Ocular Manifestations of Sickle Cell Disease: A Review

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Abstract

Problem: Sickle cell disease (SCD) is an increasingly frequent global health concern whose complications may result in decreased function and reduced quality of life. SCD is a multi-system monogenic disease resulting from a mutation that causes the abnormal 'sickling' of erythrocytes. Subsequent local and diffuse vaso-occlusion can cause both systemic and ocular damage. Although sickle cell retinopathy (SCR) is the most commonly evoked ocular sequelae of SCD, all vascularized ocular tissues can become ischemic and progressively damaged. The combination of retinal screening of high-risk patients and early detection of the ocular sequelae of SCD with advanced diagnostic technologies should result in timely intervention and preservation of vision.

Conclusion: This review of the ocular manifestations of SCD will reinforce the critical role of optometry in the multi-disciplinary care of these growing number of patients we as a profession will encounter.

Introduction

Sickle Cell disease (SCD) is the most common genetic disorder caused by a mutation in a single gene (monogenic), manifesting as acute pain, chronic multisystem damage and ultimately reduction of life expectancy by an average of 30 years.[1–4] SCD affects millions of patients worldwide and continues to increase in number. Sickle cell trait (SCT) is protective against severe Malaria and, as such, is most prevalent in areas burdened by that condition including sub-Saharan Africa, the Middle East, India and the Mediterranean basin.[1] It is not unprecedented, however, in North America as approximately 100,000 individuals in the United States and 5,000 in Canada are afflicted with SCD.[2,5] SCD can affect any organ in the body including all ocular and orbital tissues.[6,7] Although most patients will not lose vision, ocular complications of SCD can be visually devastating.[8] The major cause of vision loss in SCD is sickle cell retinopathy (SCR), specifically proliferative sickle cell retinopathy (PSR), which results from impaired perfusion and progressive retinal ischemia causing neovascularization, vitreous hemorrhage, and tractional retinal detachment.[8–10] SCD creates a burden not only on the individual but on society, with the lifetime cost of care for an individual with SCD having averaged approximately $460,000 between 2001 and 2005.[11] Improved access to care, along with recent advances in multimodal diagnostic imaging and treatment modalities may further improve outcomes in patients with SCR.[7,12] Current disease-modifying therapies and future therapies that address the specific mutation responsible for SCD continue to emerge and will potentially reduce the burden of these disease for our patients.[13]

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Sickle Cell Disease Background

Sickle cell disease (SCD) is an inherited disorder resulting in the alteration of hemoglobin within red blood cells (RBCs). Normal adult hemoglobin (Hb A) is composed of two - β-globin proteins, two α-globin proteins, and a single central heme molecule. SCD produces abnormal hemoglobin due to gene mutations that code for β-globin proteins. Multiple defects can lead to altered β-globin. Hemoglobin S (Hb S) forms when valine is substituted for glutamic acid at the sixth position of the β-globin chain. Hemoglobin C (Hb C) results when lysine is substituted for glutamic acid at the same position. Another gene variant called beta-thalassemia (β-Thal) results from multiple mutations that cause reduced hemoglobin production. These gene mutations, among others that are less common, can be combined in a variety of ways leading to a diverse disease with a wide degree of systemic and ocular severity. Abnormal β-globin results in RBCs that have a sickle shape. These RBCs have a decreased lifespan which can lead to anemia, and the altered shape results in occlusion of small blood vessels throughout the body.[6,14]

Manifestations of SCD involve multiple processes and pathways, including bioavailability of nitric oxide, endothelial activation, inflammation, adhesiveness of blood cells, and oxidative stress.[10] When exposed to hypoxia, hyperosmolarity, or acidosis, the deoxygenated Hb S polymerizes which causes the RBCs to sickle and become rigid. These sickled RBCs have increased adhesion to endothelial and subendothelial matrix proteins, which adds to the damage.[6]

SCD is inherited in an autosomal recessive pattern; therefore, two copies of Hb S or one copy of Hb S with another β-globin variant is required for disease expression.[6] SS denotes homozygous SCD genotype and indicates a person has two copies of Hb S. This is termed sickle cell anemia. Compound heterozygotes possess one Hb S allele plus one other β-globin gene variant, such as Hb C (SC) or β-Thal (Sβ-Thal).[6,10,15] Those who have one normal copy of Hb A and one copy of Hb S (AS) have SCT. While Hb AS is considered benign, vaso-occlusive features may occur under conditions of stress, concomitant systemic diseases, or trauma.10 Individuals with SCT, or Hb S carriers, are protected from malarial infection, especially during a critical period of early childhood.[16] Genotypes associated with Hb S exist in the greatest frequency in populations of African descent. However, people of Mediterranean, Caribbean, South and Central American, Arab, and East Indian descent also have high incidences of at-risk genotypes. Approximately 8% of African Americans are Hemoglobin AS type.[17]

SCD occurs in approximately 1 out of every 365 African American births and 1 out of every 16,300 Hispanic American births.[5,18] Although the frequency of the Hb C allele is only about one fourth of the Hb S allele, the prevalence of SC type disease amongst adults is nearly as great as in SS type disease. This is due to the relatively normal life expectancy of patients with SC type disease, which exhibits less severe hemolytic anemia and less frequent crises and organ infarcts compared to SS type disease.[6] SS type disease manifests as severe hemolytic anemia with symptoms that usually develop after six months of age when fetal hemoglobin (Hb F) is replaced by the abnormal Hb S. These patients exhibit an increased susceptibility to infection and retarded growth.6 SCD morbidity and mortality is predominantly due to repeated vaso-occlusive events that may affect any organ, but with greater frequency in the lungs, kidneys, skeleton, liver, and skin.[1]

Ocular Manifestations

SCD can affect both the anterior and posterior segments of the eye, as well as the retrobulbar and orbital areas.

