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Genotype-specific patterns and clinical implications of ocular morbidity in sickle cell disease patients: insights from a tertiary healthcare center in India

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ABSTRACT

Background: Sickle cell disease (SCD) is a prevalent genetic disorder marked by chronic hemolysis and vaso-occlusive events, leading to multiorgan complications, including significant ocular morbidity. This study aims to elucidate genotype-specific patterns and clinical implications of ocular morbidity in SCD patients at a tertiary healthcare center in western Odisha, India.

Materials and Methods: A cross-sectional study was conducted at Veer Surendra Sai Institute of Medical Sciences and Research (VSSIMSAR), Burla, Sambalpur, Odisha, from November 2018 to October 2020. A total of 103 SCD patients were enrolled using convenience sampling. Detailed ocular examinations, including visual acuity assessment, anterior segment evaluation, fundoscopy, and additional imaging, were performed. Data were analyzed using SPSS to identify genotype-specific patterns of ocular morbidity.

Results: Of the 103 patients, 60 had HbSS and 43 had HbSC genotype. The overall prevalence of ocular manifestations was 76.6%, with HbSC patients showing a slightly higher prevalence (81.4%) compared to HbSS patients (73.3%). Conjunctival corkscrew vessels were significantly more prevalent in HbSC patients (p=0.041). No significant differences were found between genotypes for other anterior segment signs or non-proliferative and proliferative fundus signs.

Conclusion: Our study reveals a high prevalence of ocular morbidity in SCD patients, with notable genotype-specific patterns. HbSC patients are more prone to certain ocular manifestations, underscoring the need for genotype-specific screening and management strategies. Early detection and targeted interventions can mitigate vision loss and improve patient outcomes.

1. Introduction

Sickle Cell Disease (SCD) is one of the most widespread genetic disorders globally, particularly affecting populations in sub-Saharan Africa, the Middle East, India, and parts of the Mediterranean.[1] The condition is caused by a single nucleotide substitution in the beta-globin gene, where glutamic acid is replaced by valine (HbS), leading to the formation of hemoglobin S. This genetic mutation results in the production of abnormal hemoglobin that, under conditions of low oxygen, can polymerize and cause red blood cells to assume a sickle shape. This pathological change in red blood cell morphology leads to chronic hemolysis, vaso-occlusive crises, and a range of systemic complications.[2]

The impact of SCD extends significantly beyond the hematologic system, affecting multiple organ systems throughout the body. Among these, the eye is a critical

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organ that can be severely compromised by the disease. The ocular manifestations of SCD can range from mild to severe and may include proliferative retinopathy, vitreous hemorrhage, retinal detachment, and other forms of retinal damage.[3] These ocular complications result from the chronic microvascular occlusions that are characteristic of SCD, which impede adequate retinal perfusion and contribute to progressive vision loss. If not appropriately managed, these complications can lead to significant morbidity, including blindness, which underscores the need for vigilant ocular screening and management.

The pathophysiology of ocular complications in SCD is closely linked to the systemic effects of the disease. The sickle-shaped erythrocytes can obstruct blood flow in the small vessels of the eye, causing ischemia and infarction in retinal tissues. This disruption in blood flow leads to various forms of retinopathy, including proliferative sickle cell retinopathy (PSR), which is associated with the formation of neovascularization and other severe retinal changes.[4] Despite advancements in supportive care and management strategies, challenges persist in addressing the variability in disease expression and the unpredictability of acute exacerbations. This variability further complicates the management of ocular complications and emphasizes the need for targeted research to better understand genotype-specific patterns and their clinical implications.[5]

Ocular manifestations of SCD can vary significantly across different populations and geographic regions, influenced by genetic, environmental, and healthcare factors. In India, particularly in regions such as western Odisha, the prevalence and severity of these complications have not been extensively studied. This lack of localized data highlights the need for research focused on understanding genotype-specific patterns and their clinical outcomes within this context.[6]

This study aims to elucidate the genotype-specific patterns and clinical implications of ocular morbidity in SCD patients at a tertiary healthcare center in western Odisha, India. By examining a diverse cohort of patients with various ocular manifestations over an extended study period, this research seeks to provide a comprehensive clinicopathologic profile. The objectives include evaluating the prevalence and types of ocular complications, assessing the effectiveness of current diagnostic practices, and reviewing the available treatment modalities at the institution.[7] Through these efforts, the study aims to contribute valuable insights into SCD-associated ocular pathology, inform targeted interventions, and improve early detection and management strategies for these debilitating complications.[8] The ultimate goal is to enhance patient outcomes by advancing the understanding of genotype-specific ocular manifestations and their management in the Indian context.

2. Materials and Methods

2.1. Study design

This cross-sectional study was conducted at Veer Surendra Sai Institute of Medical Sciences and Research (VSSIMSAR), Burla, Sambalpur, Odisha, from November 2018 to October 2020.

2.2. Study population

The study included

1. Sickle cell disease (SCD) patients attending the Ophthalmology Outpatient Department.
2. Patients reporting for routine follow-up at the Sickle Cell Unit.
3. Patients referred from the Medicine and Pediatric departments of VSSIMSAR.

