

# Ocular Complications in Sickle Cell Disease: A Neglected Issue

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## Abstract

Sickle cell disease is a common genetic blood disorder. It causes severe systemic complications including ocular involvement. The degree of ocular complications is not necessarily based on the severity of the systemic disease. Both the anterior and posterior segments in the eye can be compromised due to pathological processes of sickle cell disease. However, ocular manifestations in the retina are considered the most important in terms of frequency and visual impairment. Eye complications could be one of the silent systemic sickle cell disease complications. Hence, periodic ophthalmic examination should be added to the prophylactic and treatment protocols. This review article is to emphasize the ocular manifestations in sickle cell disease as it is a silent complication which became neglected issue. Once the ocular complications diagnosed, then treatment to be provided in the specialized ophthalmology centers.

## Keywords

Sickle Cell Disease, Eye, Complication

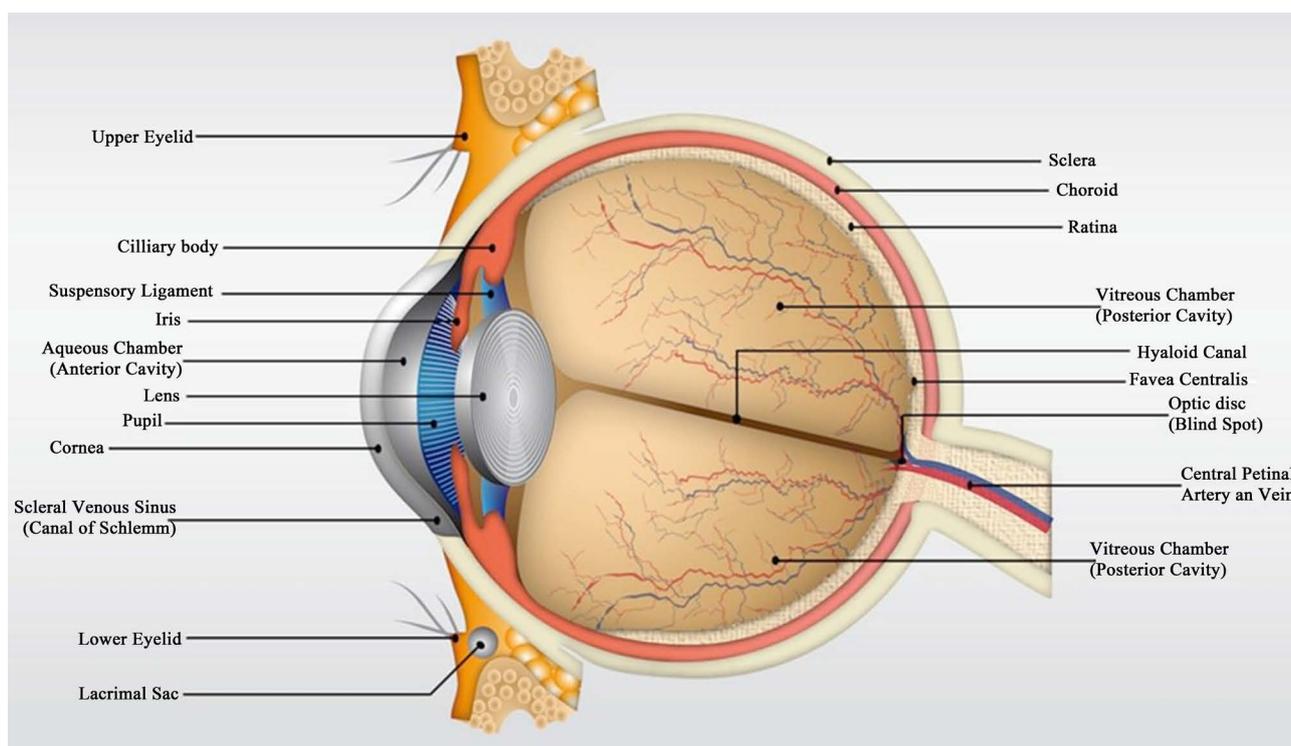
## 1. Introduction

Sickle cell disease (SCD) is one of the common inherited hemoglobinopathies. The increase in the life expectancy of SCD patients in recent years has led to the emergence of more complications of the disease. Ocular complications were uncommon in the past but these are fairly common now [1]. A variety of ocular changes have been described in patients with SCD. These changes result from vaso-occlusive crises (VOC) caused by sickled erythrocytes and from the increased adhesion of these cells to the vascular endothelium. It is also due to sec-

ondary tissue changes in all vascular structures of the eye [2]. The VOC changes are responsible for ocular and systemic manifestations of the disease [3] [4].