Orbit and Retrobulbar

SCD can affect the orbit or retrobulbar space resulting in: orbital wall infarction, orbital cellulitis, orbital compression syndrome, retrobulbar ischemic optic neuropathy, and/or bilateral lacrimal gland enlargement. Although rare, infarction to the bones of the orbit during a vaso-occlusive crisis can lead to inflammation or hemorrhaging resulting in orbital compression syndrome with findings such as proptosis, extraocular motility restriction, and optic nerve compression.[19,20] In addition, those with SCD are at increased risk of infection, and infectious orbital cellulitis can also result in orbital compression syndrome.[20,21]

Anterior Segment

Anterior segment manifestations are numerous and range from transient and benign to vision threatening. Paton initially described the "conjunctival sign", which are transient saccular and sausage-like dilations of the inferior bulbar conjunctival vessels, often described as comma-shaped. These abnormalities are proposed to reflect reduced or obstructed flow by sickled or less malleable RBCs. Conjunctival signs are common and have been reported in approximately half of SCD patients in at least one cohort.[6,8] Limited ischemia or actual microvascular infarcts of the anterior segment has been tied to pupillary irregularity, as well as diffuse and sectoral "patchy" iris atrophy. A recent publication by Alryalat et al showed that iris atrophy is actually very rare in patients with SCD, with less than 0.8% of patients showing iris atrophy bilaterally in that study.[8] When PSR is not diagnosed or managed in a timely fashion, iris neovascularization can develop, although this is a rare occurrence. Traditionally (1970s and 80s), significant anterior segment ischemia was a common complication from the surgical management (Scleral buckling and previous generation Trans Pars Plana Vitrectomy) of the sequelae of PSR.[8] However, modern surgical techniques have reduced the risk of these complications.

Independent of proliferative disease, SCD patients have a higher risk of hyphema secondary to trauma or intraocular surgery when compared to their non SCD peers.[6] As such, patient populations at risk for SCD or SCT who present with hyphema should be questioned specifically about personal or family history of SCD or SCT. If there is a positive history, ordering hemoglobin assays should be considered to fully understand the patients risk of complications.[22–24]

Those with SCD and hyphema have an increased risk of transiently elevated intraocular pressure (IOP) in excess of 30mmHg.[25] The pathogenesis of increased IOP is theorized to be mechanical as sickled RBCs are likely unable to pass through the trabecular meshwork (TM) pores, creating obstruction, decreasing outflow and subsequently increasing IOP. This rise in IOP has been shown to occur even with a relatively small amount of hyphema.[25]

Due to their already poor systemic vascular perfusion, those with SCD are also at higher risk of central retinal artery occlusion from elevation of IOP. Mechanistically, two vicious cycles in the anterior segment can result from increased IOP. First, as IOP increases, anterior segment ischemia increases, potentially increasing intravascular sickling, leading to occlusion and even greater infarction. Presumably a greater volume of sickled cells in the anterior chamber will further block TM, decrease outflow, leading to even higher IOP.[25] Hyphema in patients with SCD must therefore be managed aggressively to mitigate the risk of potentially damaging levels of IOP.[6]

Caution should be applied in the medical management of these cases as incorrect management can worsen the condition. Notably, hyper-osmotics should be avoided in patients with SCD as they can cause hemoconcentration. This results in sludging of erythrocytes, increasing the risk of visually consequential posterior segment ischemic events, as well as causing ischemia induced lowering of the anterior chamber pH. A more acidic pH has been shown to increase the likelihood of

HbAS erythrocytes to sickle. Likewise, acetazolamide should be avoided as it also lowers the pH of the AC, increasing the risk of exacerbating sickling.[25] Topical carbonic anhydrase inhibitors (CAIs) have not been shown to cause enough AC acidosis to result in sickling, but they have not been studied extensively and their safety in patients with SCD and increased IOP due to hyphema has not been demonstrated.[26]

Accordingly, initial treatment for traumatic hyphema in SCD patients should be first aimed at reducing the risk of further injury. Patients should avoid the use of anticoagulants or NSAIDs that might promote further bleeding, shield the involved eye, elevate the head of the bed to promote venous drainage, and providers should check the IOP every six hours to monitor for elevation. Topical steroids should be considered, as they have been shown to decrease the risk of a rebleed and will additionally attack any iritis present. Cycloplegics are frequently given, as is thought that reducing iris movement reduces the chance of further bleeding. If patients have increased IOP, aqueous suppressants are considered first line, including beta-blockers and alpha-agonists. Oral CAIs, as stated previously, should be avoided, and it may be prudent to avoid topical CAIs, as previously stated. Aminocaproic acid (ACA), an oral plasmin inhibitor, can reduce the risk of a rebleed by stabilizing the clot, but in doing so increases the time it takes for the clot to resorb. Interestingly, the use of ACA has not been shown to affect the ultimate visual acuity in patients with traumatic hyphema, so its use may not be consequential.[26]

If medical management is successful in lowering the IOP, ONH damage is unlikely. Furthermore, the hyphema itself is unlikely to cause glaucoma on its own, because once the red blood cells clear there should be no further obstruction in the TM and therefore no chronic dysfunction.[26] The patient is still independently at risk for traumatic glaucoma and gonioscopy should be performed regularly to rule out the development of angle recession. If, however, the IOP is not controllable medically, surgical intervention must be considered. The criterion for surgery in patients with traumatic hyphema and SCD is more stringent than that imposed in patients without SCD, given their eyes are less able to tolerate even moderately high IOP.[26] The current evidence-based guidelines call for surgical intervention in SCD patients with traumatic hyphema when there is corneal blood staining, IOP that is sustainably >24mmHg for longer than 24hrs, and if the patient experiences multiple IOP spikes that are >30mmHg.[26] There are multiple surgical options, ranging from anterior chamber washout with balanced salt solution (BSS) to Trabeculectomy, utilized to manage these cases and the decision on how to proceed will be on an individual surgeon and patient basis.

