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New Ways to Detect Pediatric Sickle Cell Retinopathy: A comprehensive review

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Abstract

Sickle retinopathy reflects disease-related vascular injury of the eye, which can potentially result in visual loss from vitreous hemorrhage or retinal detachment. Here we review sickle retinopathy among children with sickle cell disease, describe the epidemiology, pediatric risk factors, pathophysiology, ocular findings and treatment. Newer, more sensitive ophthalmological imaging modalities are available for retinal imaging, including ultra-widefield fluorescein angiography, spectral-domain optical coherence tomography, and optical coherence tomography angiography. Optical coherence tomography angiography provides a non-invasive view of retinal vascular layers that could previously not be imaged and can be quantified for comparative or prospective analyses. Ultra-widefield fluorescein angiography provides a more comprehensive view of the peripheral retina than traditional imaging techniques. Screening for retinopathy by standard fundoscopic imaging modalities detects a prevalence of approximately 10%. In contrast, these more sensitive methods allow for more sensitive examination that includes the retina perimeter where sickle retinopathy is often first detectable. Use of these new imaging modalities may detect a higher prevalence of early sickle pathology among children than has previously been reported. Earlier detection may help in better understanding the pathogenesis of sickle retinopathy and guide future screening and treatment paradigms.

Keywords

Sickle cell; Retinopathy; Fluorescein angiography; Optical coherence tomography

Introduction

Sickle cell disease (SCD) is a severe hematological disorder of chronic hemolysis, vascular injury and tissue ischemia impacting multiple organ systems. While homozygous hemoglobin S disease (HbSS) is associated with more severe clinical manifestations, HbSC disease is associated with more severe and earlier retinal disease.[1-5] This pathology leads to chronic anemia, vascular damage, and interrupted blood flow. As a result of the endothelial damage, perhaps exacerbated by anemia, arteries and arterioles can become damaged, leading to “sickle vasculopathy.”

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Ocular manifestations of SCD in the anterior segment include conjunctival comma vessels, hyphema, cataracts, and iris atrophy. Retinal vascular manifestations of SCD are the most important ocular changes by frequency and risk of visual impairment [6] and are classified as either proliferative or non-proliferative based on the presence of neovascularization. Visual loss in SCD patients primarily occurs in patients with proliferative sickle retinopathy (PSR), an outcome that can occur or be initiated in children with SCD. Pediatric screening for early detection of neovascularization can prevent consequences of undetected proliferative retinopathy including vitreous hemorrhage, retinal detachment, and epiretinal membranes.[7] Newer sensitive ophthalmological imaging modalities are increasingly used in non-sickle cell adult populations for early detection of retinal vascular pathology. Application to pediatric populations has not occurred, in large part due to low prevalence of pathology in non-sickle populations. In contrast, use of these techniques may play a role in earlier detection of sickle retinopathy in children, alone or as a precursor to increased risk of pathology in adult patients.

Here we systematically review the available evidence regarding sickle retinopathy, focusing on pediatric populations and how newer ophthalmological techniques are more sensitive than current methodologies currently used for the early detection of retinopathy.

Methods

A comprehensive literature review [8] was performed using PubMed as the information source, restricted to papers published in English. Search terms used were: “Retinopathy and sickle cell,” “Eye and sickle cell,” “Choroid and sickle cell,” “Retina and sickle cell,” “Retinopathy and sickle,” “Fluorescein and sickle cell,” “Optical coherence tomography and sickle cell,” “Optical and sickle cell”, “Retinal and sickle,” “Macular and sickle,” and “Ophthalmological and sickle.” Studies included were published between August 1954 and August 15, 2016. Studies with 3 or more patients (6 eyes) were reviewed. A total of 103 papers were identified and reviewed.