SCD effects on the eye can vary. The degree of ocular involvement is not necessarily based on the severity of the systemic disease [5]. Both the anterior and posterior segments in the eye can be compromised due to pathological processes of SCD (See **Figure 1**), but the ocular manifestations in the retina considered the most important in terms of frequency and visual impairment. Sick cell retinopathy may affect up to 42% of individuals during the second decade of life [6]. The occurrence of retinopathy in patients suffering from severe anemia is well known. The most frequent signs are retinal hemorrhages, soft exudates, ischemic retinopathy, venous tortuosity, retinal neovascularization and tractional retinal detachment. The exact mechanism leading to fundus lesions is still not completely understood, but it seems to be related to retinal hypoxia [7]. Ophthalmologic characteristics among pediatric and teenage patients from Northeastern Brazil demonstrated that retinal changes have an early onset in patients with SCD disease [8].

SCD is characterized by hemoglobin polymerization, erythrocyte stiffening, and subsequent vaso-occlusions. These changes can lead to microcirculation obstructions, tissue ischemia, infarction and acute stroke. The effects of SCD may be acute or chronic and may be clinically silent that result in significant morbidity and even mortality [4]. Early diagnosis and proper management of SCD complications require specialized team. The newly used investigations and the under ongoing research foster the hope to overcome this devastating



**Figure 1.** Eye Morphology (From: <https://www.freevector.com/eye-anatomy-vector>).

disease and its complications [9].

## 2. Anterior Segment Complications in SCD

### 2.1. Lacrimal Gland

Bilateral lacrimal gland enlargement complicating SCD may result from sickle red cells occluding the vessels supplying the lacrimal gland resulting in microinfarcts and accompanying inflammation. [10]. SCD Patients may present with swelling and pain in the lacrimal gland and periorbital regions. Differential diagnosis considerations include Sjögren disease, sarcoidosis, Wegener granulomatosis, Mikulicz disease, idiopathic orbital inflammatory disease, and lymphoproliferative lesions [11]. The prevalence of lacrimal gland involvement in general population varies across studies due to varying diagnostic criteria. Two large studies reported lacrimal gland involvement at rates of 7% and 15.8% [12].

### 2.2. Conjunctiva

Observation of the conjunctival blood vessels during sickling event will show comma-shaped obstructed vessels. The presence of comma shaped capillaries in the conjunctiva is a reliable diagnostic indicator of SCD [13]. It is one of the early VOC features in the SCD seen in the conjunctival vasculature. The abnormalities form transient saccular and the sausage-like dilations packed with red cells. These result in dark red, comma-shaped in vessel segments, and are seen most notably in the inferior bulbar conjunctiva. Conjunctival blood flow could improve following blood transfusion. The histopathologic examination of the conjunctival vessels demonstrated endothelial proliferation and aggregation of the red blood cells in the distal portion of capillaries, dilatation and thinning of the proximal segments of the vessels. Visual acuity is not affected. [5]. Friberg found the “comma sign” in 86% in 110 SCD patients [14]. Siqueira found that conjunctival changes increased in frequency with age [15]. Cheung *et al.* looked at 14 children and eight adult sickle cell patients’ conjunctiva with computer-assisted intravital microscopy. They found fewer conjunctival vessels in patients with SCD. They also found differences in vessel caliber, tortuosity, shape, and distribution. Sludged flow, boxcar flow, abnormal red blood cells morphology, abnormal artery to vein ratio, and hemosiderin deposits were also seen. It is further stated that these abnormalities are worse in adults [16]. While these changes do not affect vision, they are an easily observable way to see and estimate the damage that SCD is inflicting on the entire vascular system [17].

### 2.3. Corneal Leucoma

The leucoma is the clouding of the cornea, which emerges due to an injury, traumatic, inflammatory or ulcerative process. Corneal Leucomas can complicate SCD patients [18]. When a scar occurs, the cornea loses its transparency and the ability to transmit light. Depending on the location of the leucoma on the cornea and its size, it affects the quality of vision. The leucoma, located in

front of the pupil, can reduce vision (sometimes even blindness) [19]. Corneal leucoma accounting 23.18% over 768 eyes among other corneal disease [20]. Coşkun *et al.* investigated corneal structural changes (central corneal thickness, endothelial cell count, and cellular morphology) in patients with SCD. The prospective study included 56 patients with SCD and 50 age- and sex-matched healthy subjects without any eye disease aside from refractive errors. The results of this study indicate that patients with SCD had considerable morphologic changes in the structure of the cornea when compared to healthy subjects [21].