Posterior Segment

Given its pathophysiology, it is not surprising that virtually every vascular bed in the eye can suffer vaso-occlusive events.[10] These can manifest in a multitude of ways in the posterior segment. Although the peripheral retina, where vessels may terminate abruptly in hairpin loops, is typically the most affected, the entire eye is susceptible to these events.6 Notably, in children, only arterioles and capillaries are occluded, whereas both veins and arteries are involved with adults. It is proposed that this difference occurs because only sickled red blood cells (sRBCs) cause damage in children. However, chronic leukocyte and endothelial activation over time causes more comprehensive cumulative vascular bed damage in adults, leading to posterior pole involvement in addition to peripheral occlusions.[6]

Venous tortuosity, attributed to arteriovenous anastomoses, has been reported to occur in up to 47% of HbSS and up to 32% of HbSC patients.[6,8] Posterior pole vessel occlusion such as central retinal artery occlusion or major branch retinal artery occlusion occur more commonly in adults with SC-type disease, but have been reported in juveniles with SS disease.

Angioid streaks (AS), which result from the dehiscence of elastic lamina of Bruch's membrane and are of an unknown etiology, coexist with multiple systemic diseases, including having an association with SCD.[27] The incidence of angioid streaks has been estimated to be 1-2% in all patients with SCD. Angioid streaks are specifically more common in patients with SS disease, although they have been documented in patients with SC disease, and are more likely in patients over the age of 40. The presence of angioid streaks in patients with SCD typically results in a benign clinical course, but can be associated with recurrent hemorrhages, development of choroidal neovascularization (CNV), and loss of vision from outer retinal atrophy.[6] Independent of angioid streaks, CNV can spontaneously occur in SCD patients. These CNVs may be uneventful or can be associated with vitreous hemorrhage, posterior hyaloid fibrosis, tractional retinal detachment, and secondary vision loss.[6]

Sickle Cell Retinopathy

Development of sickle cell retinopathy (SCR) is the most common reason for vision loss in those with SCD. SCR has been reported to develop in about 40% of individuals with SCD during the second decade of life. Unlike diabetic retinopathy, which is triggered by overexposure of vascular tissues to hyperglycemia, SCR is triggered by vaso-occlusion of the microvasculature of ocular structures.[15] Broadly, SCR can be classified as either non-proliferative or proliferative with the presence of retinal neovascularization indicating proliferative disease. Early signs of non-proliferative SCR include superficial retinal hemorrhages, known as salmon patch hemorrhages, and alterations to the retinal pigment epithelial (RPE) called black sunburst sign. Salmon patch hemorrhages (Figure 1) are circumscribed lesions between the neurosensory retina and internal limiting membrane (ILM).[6] While the lesions are initially red, they become salmon colored with the hemolysis of RBCs. As the hemorrhage resolves, iridescent deposits remain in the retina. These are deposits of hemosiderin and macrophages that are located just under the ILM.[28] Additionally, RPE hyper-reactivity leads to hyperpigmentation, known as the black sunburst sign. This sign is thought to represent choroidal ischemic damage to the RPE.[6]

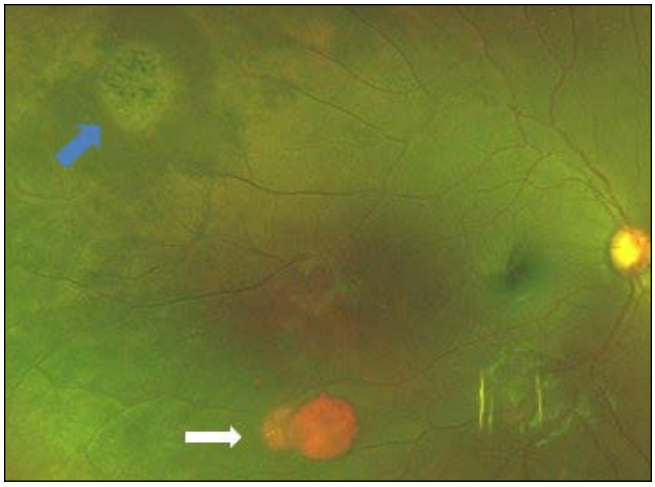


Figure 1. Salmon Patch hemorrhage (white arrow), black sunburst (blue arrow)

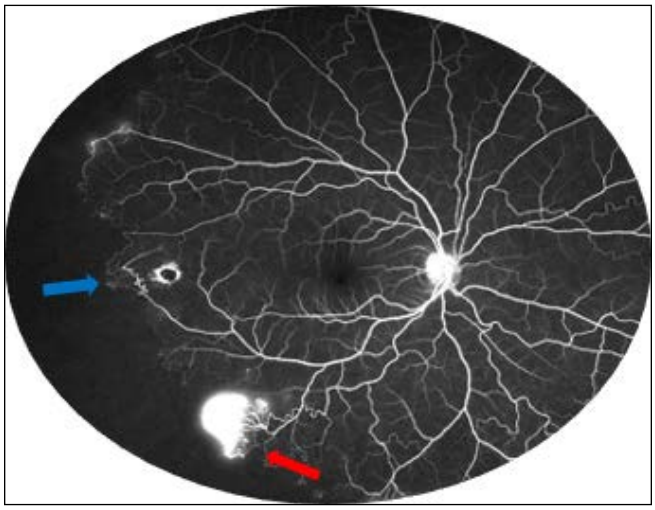


Figure 2. IVFA showing capillary non-perfusion of the peripheral retina (Large hypo-fluorescent regions temporally), arterio-venous anastomoses (blue arrow), and sea fan neovascularization (red arrow).