Results

Pediatric Epidemiology

Sickle retinopathy is an age-dependent process, with older people being at substantially higher risk [9]. As found in adult SCD,[10] the prevalence of proliferative sickle retinopathy (PSR) in pediatric patients is several times higher for HbSC than HbSS or HbS-Beta thalassemia.[11, 12] Prevalence of pathology reported has differed among studies in pediatric populations. These discrepancies are in large part due to differing definitions of retinopathy among the different studies, differing examiner ability, differing age ranges of patients studied and, more recently, the use of therapies such as hydroxyurea.[13] Table 1 summarizes the rates of overall retinopathy, as well as proliferative and non-proliferative retinopathy in several pediatric sickle populations. In contrast to pediatric populations, a prevalence study in a population aged 11-63 found the prevalence of proliferative retinopathy to be 45% in HbSC disease, 14% in HbSS disease and 17% in sickle-beta thalassemia.[10]

Risk Factors Associated with PSR

Risk of PSR increases with age in both genotypes. Prevalence of PSR is much higher in HbSC disease than in HbSS (HR 6.32) or other sickle cell disease types.[1, 2] The youngest case of PSR reported to date in HbSC was an 8 year-old patient and in HbSS in a 13 year-old patient.[14, 15] Several different risk factors have been reported by multiple independent cross-sectional studies of patients with sickle disease.[2, 3, 9, 14, 16-21] Not all of these cohorts reported the same risk factors as significantly associated with sickle retinopathy, possibly due to patient population, sample size, age range, method of eye examination, and concurrent disease therapies.

For HbSS, one or more of these studies have identified older age, male sex, and history of splenic sequestration or splenectomy as risk factors for PSR. One common factor, G6PD deficiency, has been identified as a risk factor, but not at a level of statistical significance (OR 4.20, p=0.054).[17] Overall, more serious disease phenotype, such as previous multiple pain crises or lower hemoglobin or fetal hemoglobin (HbF) levels have been associated with higher prevalence of PSR.[2, 17] To summarize, clinical and hematological factors that have been associated with PSR in HbSS patients are: older age (OR 1.12), longer disease duration (p=0.00), splenectomy (p=0.004), splenic sequestration (OR 4.00), pain crisis (OR 5.00), male sex (OR 2.58-4.20), acute pyelonephritis (OR 2.81), low fetal hemoglobin (p<0.001), and low weight (p<0.05).

For HbSC, risk factors are: splenic sequestration (OR 4.00), pulmonary involvement (OR 3.65), deafness or tinnitus (OR 3.49), no history of osteomyelitis (OR .10 – history of osteomyelitis), pain crisis (OR 5.00), male sex (OR 4.20), high mean cell volume in males (p<0.001), low fetal hemoglobin (p=0.01), low platelet count (p<0.01), and high reticulocyte count (p<0.05).[2-4, 9, 14, 16-25]

Pathophysiology

Prior to the expanded understanding of pathophysiology, development of retinopathy was believed to be initiated by vaso-occlusion at the junction of nonperfused and perfused peripheral retina leading to neovascularization.[26] Contemporary understanding of sickle vasculopathy is of a complex interaction between sickled erythrocytes, vasoactive factors, inflammation, activated endothelium, and other blood cells.[27-30]

Rodent models have been used for uncovering the pathophysiology of PSR. A rat model demonstrated that RBC trapping, not adhesion, is responsible for the retention of RBCs in retinal vasculature in HbSS, as preferential retinal retention of cells with low adherence propensity were observed. In contrast, for HbSC, low retention of HbSC cells was observed, suggesting that extra-erythrocytic factors like adhesive molecule and cytokines may be involved.[31]

The mechanism of angiogenesis in the formation of so-called “sea fans” has been an active area of study in PSR. Both vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) appear to be associated with sea fan formation in PSR. [32] Pigment epithelium-derived factor (PEDF), a known inhibitor of angiogenesis and a neurotrophic factor in the eye, may be elevated in viable vessels of sea fans.[33] Elevation of PEDF

production appears to follow increased angiogenesis.[34] In addition, plasma angiopoietins (Ang-1 and Ang-2) and von Willebrand factor are present in higher levels in SCD patients compared to controls.[35]

Endothelial cell adhesion molecules, inflammatory cytokines, and leukocytes also play an important role in the pathophysiology of retinopathy. Circulating intercellular adhesion molecule 1 (sICAM-1) is significantly decreased in HbSC patients with retinopathy. sICAM-1 has immunosuppressive effects, [36] so high levels may be protective against retinopathy by preventing leukocyte extravasation in the retina. Additionally, increased levels of ICAM-1, VCAM-1, and P-selectin immunoreactivities have been demonstrated in SCD patients compared to controls.[37] Also, studies have shown that the number of intraretinal PMNs increases with disease progression which suggests, similar to previous sICAM-1 findings, that leukocyte adhesion might have an important role in the vaso-occlusive phase of sickle cell retinopathy.[37] Finally, certain circulating cytokines have been shown to play a role in the pathophysiology of retinopathy. For example, TNF-alpha stimulates retention of sickled erythrocytes in the retinal vasculature.[38, 39]

Ocular Findings

Retinal pathology is not readily visible except under ophthalmologic examination. Common clinical findings in non-proliferative retinopathy include salmon patch hemorrhages, iridescent spots, and black sunburst lesions, all of which are the sequelae of peripheral arterial occlusions.[27, 28, 40-42] Other findings include angioid streaks, posterior vascular tortuosity, sickle disc sign, retinal depression sign, and retinoschisis.[27, 28] These finding are defined in Table 2.