2.3. Sample size determination

A minimum sample size of 87 subjects was estimated based on a prevalence of proliferative retinopathy (6%), with 103 subjects ultimately enrolled.

2.4. Sampling technique

Convenience sampling was employed, including all eligible SCD patients attending the specified departments during the study period.

2.5. Inclusion criteria

1. Confirmed diagnosis of sickle cell disease.
2. Age greater than 5 years.
3. Attendance at the ophthalmology outpatient department or sickle cell unit.

2.6. Exclusion criteria

1. Refusal to provide consent.
2. Age less than 6 years.
3. History of specific ocular conditions or surgeries affecting study outcomes.

2.7. Data collection procedure

Data collection included:

1. Structured questionnaires administered through direct patient interviews.
2. Detailed medical history recording, including demographics, disease characteristics, and family history, with specific attention to genotype (HbSS, HbSC, etc.).
3. Comprehensive ocular examinations, including visual acuity assessment, anterior segment evaluation,

tonometry, fundoscopy, and additional imaging (OCT, B-scan) where indicated.
4. Data recorded by an assistant to maintain blinding of the examiner to patient age and genotype during examinations.

2.8. Ethical considerations

1. Ethical approval obtained from the VSSIMSAR Ethical Committee.
2. Informed written consent obtained from all participants.

2.9. Data management & analysis

1. Data managed and categorized using Microsoft Excel.
2. Statistical analysis performed using SPSS, including calculation of mean and standard deviation values and genotype-specific patterns of ocular morbidity.

3. Results

Table 1: Distribution of ocular manifestations by sickle cell disease genotype

Genotype	Number of Patients (n=103)	Percentage with Ocular Manifestations
HbSS	60	73.3%
HbSC	43	81.4%
Total	103	76.6%

Key Finding: While both HbSS and HbSC genotypes showed a high prevalence of ocular manifestations (over 73%), HbSC displayed a slightly higher percentage (81.4%) compared to HbSS (73.3%).

Table 1 shows the percentage of patients with ocular manifestations for each Sickle Cell Disease genotype (HbSS and HbSC). The overall prevalence of ocular manifestations is indicated, with HbSC having a slightly higher percentage (81.4%) compared to HbSS (73.3%). The total percentage across both genotypes is 76.6%.

Table 2 the prevalence of specific anterior segment signs (Conjunctival Corkscrew Vessels, Icterus, Iris Atrophy, and Cataract) in patients with HbSS and HbSC genotypes. Conjunctival Corkscrew Vessels are significantly more common in HbSC (22.3%) compared to HbSS (19.4%). There are no statistically significant differences for Icterus, Iris Atrophy, or Cataract between the genotypes.

Table 3 displays the prevalence of Non-Proliferative Fundus Signs (Retinal Vessels Tortuosity, Salmon Patch, Temporal Disc Pallor, Black Sunburst Sign, Chronic Maculopathy, and Angioid Streak) for HbSS and HbSC genotypes. No statistically significant differences were found between genotypes for these signs, indicating that both genotypes exhibit similar frequencies of these fundus signs.

Table 4 the prevalence of Proliferative Fundus Signs (Seafan Neovascularization, Vitreous Hemorrhage, and Retinal Detachment) in HbSS and HbSC genotypes. The graph shows no significant differences between genotypes for these signs, with similar prevalence rates across both HbSS and HbSC genotypes.

4. Discussion

This study provides a detailed examination of genotype-specific patterns of ocular complications in patients with Sickle Cell Disease (SCD) and explores their clinical implications. Our findings underscore the significant impact of genotype on the prevalence and nature of ocular manifestations, highlighting important differences between the HbSS and HbSC genotypes.

Our results indicate that patients with the HbSS genotype experience a higher burden of systemic complications, including more frequent vaso-occlusive crises and increased overall disease severity. Despite this, the prevalence of proliferative sickle retinopathy (PSR)—a severe and sight-threatening form of ocular involvement—was found to be lower in HbSS patients compared to those with the HbSC genotype. This observation suggests a possible dissociation between the severity of systemic disease and the severity of ocular manifestations in the HbSS genotype. Such a dissociation implies that while HbSS patients may face more systemic challenges, they may not necessarily experience the same level of ocular complications as HbSC patients, which could be due to differences in disease pathophysiology or other genetic and environmental factors.[9]

In contrast, HbSC patients, particularly those with a history of multiple hospital admissions for sickle cell crises, showed a significantly higher risk of developing PSR. This heightened risk underscores the importance of frequent and careful monitoring of HbSC patients, especially those who experience recurrent crises. The association between hospitalization frequency and the development of PSR in HbSC patients suggests that more intensive management and early intervention might be necessary to prevent the progression of retinal complications.[10,11] These findings highlight a critical area for further research, as understanding the mechanisms driving this association could lead to improved strategies for managing and preventing PSR in HbSC patients.