In the peripheral retina, vaso-occlusive events within smaller arteries and arterioles, particularly at vessel bifurcations, leads to ischemia (Figure 2) and subsequent angiogenic mediator release. These occlusions result in a cascade of events that typically occur in succession leading to proliferative disease. Initially, occlusion of the arterioles and capillary loss drives formation of abnormal arteriovenous communications at the border of vascular and avascular retina. (Figure 2) These anastomoses occur more predominantly in the temporal retina.[6] As there is additional ischemia and release of vascular growth factors, retinal neovascular growth occurs. These vessels are initially flat and tend to have a classic "sea fan" appearance (Figure 2).[10] Retinal neovascularization can lead to sight threatening complications such as traction retinal detachment, combined tractional/rhegmatogenous retinal detachment, pre-retinal, and vitreous hemorrhage (Figure 3).[10]

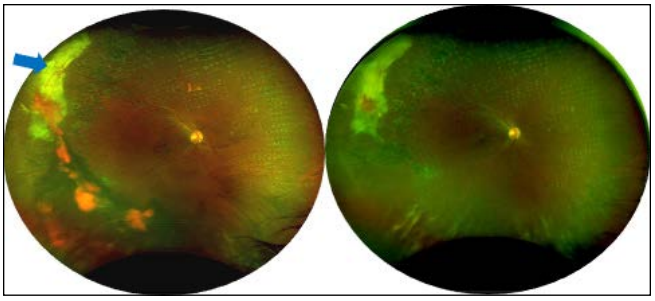


Figure 3. (A) PSCR previously treated with PRP. Superficial retinal fibrosis located supratemporally with new region of active neovascularization (blue arrow). Pre-retinal and vitreous hemorrhage cascading down from the area of active neovascularization leading to symptoms of floaters and decreased vision. (B) partial regression of NVE and improved hemorrhage 1-month post injection with anti-VEGF.

The most commonly utilized classification of SCR is the Goldberg system which divides retinopathy into five stages.[29] The classification developed in 1971 remains clinically useful as most patients will progress through each stage as their disease becomes more advanced. The classification is shown below:

Stage I: Peripheral arterial occlusion
Stage II: Peripheral arteriovenous anastomoses, representing dilated pre-existing capillaries (hairpin loop)
Stage III: Neovascular and fibrous proliferation (sea fan) occurring at the posterior border of non-perfusion. Auto-infarction of the neovasculature leads to subsequent white sea fan appearance
Stage IV: Vitreous hemorrhage
Stage V: Tractional retinal detachment

Another important classification of retinopathy was developed by Penman in 1994. He evaluated peripheral vascular patterns in patients with SS and SC disease versus those with normal hemoglobin in an attempt to understand why there is increased prevalence of SCR in SC disease. He determined that there were two distinct vascular patterns in the peripheral retinas of those with SCD. Type I was called qualitatively normal and Type II was qualitatively abnormal. (Figure 4) While both retinas showed capillary dropout, in Type I, the vascular pattern remained regular, with smooth, continuous arteriovenous loops. Penman considered that this was from a slow, progressive loss of the capillary beds. Type I was seen more in SS disease, and was less associated with PSCR. The Type II pattern showed jagged vascular borders with abrupt terminations of the vessels. Type II was more prevalent in SC disease and had higher incidence of PSCR. Penman considered that Type II patterns were a result of accelerated vascular death without the ability for vascular remodeling.[30]

Further, a study by Sayag et al. more recently broke the Goldberg stage III category into 5 different classes (A-E) based on several characteristics of the sea fan lesion. Their attempt was to determine what types of lesion where more likely to progress and require treatment, and which lesions may be monitored.

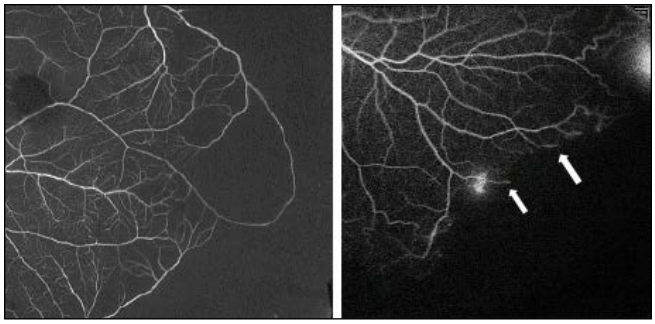


Figure 4. Left image is Type I (qualitatively normal). Type I has a smooth, regular border between vascularized and avascular retina with well-formed arteriovenous anastomoses. Right image is Type II (qualitatively abnormal) Type II has a jagged, irregular border with vessels that make abrupt stops (white arrows)

They suggest that those with stage IIIA and IIIC may be initially monitored without intervention.[31]

III A: Flat sea fan with leakage less than 1 MPS (macular photocoagulation study) disc area
III B: Elevated sea fan with hemorrhage
III C: Elevated sea fan with partial fibrosis
III D: Complete sea fan fibrosis without well demarcated vessels
III E: Complete sea fan fibrosis with well demarcated vessels

Researchers and clinicians continue efforts to determine findings that may suggest risk of progression and to determine who may or may not need treatment of PSCR.