Proliferative retinopathy is defined by the presence of neovascularization, traditionally identified by slit-lamp examination and indirect ophthalmoscopy. PSR begins with retinal vessel occlusion, which occurs most often in the peripheral retina. PSR has classically been defined by five stages developed by Goldberg et al.: 1) only peripheral arteriolar occlusions; 2) arteriolar-venous anastomoses at the retinal border; 3) neovascularization as evidenced by sea-fans; 4) vitreous hemorrhage; 5) retinal detachment.[43] Penman later revised this classification scheme of the peripheral vascular border, and more strictly defined proliferative retinopathy as requiring the presence of neovascularization (Goldberg Stage 3-5).[22]

While findings on clinical exam are important in detecting early signs of retinopathy and prevention of visual loss, newer advances in imaging modalities have made earlier detection and screening for retinopathy possible.

Current Ophthalmic Imaging Techniques

Recent advances in retinal imaging modalities including ultra-widefield fluorescein angiography (UWFA), spectral-domain optical coherence tomography (SD-OCT), and optical coherence tomography angiography (OCT-A) have revealed significant retinal findings in asymptomatic sickle cell patients (Figure 1).[44-51] Some of these silent findings have been shown to be significantly associated with the presence of PSR.[49]

Ultra-widefield Fluorescein Angiography—Fluorescein angiography (FA) has served as the gold standard for the detection of proliferative sickle retinopathy for over 40 years.[43] This study allows dynamic visualization of blood flow and observation of areas of dye leakage, pooling, and staining so that vascular abnormalities particularly in the periphery of the retina can be assessed and graded on the Goldberg scale. Traditional FA cameras offered views ranging from 30° to 60° in one exposure. 7-standard fields were used to cover an approximately 75° field of view. Previous techniques to expand the field of view posed technical challenges and required significant patient cooperation.[52]

Ultra-widefield fluorescein angiography (UWFA) captures up to 200° of the retina in a single image and has been shown to capture up to twice as much retinal areas as conventional FA.[53] Since it is more efficient in imaging the retina, this technology reduces the amount of patient cooperation and technical expertise necessary for operation.[52] As mentioned earlier, PSR particularly affects the peripheral vasculature and therefore UWFA has significant utility. In 2011, a retrospective case series of 12 eyes of 6 patients with SCD was performed. In all but one eye, UWFA detected peripheral vascular changes missed on the classical 7-standard fields photograph. Additionally, in 25% of eyes, peripheral vascular changes missed on clinical exam by experienced ophthalmologists were detected by UWFA.[45] Although the data are limited in comparisons of UWFA vs standard FA, UWFA is likely more sensitive in the detection of peripheral proliferative retinopathy.

Spectral Domain Optical Coherence Tomography and Optical Coherence Tomography Angiography—SD-OCT and OCT-A are both non-invasive imaging techniques that utilize reflected light, similar to ultrasound's use of sound, to produce detailed cross-sectional and en-face images of the retina and allow visualization of blood flow in retinal layers. SD-OCT provides near-histological cross-sectional images of the retina and can highlight areas of photoreceptor loss, nerve fiber layer change, and thinning or thickening of the retina in response to ischemic insults and neovascularization. OCT-A is a more recent modality that harnesses the speed and sensitivity of SD-OCT to capture detailed maps of the different layers of retinal and choroidal vasculature. Both have emerged as important modalities for the detection of early signs of PSR.