### 3. Posterior Segment Complications in SCD

#### 3.1. Optic Nerve Pallor

The optic nerve transmits all visual information including brightness perception, color perception and contrast [22]. George *et al.* examined a total of 94 children with hemoglobin SS genotype. The prevalence revealed 10.6% having optic nerve pallor [23]. The optic pallor is described as “band” or “bow-tie” atrophy, affecting primarily nasal and temporal regions with preservation of the superior and inferior regions of the disc [24]. However, in a sickle cell patient, the risk of developing optic nerve atrophy is much higher, even when Intraocular pressure (I.O.P.) is lower than 35 mm Hg [25]. Optic nerve atrophy is degeneration or gradual damage to the optic nerve. There could be numerous causes like the eye not getting proper blood flow, some underlying diseases like brain trauma, inflammation, degenerative disorders, hemorrhage, tumor, or exposure to a toxic substance. Manifestations may include blurred vision, decrease in visual function such as a decrease in sharpness and clarity of vision, or decreases in side (peripheral) vision. Color vision and contrast sensitivity may also affect, poor constriction of the pupil in light, and decreased brightness in one eye relative with the other change in the optic disc [26].

#### 3.2. Sickle Cell Retinopathy

Sickle cell retinopathy is known complication of SCD that occurs due to occlusion of retinal vessels, especially in the temporal periphery. Vitreous hemorrhage caused by vaso-occlusion in SCD patients may cause transient visual impairment whereas tractional retinal detachment may lead to permanent blindness [27]. The vaso-occlusion of the retina is responsible for non-proliferative and proliferative ocular changes. The non-proliferative sickle lesions (NPSR) consist of “salmon patches,” vessel tortuosity, “black sunbursts,” iridescent spots, and angioid streaks. The proliferative retinal lesions (PSR) can result in partial or total loss of vision. These proliferative changes are classified into clinical stages: Stage I is characterized by the arteriolar obstruction; stage II by the arteriovenous anastomoses; stage III by neovascularization; stage IV by the vitreous hemorrhage, and stage V by retinal detachment [28]. The sight-threatening changes in the retina are well-recognized complications of SCD. It can develop even in children. So there is a need for detection and treatment to prevent the progression of

the disease. Hence, a yearly examination is recommended irrespective of age or the electrophoretic pattern of the patient, and to screen the high-risk patients with frequent VOC [29]. Angioid streaks usually develop in the second decade of life and associated with subretinal neovascular membranes, macular degeneration, and visual loss in more than 50% of eyes, often at a young age [30]. Proliferative sickle retinopathy patients with SCD are susceptible to develop peripheral retinal neovascularization or proliferative sickle retinopathy, which carry the threat of permanent visual loss [31]. SCD patients may present with retinal artery occlusion while most presented with increased retinal vascular tortuosity [32]. The condition remains asymptomatic till complications such as vitreous hemorrhage or retinal detachment develop. Retinopathy is a cause of reduced visual acuity confounded by the spontaneous regression of neovascular complexes [33]. It usually occurs in patients over 20 years of age, and many authorities confirm the need for prophylactic ocular examination in people with SCD [29]. Estimated prevalence of retinopathy in USA is about 15% - 40% among SCD patients [34]. Moreover, there is an increase with age in the incidence and prevalence rates of all ocular complications of SCD. The highest prevalence of proliferative sickle cell retinopathy in SCD patients occurs between 14 and 39 years in both men and women [35] [36].

### 3.3. Retinal Detachment

Patients with SCD experience obliteration of retinal arterioles and venules and develop areas of retinal avascularity. This may result in proliferative vitreoretinopathy, which in many cases, progresses to retinal hole formation and retinal detachment (RD). These patients do poorly with scleral buckling procedures to repair their detachments [37] [38]. Approximately 15% of individuals with RD in one eye develop detachment in the fellow eye. The risk for bilateral RD ranges from 6% - 34% depending on the population studied and the associated risk factors. Men seem slightly more affected than women [39]. An incidence of visual loss has been estimated at 1.5% per person-years [40].

### 3.4. Salmon Patch Hemorrhage

A salmon patch hemorrhage is observed in SCD and appears as an oval-shaped area of intraretinal or pre-retinal blood. It is believed to occur secondary to an obstructed retinal arteriole which subsequently ruptures. After re-absorption of the salmon patch hemorrhage, the retina may appear entirely normal without any evidence of residual blood. In the location of the hemorrhage, however, there may be also a faint indentation or depression representing thinning of the inner retina. Venous tortuosity is an early sign of ophthalmic SCD, and “silver wiring” of the arterioles is also a feature [41]. Salmon patch retinal hemorrhage were observed in 6.4% of Nigerian SCD subject [42].