While SCR is typically considered to be a disease of the peripheral retina, as mentioned above, retinal vasculature can be affected in the macula as well. Sickle cell maculopathy (SCM) represents localized or diffuse macular thinning secondary to ischemia. The macular thinning in SCM involves multiple retinal layers, which suggests that ischemic vasculopathy occurs in both the superficial and deep capillary plexi. In addition, documentation of outer retinal thinning suggests that vaso-occlusive ischemic events may also occur in the choriocapillaris.[32]

SCM tends to be more pronounced within the temporal macula and occurs to a greater extent in those with more significant peripheral retina disease. A relationship between macular ischemia and peripheral ischemia has been suggested, which may be due to subclinical ischemia from vascular occlusions in terminal arteriolar branches that supply both the temporal macular areas and the retinal periphery.[32] Dell'Arti et al noted generalized thinning of inner and outer retinal layers of the macula and temporal retina in SCD patients on SD-OCT compared to controls.[32] An enlarged foveal avascular zone may also be seen on OCT-A.[15] In addition to vascular disease in the macula, patients with proliferative retinopathies are more prone to the development of vitreomacular interface disease such as epimacular membranes, vitreomacular traction, and macular holes.[15] (Figure 5)

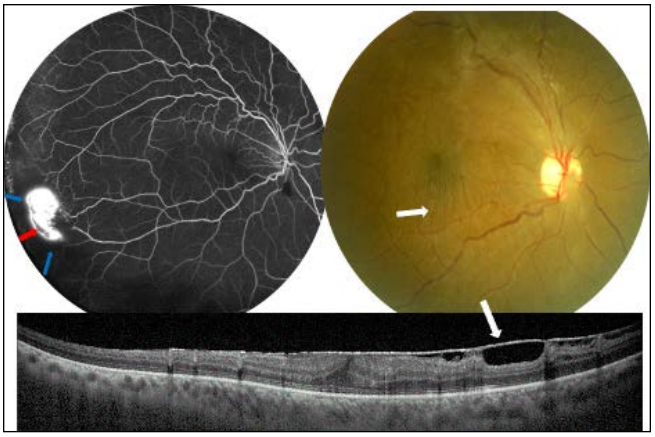


Figure 5A. (Top left) IVFA shows peripheral non-perfusion (blue arrows) and NVE (red arrow). Diffuse epimacular membrane visible on fundus photo (top right) and OCT (bottom, white arrow) present in patient with proliferative SCR.

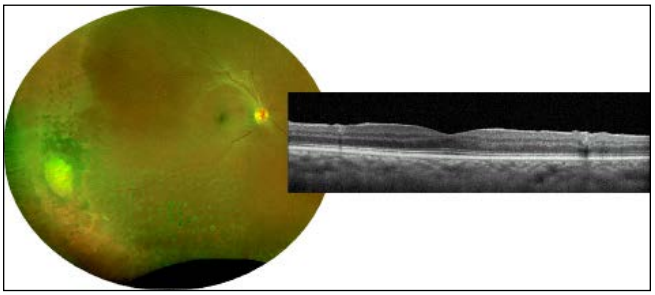


Figure 5B. Patient from image 5A after treatment with sector PRP for the NVE and vitrectomy with ILM peel to manage the epimacular membrane.

SCR and various SCD Genotypes

With improved life expectancy in patients with SCD, the incidence of SCR has also increased and, depending on the genotype, can provide clues to the extensiveness of the systemic disease present. An inverse relationship exists between the severity of systemic disease and the severity of SCR in SS type disease individuals, but not in those with SC type. With SS type disease, systemic vaso-occlusive events are more frequent and severe with secondary organ damage. SC type disease generally exhibits fewer systemic signs, but has a greater frequency and earlier onset of retinal neovascularization.[15,33] This may be due to an enhanced circulatory competence in Hb SC RBCs, which would preserve retinal circulation and allow posterior development of proliferative lesions. However, Hb SS type disease exhibits early and more complete occlusion of peripheral retinal vessels. One hypothesis to explain the relationship between SC and SS type disease and SCR involves three models with vaso-occlusive tendencies.[34] Individuals with low vaso-occlusive tendencies are unlikely to develop retinal ischemia, and therefore lack the stimulus for proliferative retinopathy. Those with moderate vaso-occlusive indices develop peripheral retinal occlusions, causing pre-proliferative or proliferative disease. Individuals with high vaso-occlusive indices develop extensive closure of

peripheral retinal vasculature, which provides the stimulus for proliferative retinopathy. Also, due to the high vaso-occlusive tendency, pre-proliferative arteriovenous anastomoses would also be occluded. In this hypothesis, SC type disease is thought to be represented by the moderate vaso-occlusive model.[34] Peak incidence of SCR in SS type disease is between 25 and 39 years independent of gender. Peak incidence of SCR in SC type disease differs between genders, occurring in males between 15 and 24 years and occurring in females between 20 and 39 years. Therefore, SC type disease exhibited an earlier onset of SCR with a higher peak of incidence.[6,34,35]

Risk factors for SCR development include low Hb F in both genders in SS and SC type disease. The risk of SCR with SS type disease increases with high total hemoglobin in males, while the risk of SC type disease in males and females increases with increased mean cell volume.[6,15] In SC type disease, severe proliferate SCR (stages III-V) were independently associated with increasing age, lower serum ferritin, pulmonary involvement, deafness or tinnitus, and absence of osteomyelitis.[10,36] In SS type disease, severe proliferative SCR was associated with increasing age, male sex, and acute pyelonephritis.36 Chronic iron chelation therapy and potentially high levels of Hb F have been found to be possible protective factors against SCM.[32]

Impact of SCR

With all of the potential complications from proliferative SCR, only 10-20% of affected eyes will experience visual impairment (worse than 20/40).[15] This is primarily due to peripheral involvement in most SCR cases as well as the high frequency of spontaneous regression of proliferative SCR. Through the development of atrophic lesions and/or auto infarctions, 20-60% of proliferative SCR cases spontaneously regress. This is most frequent within two years of proliferative SCR development.[6,10,15] In SCM, conventional Snellen acuity testing may indicate that visual acuity is preserved, misrepresenting the fact that damage has been done, in spite of a patient's subjective lack of symptoms. However, chronic nonperfusion to the retinal capillary plexi, often involving the temporal macula, may result in irreversible vision loss which can be quantified by perimetric testing. Notably, paracentral scotomas have been shown on perimetry, which aligns with the structural findings of local macular thinning noted on OCT and OCT-A.[32] SCR affects central vision mainly through vitreous hemorrhage and tractional retinal detachments.[6]