Recently, multiple groups have reported using SD-OCT imaging to assess the presence of subclinical macular thinning due to macular ischemia. SD-OCT has revealed temporal and central macular thinning (also referred to as macular splaying) in some patients with SCD.[44, 48, 49] Thinning of inner retinal layers in SCD patients with both symptomatic and asymptomatic retinopathy has also been reported in previous case series and histopathological studies.[41, 54-56] A 2015 retrospective study demonstrated that these discrete areas of macular thinning are significantly associated with PSR.[49] This finding was corroborated by a 2016 retrospective, case-controlled study that examined the predictive ability of temporal macular atrophy (thinning) for neovascularization in PSR in 38 patients. Temporal macular atrophy was found to have a positive predictive value of 83% and a negative predictive value of 13% for identifying neovascularization, demonstrating that the presence of temporal macular atrophy suggests the concurrent presence of neovascularization and PSR.[57] Finally, a recent retrospective case series reported that areas of macular thinning on SD-OCT correlated to the degree of peripheral ischemia on

UWFA.[58] Taken together, these findings suggest that SD-OCT may be useful for diagnosis and screening of retinopathy because macular thinning observed on SD-OCT is associated with PSR.

The etiology of this macular thinning seen on SD-OCT is not entirely understood. Various studies have suggested that macular thinning may be in part due to ischemia of the deep capillary plexus.[59, 60] Additionally, the functional consequence of macular thinning is not entirely clear. A prospective study in 19 patients demonstrated that SCD patients with focal macular thinning on SD-OCT have significantly decreased retinal sensitivities using microperimetry (a sensitive measurement of macular function) compared to those without thinning or controls suggesting functional consequences of this observed macular thinning. [61] Furthermore, SCD patients with focal macular thinning have significant thinning in the peripapillary retinal nerve fiber layer (characteristic of glaucoma) compared to SCD patients without focal macular thinning. [46] Finally, a recent report found no evidence to support an association between retinal thinning and neurocognitive function.[62]

When compared to traditional FA, OCT-A is probably more sensitive in identifying early regions of ischemia in the macula.[63] This difference was corroborated by a 2016 study that reported that OCT-A demonstrated microvascular abnormalities in the macula in 18 eyes of 9 patients, whereas FA appeared normal in nine of 18 eyes.[50]

Ophthalmological Imaging in Pediatric Populations—SD-OCT has dramatically altered the practice patterns of ophthalmologists over the last decade and is frequently used in patients seen by both adult and pediatric retina specialists for early detection of macular pathology. Both SD-OCT and OCT-A are non-invasive, and individual scans take only seconds to perform. While no studies have reported SD-OCT or OCT-A findings in pediatric sickle populations, the above findings raise the question of whether these technologies may prove useful in early identification of retinopathy. Our own preliminary data suggest that children with sickle cell disease commonly exhibit retinal vascular abnormalities by these sensitive testing modalities, including Goldberg Stage I and II retinopathy identified on UWFA, temporal macular thinning on SD-OCT and vessel dropout on OCT-A. (DP, manuscript in preparation). These abnormalities were not seen in controls within the same age range. Clinical implications of finding abnormalities in retinal vessels by sensitive testing remain unclear and will require longitudinal testing to assess what risk these patients have for serious eye pathology and what, if any, future intervention may be required for vision preservation.

Treatment

In a large prospective cohort of Jamaican children with SCD, proliferative disease developed in 43% of HbSC patients and 14% of HbSS patients over a 20-year period, [1] underscoring the increased prevalence in children with HbSC. However, most patients with PSR do not progress to visual loss. In patients with PSR, neovascular sea fans frequently undergo spontaneous autoinfarction, with the prevalence of this outcome reported as high as 60%. [26, 64-68] This outcome decreases the risk of visual complications, hence treatment has not been standardized. If autoinfarction does not occur, neovascularization can lead to visual

loss from vitreous hemorrhage, rhegmatogenous and tractional retinal detachment.[6] In a study of 120 adult patients with HbSS and 222 with HbSC, 10% of untreated eyes developed visual acuity loss over a period of ten years due to PSR.[7]

Treatment is usually undertaken for patients with bilateral proliferative disease, spontaneous hemorrhage, large elevated sea fans, or rapid growth of neovascular tissue.[69] Treatment options have been well summarized and described by previous reviews.[27, 28, 69] The preferred treatment for stage III proliferative lesions is scatter laser photocoagulation. It is effective in reducing the incidence of loss of visual acuity as well as the incidence of vitreous hemorrhage.[64, 70, 71] One study of 21 eyes with PSR found complete regression in 24 of 28 sea fan lesions treated with scatter laser photocoagulation.[72] Others have found complete regression in 30.2% of treated eyes compared to 22.4% of untreated control eyes.[64] Finally, treatment options for the vitreoretinal complications of PSR, which include epiretinal membranes, vitreous hemorrhage and retinal detachment, are pars plana vitrectomy and scleral buckling.[73, 74] However, as previously indicated treatment is not typically required in pediatric populations as advanced stages of PSR and the vision-threatening consequences of retinopathy do not generally occur until later in life.