### 3.5. Macular Infarction

Macular infarction due to SCD has been documented using fluorescein angio-

graphy, electroretinography, and histopathologic examination [43]. In SCD, sickle-shaped RBCs increase the blood viscosity and thereby can trigger vascular obstruction, ischemia, hypoxia, and tissue necrosis [44] [45]. Mathew *et al.* observed areas of retinal thinning in the temporal macular area in 44% of the SCD eyes [46]. Also Brasileiro *et al.* observed focal retinal thinning in 35% of the SCD patients, with a higher frequency in eyes with proliferative changes [47]. In a study of Ghasemi Falavarjani *et al.* inner retinal atrophy was detected in 11 eyes (61.1%). It was associated with a higher ischemic index, which is a parameter previously used to quantify retinal ischemia in patients with retinal vein occlusion. Overall, these findings suggest that macular ischemia and peripheral ischemia are related to each other [48].

#### **4. The Role of Doppler Ultrasonography in Eye Examination**

Color Doppler Imaging (CDI) is real-time duplex color doppler examination. This modality gives the approximate flow velocity of the principal vessels in the eye and orbit, enabling the sample volume to be accurately positioned on the doppler display for pulse doppler examination. CDI has been proposed as a tool for diagnosis or study vascular disorders in the eye and orbit. Several CDI studies have examined the ocular vessels, primarily via assessment of measured velocity or calculation of resistive index. However, the velocity wave gained by CDI may be utilized not only to investigate changes in blood flow but also to detect the presence or absence of regional blood flow [49]. Doppler ultrasound of the eye permits the noninvasive evaluation of arterial vascular resistance through the calculation of two indices-the resistance index and the pulsatility index especially in the study of blood flow in ocular diseases [50]. Little is known about the orbital vascular changes in patients with SCD, or about the relationships with biomarkers of hemolysis [51].

#### **Prophylactic Measures**

SCD patients need prophylactic measures from early life to stop or control the systemic complications of SCD disease including the eye complications [52] [53]. In general, the sickle patients require the FDA approved treatment Hydroxycarbamide daily from the age of nine months. Another agent L-glutamine, which was launched on 2017, is a precursor of the antioxidant glutathione. Ox-bryta (voxelotor) has recently been granted accelerated approval for the treatment of SCD in patients ages 12 years and older by U.S. Food and Drug Administration (2019). Such patients require drinking enough water daily to avoid dehydration which precipitate the VOC and other SCD complications [54]. Prophylactic therapy has a significant impact on retinopathy development and progression. In SCD therapy, the goal is to reduce the HbS containing erythrocytes to ensure better tissue oxygenation and thus prevent vascular occlusion. Children with a HbF < 15% had 7.1-fold higher odds of developing retinopathy, and

those with retinopathy had lower HbF levels compared with children without retinopathy. Hydroxycarbamide promotes the production of HbF, which does not polymerize and deform red blood cells like the mutated HbS and thus has a favorable effect in preventing retinopathy. The L-glutamine increases the proportion of the reduced form of nicotinamide adenine dinucleotides in sickle cell erythrocytes, which reduces oxidative stress and could result in fewer episodes of sickle cell–related complications [55]. Periodic checkup for ophthalmic, blood and other systemic investigations are required to detect early complications. Quality of life and expectancy for SCD patients have improved with the new prophylactic and treatment measures from 5 years to over eighty years nowadays [56].

## 5. Conclusion

Ophthalmic complications of sickle cell disease need hematological attention. Early detection warrants prompt referral to the ophthalmologist. The ophthalmic complications in sickle cell disease could be serious and cause visual loss if neglected. Ocular clinical findings are important part of the systemic complications in sickle cell disease. The periodic assessment of the severity is highly crucial in sickle cell disease as it is a chronic disorder with multisystemic complications. Regional ophthalmic controlled studies are required to screen and treat eye complications in sickle cell disease. The study's results may highlight the complications and the preventive measures required to control ophthalmic complications in sickle cell disease. Because the ocular complications in sickle cell disease are silent, so it is very much neglected, but once it is investigated and diagnosed, then treatment to could be provided in the specialized ophthalmology centers.

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## Conflicts of Interest

The authors have no conflict of interest in this study.

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### Abbreviation

SCD	Sickle Cell Disease
VOC	Vaso occlusive crises
NPSR	Non-Proliferative Lesions
PSR	Proliferative Retinal Lesions
RD	Retinal detachment
CDI	Color Doppler Imaging,
FDA	Food and Drug Administration