Diabetes and Sickle Cell Trait

The worldwide prevalence of diabetes in 2017 was estimated to be 8.8% of the world's population and continues to rise, with a projected global prevalence of 9.9% in 2045, amounting to 629 million people.[37] It is not surprising, then, that diabetes is rapidly increasingly in regions already frequented by SCT.[38] In contrast to its anemic counterpart, SCT has been historically considered benign. Studies now show there may be an increased risk of end-stage renal disease, venous thromboembolism and CVA in patients with SCT.[39]

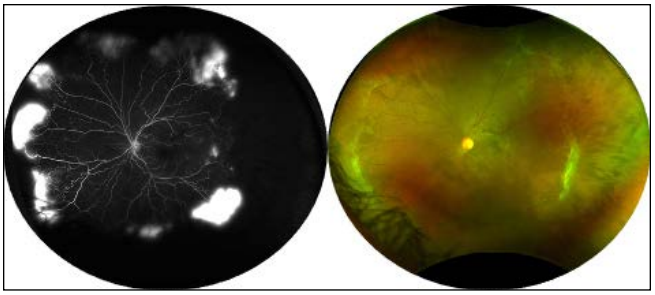


Figure 6. Ultrawidefield FA (Left) and fundus photo (Right) taken with Optos California. Fundus photography shows partially regressed neovascularization in the peripheral retina. There is patchy vitreous hemorrhage present creating shadowing of the image. FA of the same patient shows significant retinal neovascularization scattered 360 degrees and substantial vascular non perfusion in the peripheral retina.

Although early studies also suggested that SCT did not affect the presence or progression of microvascular complications in diabetes and might even protect against the development and progression of DR, more recent evidence shows that SCT more likely increases the development of diabetes related complications.[40–42] Specifically patients with both DM and SCT (DM-SCT) had increased oxidative stress, exacerbated abnormal blood rheology, and more marked vascular dysfunction when compared to patients having DM or SCT in isolation.[43] In 2018 Skinner et al found an increased prevalence of retinopathy in Senegalese patients with combined type 2 diabetes (T2D) and SCT when compared to those without that combination, reinforcing the notion that possessing SCT does not lead to a benign clinical course, especially when combined with T2D.[39] Skinner et al suggests that given the increasing prevalence of T2D in populations where SCT is common, more research needs to be done to develop guidelines for better individualizing diagnosis of T2D in patients with known SCT, and for detection of SCT in patients suspected of having T2D with the unknown presence of SCT, as the combination of T2D-SCT can result in greater systemic complications.[38] From an optometric standpoint, proper classification leads to appropriate risk assessment and monitoring so it is important for clinicians to know whether their diabetic patients also have SCT.

Ocular Imaging

Angiography

Fluorescein angiography (FA) has traditionally been the tool of choice for obtaining detailed information regarding retinal vasculature. FA can be used to image vasculature in both the peripheral retina and the posterior pole. It is useful in identifying findings such as capillary dropout, arteriovenous anastomosis, and retinal neovascularization that may not be visible with fundus evaluation alone.[44–46] (Figure 2). Areas of capillary dropout or retinal non-perfusion will appear as hypo-fluorescent on the study. Areas of retinal neovascularization will exhibit hyper-fluorescence that increases in intensity throughout the study.[45] (Figure 2)

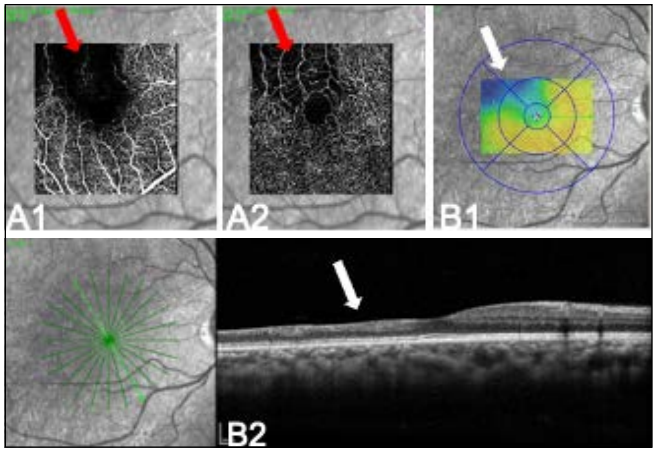


Figure 7A-B. Macular imaging from patient shown previously in image 2. Image A shows significant non-perfusion in both the superficial (A1) and deep vascular plexi (A2) supratemporally OD (red arrows). OCT thickness map (B1) and B-scan (B2) through this area show significant retinal thinning (white arrows).

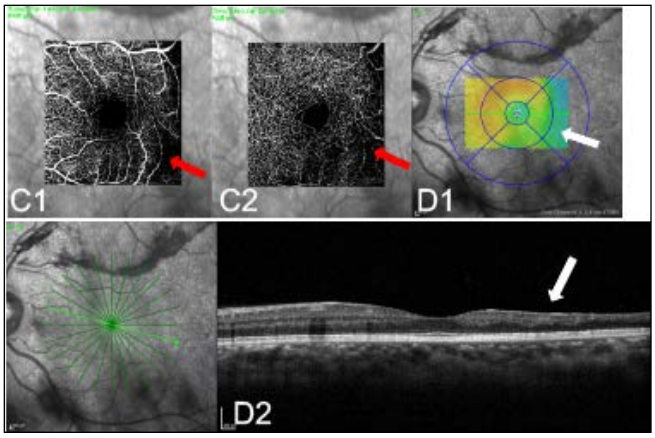


Figure 7C-D. Image C shows capillary dropout temporally in both the superficial (C1) and deep vascular plexi OS (C2) (red arrows). OCT thickness map (D1) and B-scan through this area (D2) show retinal thinning (white arrows).