Prevention by Referral for Ophthalmic Evaluation

Screening for early detection and treatment remain the mainstay of prevention. Based on the risk factors previously discussed, current recommendation by the American Academy of Pediatrics is for retinopathy screening of children by dilated fundoscopic examination with HbSS and HbSC beginning at age 10 years.[75] Other recommendations include biannual or annual examinations as early as age 9. [11, 16, 76, 77]

In addition to the current screening recommendations, patients with more severe systemic disease and a higher number of risk factors for PSR (e.g. splenic sequestration, increased number of pain crises) should be referred to an ophthalmologist. Patients with complaints of sudden or gradual decreased vision, floaters, or flashing lights should also be referred, as these symptoms could reflect the development of macular ischemia, vitreous hemorrhage, retinal tears, or retinal detachment.

A retrospective review of 123 children with SCD demonstrated an association between elevated HbF and lower prevalence of retinopathy. [13] These data suggest that induction of HbF by hydroxyurea, along with other possible drug effects, may prevent pediatric retinopathy and the development of visual loss from proliferative disease.

Future Directions

Given the ubiquity of SD-OCT and the ease of image acquisition in both adult and pediatric populations, it is likely that SD-OCT will be used more frequently in the screening examination of pediatric patients with SCD. OCT-A imaging is a newer technology that is less widely adopted than SD-OCT, but its ability to image the retinal vasculature in a non-invasive fashion makes it a useful research tool for the characterization of microvascular changes in SCD patients.

Future studies will need to explore the connection between temporal macular thinning on SD-OCT, microvascular changes on OCT-A, and proliferative retinopathy as detected on UWFA. If correlations between the imaging modalities are found in the pediatric population as they have been found in adults, abnormal SD-OCT studies may prompt differing monitoring strategies for patients with SCD.

Conclusion

Retinopathy is a serious chronic complication of SCD. By standard dilated fundoscopic examination of pediatric patients, the prevalence of retinal vascular pathology has been estimated to be anywhere between 17% and 94%.[78, 79] Most of the pathology found reflects early vascular changes rather than the more serious injury that can progress to visual loss found in adult patients. Future studies could include the prevalence, progression, clinical outcomes and clinical utility of the newer diagnostic imaging techniques such as SD-OCT, OCT-A, and UWFA and the impact of new early screening and therapeutic approaches on eye health in pediatric SCD.

Future studies using SD-OCT, OCT-A and UWFA may generate more refined data on SCD retinal vascular disease. Understanding the pathogenesis and evolution of retinal vasculopathy could also be targets for these techniques. For example, improved detection of vascular pathology and its sequellae could be compared to effects of SCD vasculopathy in other organs, such as those appreciated through MRI evaluation of pediatric sickle vasculopathy in pediatric central nervous systems.[27, 80]

