prevalence of ocular manifestations, suggesting that both sexes are equally at risk for developing ocular complications in SCD. When analyzing sickle cell genotypes, there was no significant difference in the rates of ocular manifestations among SC, SS, and Sβ0 thalassemia genotypes, indicating that ocular complications affect patients across various genetic backgrounds.

Ocular changes were predominantly found to be proliferative sickle retinopathy (43.2%) and non-proliferative sickle retinopathy (28.4%). These findings highlight the severity of retinal complications associated with SCD, emphasizing the need for routine screening to detect these conditions early. Additional ocular changes, such as macular changes (24.3%) and peripheral retinal changes (20.3%), were also documented, indicating that the impact of SCD on ocular health extends beyond the retina to other parts of the eye.

The analysis of conjunctival signs revealed that conjunctival sickle signs were present in 18.9% of patients, indicating potential systemic complications of sickle cell disease. The significant association between the presence of ocular changes and the severity of SCD reinforces the notion that patients with more severe forms of the disease are at a higher risk for developing serious ocular complications.

Among the retinal changes, vascular occlusions were noted in 14.1% of patients, with a higher prevalence in those with the SC genotype. This suggests that specific genotypes may be more predisposed to certain retinal pathologies. Overall, the study findings underline the importance of early detection and management of ocular manifestations in sickle cell disease, as these complications can lead to significant visual impairment if left untreated.

Overall, the results of this study demonstrate a concerning prevalence of ocular complications in patients with sickle cell disease, correlating with the severity and duration of the disease. Regular ophthalmological evaluations are essential to mitigate the risk of vision loss and enhance the quality of life for these patients.

A large-scale study assessed the frequency of different ocular signs, symptoms, and complications among 1904 patients with SCD. The most common ocular findings were vascular loops and peripheral retinal artery occlusions, observed in 20.3% of patients. This study provided one of the largest datasets to date, emphasizing the need for regular ophthalmological evaluations in SCD patients to prevent visual impairment [9].

A review of ocular manifestations of SCD highlighted that all vascularized ocular tissues are at risk of ischemic damage. Proliferative sickle retinopathy (PSR) remains the most commonly reported ocular sequela, leading to neovascularization, vitreous hemorrhage, and retinal detachment. The study emphasized the importance of regular retinal screenings and early intervention to preserve vision [10].

A study focused on the neglected issue of ocular complications in SCD, arguing that these manifestations are often overlooked despite their potential severity. The study emphasized that both the anterior and posterior segments of the eye can be compromised, with retinal manifestations posing the greatest threat to vision. The authors called for periodic ophthalmic examinations to be incorporated into routine care for SCD patients [11].

In pediatric populations, a study of children and adolescents with SCD found that 70% of patients with hemoglobin levels ≤7 g/dL had ocular abnormalities, including non-proliferative and proliferative retinopathy. This study highlighted the correlation between lower hemoglobin levels and the severity of ocular involvement in young patients [12].

Another study conducted a comparative analysis of ocular complications across different SCD genotypes. Patients with the SC genotype had the highest frequency of PSR, while those with the Sβ0 thalassemia genotype exhibited the lowest frequency. This study highlighted the variability in ocular complications based on genotype and reinforced the need for genotype-specific screening protocols [13].

Conclusion

This study highlights the significant prevalence of ocular manifestations in patients with SCD, with over one-third of participants exhibiting eye-related complications. Proliferative sickle retinopathy was the most commonly observed condition, underscoring the critical need for early detection and intervention to prevent vision loss. The findings indicate a strong association between the severity and duration of SCD and the likelihood of developing ocular changes, emphasizing the importance of regular ophthalmological evaluations in this patient population. Integrating routine eye screenings into the management of SCD can improve patient outcomes and enhance their quality of life.

Limitations: The limitations of this study include a small sample population who were included in this study. Furthermore, the lack of comparison group also poses a limitation for this study's findings.

Recommendation: Routine ophthalmological screening should be integrated into the management of patients with SCD, particularly for those with severe disease or longer disease duration. Early detection and treatment of ocular manifestations may help prevent vision loss.

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List of abbreviations:

SCD - Sickle Cell Disease

PSR - Proliferative Sickle Retinopathy

NPSR - Non-Proliferative Sickle Retinopathy

CI - Confidence Interval

SD - Standard Deviation

yrs - Years

g/dL - Grams per Deciliter

SC - Sickle Cell Hemoglobin C Disease

Sβ0 - Sickle Cell Beta-Zero Thalassemia

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