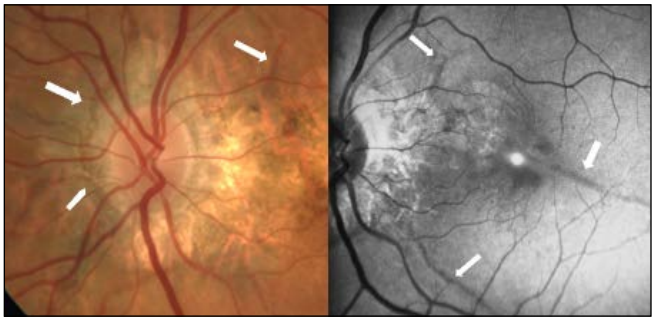


Figure 8. Color Fundus Image (Left) and FAF (Right) of patient with Angioid Streaks (white arrows).

Widefield Imaging

Historically, the major limitation of diagnostic imaging in SCD was the inability to image the far peripheral retina. Now, a wide variety of widefield and ultra-widefield instruments provide photo-documentation as well as angiography up to 200° in a single, non-montaged image.[45,46] This far exceeds the capabilities of imaging tools that were used in historical classifications such as the Goldberg system and Penman's classification.[29,30] For example, in Penman's work, the peripheral border of vascularized and avascularized retina was too far anterior to image with angiography in one half of the eyes evaluated.[30] These widefield imaging strategies allow for greater detection of vascular changes and retinopathy as well as documentation of these findings.[45,47,48]

OCT, OCTA, and FAF

OCT and OCTA are currently best suited for evaluation of the macular structure and vasculature. SCM is subtle and likely impossible to detect with fundus evaluation alone. Tools such as FA, OCT, and OCT-A must be utilized to detect these changes. As mentioned previously, SCM leads to retinal thinning that can involve both the inner and outer retinal layers which can be detected on OCT. This thinning may be diffuse or localized, but often is present to a greater extent in the temporal macula. (Figure 4).[32,46] FA and OCTA can show alterations to the macular vasculature with OCTA potentially being a more sensitive tool than FA. OCTA breaks down the retinal circulation to show the superficial and deep vascular plexi separately. Loss of vascular density has been shown in both the deep and superficial plexi on OCTA. Once again, these findings may be diffuse or localized, but often occur to a greater extent in the temporal macula. There may also be increased foveal avascular zone visible on OCTA.[46,49,50] (Figure 7A-D)

OCT is also useful in the detection and monitoring of vitreomacular interface disease such as epimacular membranes, vitreomacular traction, and macular holes. In patients with angioid streaks, both OCT and OCTA are useful to monitor for development of CNV.[51]

Fundus autofluorescent (FAF) imaging is beneficial in visualizing alterations of the RPE in a variety of conditions. FAF essentially uses a light source to excite certain autofluorescent molecules in retina. Lipofuscin housed in the RPE is the main autofluorescent molecule in the retina. Damaged RPE has decreased ability to metabolize lipofuscin, and as the molecule accumulates in the RPE there is resultant hyper-autofluorescence on the FAF. (Figure 8) Areas where RPE has atrophied present as hypo-autofluorescence on the FAF. Angioid streaks (AS) present as a variety of hyper- and hypo-autofluorescent changes that radiate in a linear fashion away from the optic nerve. AS can present subtly with fundus evaluation, but may show more prominently with FAF imaging.[27,52]

Treatment and Management

Due to extensive and varying potential systemic and ocular manifestations of the various genotypes of SCD, these patients require a multidisciplinary health care team whose goals are aligned and well-coordinated. This team should include hematologists, geneticists, molecular biologists, optometrists and ophthalmologists, cardiovascular specialists, phlebotomists, pain management specialists, pharmacists, family physicians, internists, nurses, and biomedical researchers.[10]

Systemic Management

Over 90% of patients with SCD now reach 20 years of age and the current median life expectancy in countries with advanced health care systems is over 50 years of age. Primary prevention of the condition is through genetic counseling before marriage and childbirth.[10] Once a patient is born, however, one way to prevent or manage SCR is through management of the systemic condition. Many systemic treatments have been employed or are being researched. Current noncurative treatments include early prophylaxis with penicillin to prevent bacteremia, chemotherapy with hydroxyurea (which increases Hb F synthesis and has been shown to mitigate long term organ damage), omega-3 fatty acids (inhibits adhesion of leukocytes to other blood cells and endothelium), and oral calcium channel blockers (eg nifedipine, induces vasodilation).[6,13] Iron chelation therapy is an option in patients with hemochromatosis.[10] Phlebotomy with long-term blood transfusions for cell exchange reduces Hb S RBC concentration. At present there are additional noncurative therapies in clinical trials, but the long-term success of these therapies is unknown. Gene therapy is a constantly evolving field in the treatment of ß-hemoglobinopathies and may ultimately proof to be an additional curative option. These therapies may involve the use of viral vectors, gene editing, and modulation of globin expression regulators. Initial trials with gene therapy are promising but further long-term study is needed and the future of these treatments is currently unknown.[13] The only current cure for SCD is hematopoietic stem cell transplantation from a highly human leukocyte antigen (HLA) matched donor (best outcomes are with HLA-matched sibling donors). Problematically, the pre-transplant conditioning with chemotherapy or chemotherapy with radiation is burdensome, and post-transplant complications are substantial in a minority of patients.[13,18]