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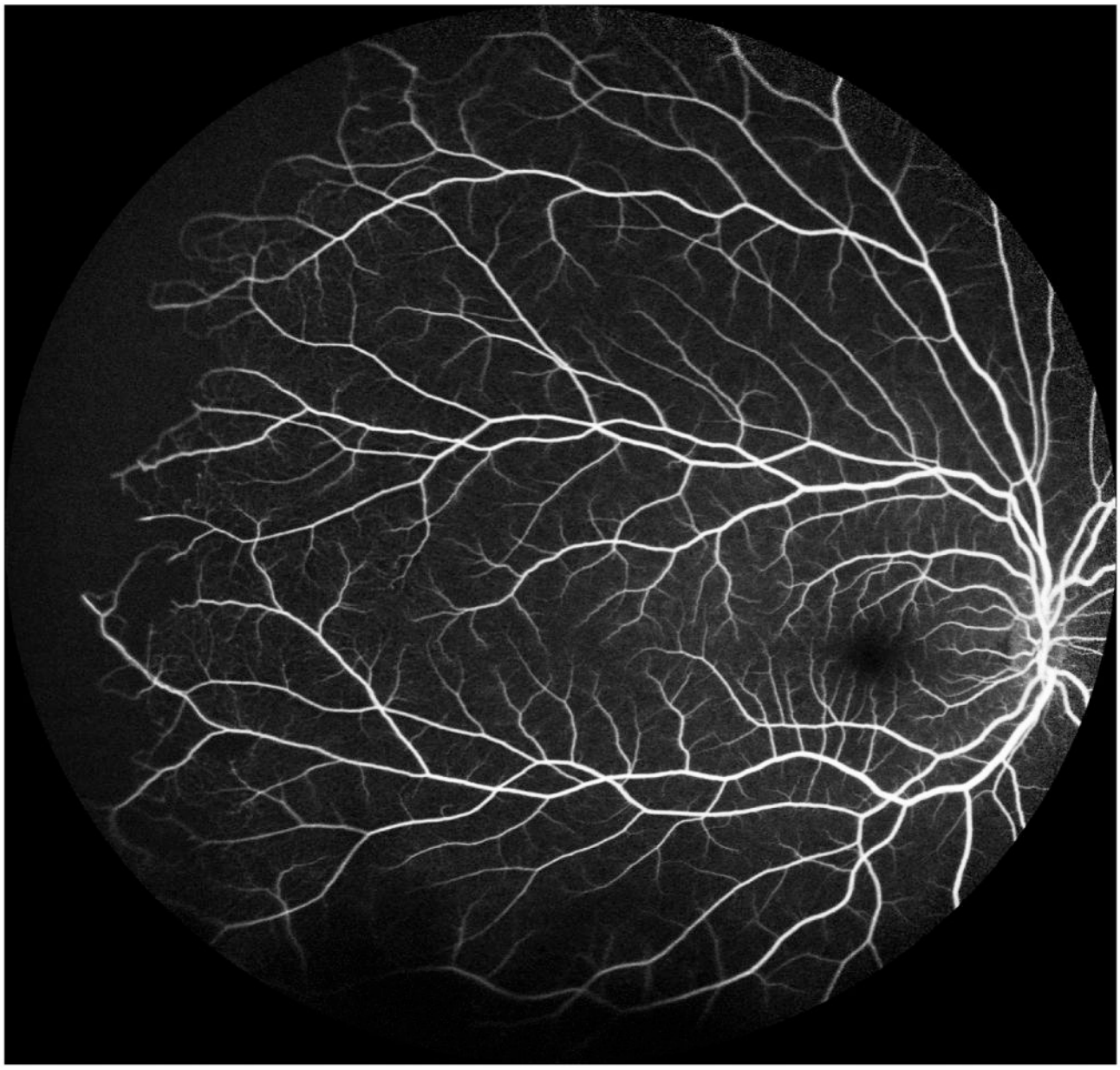