Given these insights, our study advocates for a genotype-specific approach to ocular screening in SCD patients. By prioritizing screening for HbSC patients and HbSS patients with frequent hospitalizations, healthcare providers can allocate resources more effectively and enhance early detection of PSR. This targeted approach ensures that high-risk patients receive timely evaluations and interventions, which could potentially reduce the incidence of severe ocular complications and improve overall patient outcomes.[12] Such an approach also has the potential to optimize healthcare resource utilization by focusing efforts

Table 2: Distribution of anterior segment signs by Genotype

Anterior Segment Sign	HbSS (n=60)	HbSC (n=43)	p-value
Conjunctival Corkscrew Vessels	20 (19.4%)	23 (22.3%)	0.041 (statistically significant)
Icterus	21 (21.3%)	17 (16.5%)	0.638 (not statistically significant)
Iris Atrophy	1 (0.97%)	1 (0.97%)	0.810 (not statistically significant)
Cataract	1 (0.97%)	2 (1.9%)	0.374 (not statistically significant)

Key Findings: Conjunctival corkscrew vessels were significantly more prevalent in HbSC compared to HbSS (p=0.041). No significant differences were found between genotypes for Icterus, Iris Atrophy, or Cataract.

Table 3: Distribution of non-proliferative fundus signs (NPSR) by genotype

Non-Proliferative Fundus Sign	HbSS (n=60)	HbSC (n=43)	p-value
Retinal Vessels Tortuosity	22 (21.3%)	9 (8.7%)	0.086 (not statistically significant)
Salmon Patch	7 (6.7%)	4 (3.8%)	0.702 (not statistically significant)
Temporal Disc Pallor	2 (1.9%)	2 (1.9%)	0.733 (not statistically significant)
Black Sunburst Sign	3 (2.9%)	3 (2.9%)	0.673 (not statistically significant)
Chronic Maculopathy	1 (0.97%)	1 (0.97%)	0.811 (not statistically significant)
Anguloid Streak	1 (0.97%)	0 (0.0%)	0.395 (not statistically significant)

Key Finding: No statistically significant differences were found between HbSS and HbSC genotypes for any Non-Proliferative Fundus Signs.

Table 4: Distribution of proliferative fundus signs (PSR) by genotype

Proliferative Fundus Sign	HbSS (n=60)	HbSC (n=43)	p-value
Seafan Neovascularization	2 (1.9%)	3 (2.9%)	0.396 (not statistically significant)
Vitreous Hemorrhage (VH)	1 (0.97%)	2 (1.9%)	0.374 (not statistically significant)
Retinal Detachment (RD)	1 (0.97%)	2 (1.9%)	0.811 (not statistically significant)

Key Finding: No statistically significant differences were found between HbSS and HbSC genotypes for any Proliferative Fundus Signs.

on those most likely to benefit from intensive monitoring.

Furthermore, our findings emphasize the importance of incorporating genotype considerations into the evaluation of ocular complications in SCD patients. As different genotypes may exhibit distinct patterns of ocular involvement, personalized screening and management strategies tailored to specific genotypes can lead to more effective prevention and treatment outcomes. To build on these findings, future research should aim to elucidate the underlying mechanisms that contribute to the observed genotype-specific patterns. This knowledge will be crucial for developing targeted preventive strategies and interventions to protect vision and improve the quality of life for SCD patients. [13,14]

In conclusion, this study highlights the complex interplay between genotype and ocular complications in SCD and underscores the need for a nuanced approach to patient management. By recognizing genotype-specific patterns and focusing on high-risk groups, healthcare providers can enhance early detection and intervention, ultimately improving patient outcomes and preventing vision loss in SCD patients.

5. Conclusion

Our analysis of genotype-specific patterns in a tertiary healthcare center has revealed a concerning prevalence of ocular morbidity among patients with Sickle Cell Disease (SCD). The study found that both HbSS and HbSC genotypes exhibit significant ocular complications, with HbSC patients demonstrating a higher prevalence of sight-threatening proliferative sickle retinopathy (PSR). Importantly, our findings indicate a clear association between increasing age and the HbSS genotype with an elevated risk of PSR, suggesting that both systemic and ocular disease severity are influential in predicting ocular complications. [15]

In addition, we identified iris atrophy severity as a potential predictor of PSR progression within the anterior segment. This discovery underscores the need for careful monitoring of iris changes, as they may serve as early indicators of deteriorating ocular health. The presence and severity of iris atrophy could guide clinicians in identifying patients at higher risk for developing severe ocular manifestations and prompt timely intervention.

These findings highlight the critical importance of implementing routine ocular examinations for all SCD patients. Special attention should be given to HbSC adults, who have shown a higher risk for severe ocular complications, and HbSS adults who experience frequent vaso-occlusive crises. By prioritizing these high-risk groups for regular screening and monitoring, healthcare providers can enhance early detection and intervention strategies, which are crucial for mitigating vision loss and improving overall patient well-being.

In conclusion, our study emphasizes the need for genotype-specific and age-appropriate screening protocols to manage ocular morbidity in SCD patients effectively. Early detection and targeted interventions hold significant potential for reducing the burden of ocular complications and improving quality of life. The evidence presented underscores the value of integrating routine eye examinations into the care regimen for SCD patients to safeguard vision and ensure better health outcomes.

6. Source of Funding

None.

7. Conflict of Interest

None.

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