Retinal Screening

Due to the often-asymptomatic nature of SCR, regular ocular monitoring is essential in screening for and managing the condition. Retinal screening with dilated fundus examination (DFE) is necessary for children with SCD; however, the recommended age varies depending on the source. Gill et al. suggest that those with SC genotype should be screened with DFE at age 9 and those with SS or Sβ-Thal be screened at age [13]. Those with normal findings can then be examined every 2 years. They recommend that those with abnormal findings should have FA performed.[53] Babalola et al. recommended that all patients with SCD have a DFE by the age of 10 and then be evaluated biennially until the age of 20 at which time they should be evaluated yearly.[54] Rosenberg et al. found pain crisis and splenic sequestration to be associated with higher incidence of SCR and recommended earlier screening for patients with those conditions.[55] Unlike proliferative diabetic retinopathy (PDR), PSR treatment is much more observatory in the absence of a non-clearing vitreous hemorrhage and/or retinal detachment. This is due to the nature of the condition, as well as the potential for spontaneous regression of SCR.

Laser Photocoagulation

Management of the ocular complications of SCD are primarily targeted at controlling SCR, particularly the development of proliferative disease and complications that stem from the formation of retinal neovascularization. Treatment of SCR remains somewhat controversial, largely due to the fact that a substantial amount (20-60%) of retinal neovascularization from SCR will self-involute without causing sight threatening complications.[6,10,15,56]

Laser photocoagulation is a long-standing, proven treatment for proliferative retinopathies of various etiologies. Large, controlled studies such as the Diabetic Retinopathy Study and the Early Treatment of Diabetic Retinopathy Study have shown the benefit of panretinal photocoagulation (PRP) for PDR, and have given clear advice on what stages to consider treatment.[57,58] While there is consensus regarding the benefit of PRP in PSCR, controversy exists on what stage is the most appropriate (unlike PDR) to initiate treatment and how treatment should be performed.[59–62]

Feeder vessel photocoagulation is an antiquated treatment strategy for PSCR in which high laser energy was used to ablate the feeder vessel supplying the neovascularization. This technique is no longer used due to adverse effects such as vitreous and retinal hemorrhaging.[5] Instead, most physicians utilize PRP to manage sight threatening neovascular lesions. PRP may be applied circumferentially or sectorally, targeting localized areas of neovascularization and retinal ischemia. Historically, sectoral PRP was considered to be safer, as circumferential PRP had reported adverse events such as choroidal ischemia.[6] However, with newer laser technologies that have better control of spot sizes and laser distribution, this is likely to be less of an issue. Sayag et al. suggest that not all patients with stage III retinopathy require treatment and recommend that those with Grade IIIA (flat sea fan < 1 MPS disc area in size) and IIIC (elevated sea fan with partial fibrosis) may be initially watched without treatment.[31] Yet there are others that advocate for the treatment of all sea fan lesions.[62] Treatment is ultimately up to the discretion of the managing physician or retinal specialist.[59]

Anti-VEGF

Since its initial use intraocularly to treat exudative macular degeneration, anti-VEGF has shown potential in the management of practically any proliferative retinal disease.[63]

Multiple case reports have demonstrated that intravitreal anti-VEGF is effective in regressing retinal neovascularization in those with PSCR.[64–66] It may be used alongside PRP to manage sight threatening neovascular lesions, and may be particularly helpful in eyes where additional PRP is difficult to perform due to vitreous hemorrhage, retinal fibrosis, or other limiting factors.[65] (Figure 3.) In addition, anti-VEGF may be considered prior to surgical repair of retinal detachment as a means to regress neovascularization and decrease bleeding during surgery.[66] Similar to PRP in the management of PSCR, the best use of anti-VEGF remains uncertain. Questions persist regarding the recommended treatment schedule, when to initiate treatment, and how does anti-VEGF treatment alone compare to treatment with PRP. In addition to treating PSCR, anti-VEGF could be utilized in the treatment of CNV resulting from angioid streaks or other causes.[27,67]

Surgery

Retinal surgery may be necessary to treat a variety of PSCR complications. Patients with persistent vitreous hemorrhage may require vitrectomy to recover vision. Those with traction retinal detachment or combined tractional/rhegmatogenous retinal detachment may require vitrectomy with retinal detachment repair or less commonly scleral buckling.[68,69] Additionally, patients who develop vitreomacular interface disease may require vitrectomy and surgical repair of conditions such as epimacular membranes, vitreomacular traction, or macular holes.[69,70] (Figure 5B) Possible complications following vitreoretinal surgery include iatrogenic retinal breaks, intraocular bleeding, secondary glaucoma, anterior segment ischemia, cataract formation, and/or systemic sickling.[6] Patients with vitreous hemorrhage or vitreomacular interface disease tend to have more favorable surgical outcomes than those with traction retinal detachments.[69]

Conclusion

SCD is an increasingly prevalent global health concern whose systemic and ocular manifestations vary widely based on genotype and environmental factors. While no cure for SCD currently exists, there is significant ongoing research which may ultimately reduce the disease' burden on our patients. From a holistic perspective, patient education as well as genetic counseling is essential to current and future comprehensive management of this condition. Patients with SCD won't be allowed to donate blood, but patients with the sickle cell trait may donate platelets. From an optometric perspective, vigilant screening, early detection of vision threatening ocular complications with advanced technology, and early intervention will help to preserve functional vision. As life expectancy in these patients continues to improve, there is projected to be an increase in both systemic and ocular complications. The optometric community needs to understand this disease and the critical role they play in the interdisciplinary medical team that will combat it.

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