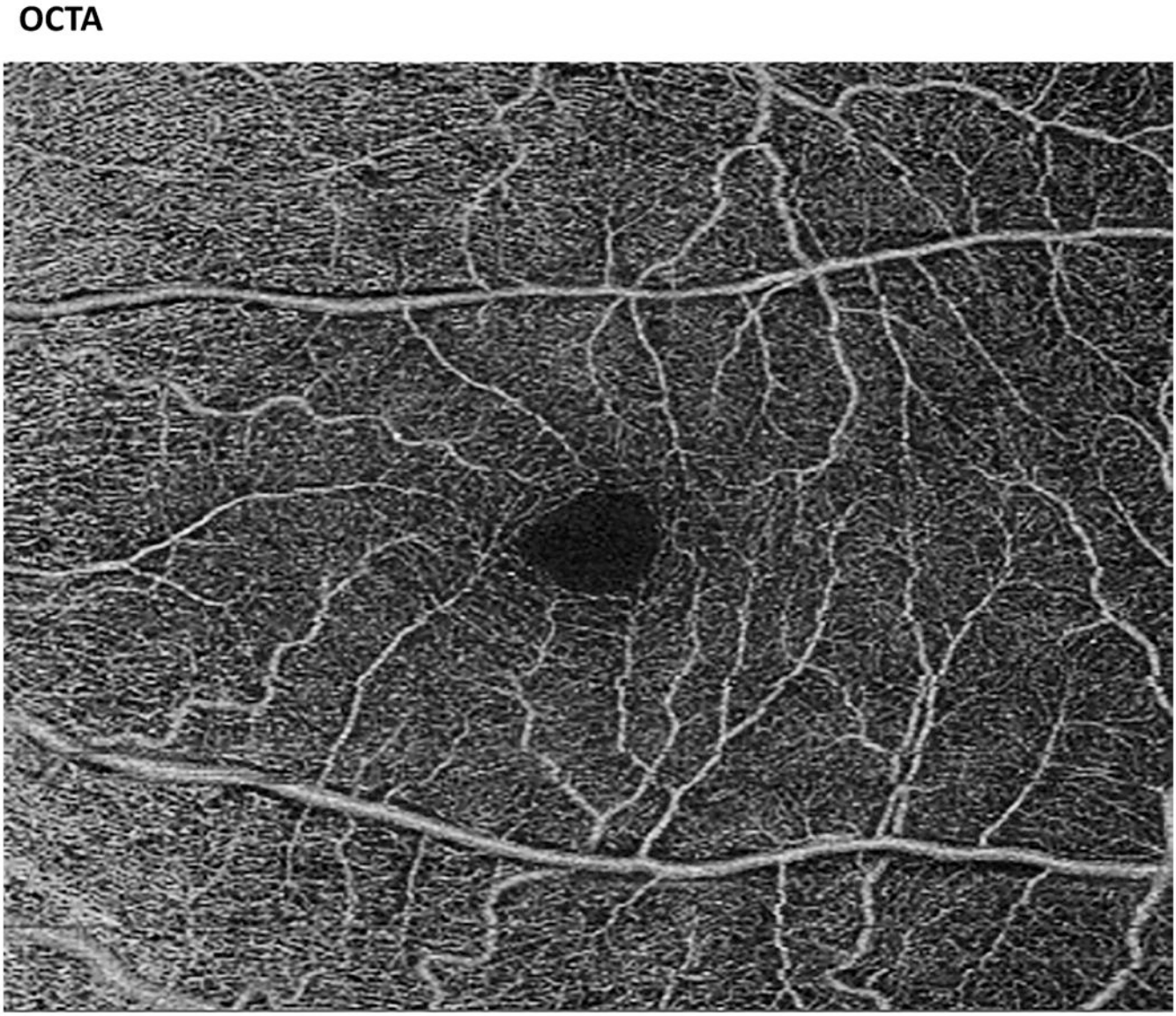

Figure 1.

Images of the fundus by ultra-widefield fluorescein angiography (UWFA, left) and optical coherence tomography angiography (OCT-A, right). The UWFA image demonstrates peripheral arteriolar disease in a sickle cell patient. The OCT-A demonstrates a healthy superficial vascular plexus.

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Table 1

Literature on the epidemiology of pediatric sickle cell retinopathy

Study	Number of patients	Age Range	Retina Exams Done		Prevalence	Study Type	Additional Findings
Abiose et al. (1978) [24]	91 (91 HbSS, 0 HbSC)	5 to 14	**1** **2** **3**	Direct Ophthalmoscopy Indirect Ophthalmoscopy Three-mirror contact lens where indicated	Any retinopathy - 58% PSR – 1% with neovascularization and 5.5% with peripheral arteriolar occlusion	Cross-sectional	Vascular tortuosity - 27%; Black sunbursts - 11%; Salmon patch hemorrhage - 4%; Abnormal conjunctival vasculature – 81%
Condon et al. (1974) [79]	54 (0 HbSS, 54 HbSC)	2 to 15	**1** **2** **3** **4**	Direct Ophthalmoscopy Indirect Ophthalmoscopy Three-mirror contact lens where indicated No fluorescein unless indicated on exam (5%)	Any retinopathy (peripheral retinal vessel disease) - 94% PSR - 11%	Cross-sectional	Vascular tortuosity - 32%; Black sunbursts - 4%; Arterio-venous fistulae - 17%; Angioid streaks - 0%; Retinoschisis – 2%
Downes et al. (2005) [1]	474 (307 HbSS, 166 HbSC)	5 to 26	**1** **2**	Fundus examination through dilated pupils (exact methodology not specified) Fluorescein for all	PSR - 43% of HbSC and 14% of HbSS by ages 24-26 CHANGE TO 18-20 AGE RANGE	Longitudinal observed over 20 yrs	Spontaneous regression in 32% of PSR-affected eyes
El-Ghamrawy et al. (2014) [16]	40 (26 HbSS, 14 HbS/ Beta-thal)	2 to 28	**1** **2** **3**	Biomicroscopy Indirect Ophthalmoscopy Fluorescein for age 12+ or when indicated on exam	Any retinopathy - 47.5% (46.2% of HbSS and 50% of HbS/Beta-thal) PSR - 32.5% NPR - 27.5%	Cross-sectional	Vascular tortuosity - 25%; Black sunbursts - 5%
Eruchalu et al. (2006) [77]	37 (37 HbSS, 0 HbSC)	3 to 14	**1** **2**	Direct Ophthalmoscopy Indirect Ophthalmoscopy	Any retinopathy - 32.4% PSR - 5.4% NPR - 27%	Cross-sectional	Retinal infarcts - 14.9%; Vascular tortuosity - 54%; Black sunbursts - 6.8%; Salmon patch hemorrhage - 6.8%; Comma vessels – 70.3%
Estepp et al. (2013) [13]	123 (123 HbSS, 0 HbSC)	11 to 16	**1** **2**	Dilated fundoscopic examination (exact methodology not specified) No fluorescein unless indicated on exam	Any retinopathy - 10.6% PSR- 1.6% NPR - 8.9%	Retrospective review between 2003-2010	
Gill et al. (2008) [11]	236 (163 HbSS, 73 HbSC, 27 HbS/Beta-thal)	1 to 18	**1**	Dilated fundoscopic examinations (exact methodology not specified)	Any retinopathy - 18.7% PSR- 2.7% (8.2% of HbSC, 0.6% of HbSS, and 0% of HbS/Beta-thal)	Retrospective longitudinal survival analysis between 1987-2005	

Study	Number of patients	Age Range	Retina Exams Done		Prevalence	Study Type	Additional Findings
			2	No fluorescein unless indicated on exam	NPR - 18.6% (24.7% of HbSC, 14.1% of HbSS, and 11.1 % of HbS/Beta-thal		
Kimmel et al. (1987) [15]	135 (Breakdown not available)	0 to 20	**1** **2**	Dilated fundoscopic examination (exact methodology not specified) No fluorescein unless indicated on exam	PSR - 5.2%	Retrospective review between 1976 to 1985	
Oliveira et al. (2014) [12]	51 (36 HbSS, 15 HbSC)	4 to 18	**1** **2** **3**	Biomicroscopy Indirect Ophthalmoscopy Fluorescein for age 10+	Any retinopathy (ages 10 to 18) - 17.5% (80.0% of HbSS and 22.2% of HbSC ages 10-18) PSR (ages 4 to 18) - 39.2% (30.6% of HbSS and 60.0% of HbSC) NPR (ages 4 to 18) - 39.3% (38.9% of HbSS and 40.0% of HbSC)	Cross-sectional	Neovascularization - 0%; Vascular tortuosity - 19.6%; Black sunbursts - 9.8%; Salmon patch hemorrhages - 2.0%; Angioid streaks - 0%; Iridescent spots - 7.8%
Rosenberg et al. (2011) [17]	258 (186 HbSS, 55 HbSC, 12 HbS/Beta-thal	10 to 18	**1**	Dilated fundoscopic examination (exact methodology not specified)	Any retinopathy - 20.9% (17.2% of HbSS, 32.7% of HbSC, 33.3% of HbS/Beta-thal) PSR - 4.3% (0.54% of HbSS, 16.4% of HbSC, 8.3% of HbS/Beta-thal) NPR - 16.3%	Retrospective review over 10 year period	
Talbot et al. (1982) [25]	96 (59 HbSS, 37 HbSC)	5 to 7.5	**1** **2** **3**	Direct Ophthalmoscopy Indirect Ophthalmoscopy Fluorescein for age 6.5+ and when indicated on exam for younger	PSR - 0.0%	Cohort	Peripheral arteriolar closure- 24% HbSS and 16% HbSC; Arteriolar sheathing- 51% HbSS and 30% HbSC; Arteriovenous anastomoses - 3.1%; Retinal patches - 37% of HbSS and 24% of HbSC
Talbot et al. (1983) [19]	85 (54 HbSS, 31 HbSC)	6.5 to 8.5	**1** **2** **3**	Direct Ophthalmoscopy Indirect Ophthalmoscopy Fluorescein for all		Cohort	Peripheral arterial closure - 66.6% HbSS and 51.6% HbSC
Talbot et al. (1988) [14]	389 (219 HbSS, 135 HbSC, 24 HbS/Beta-thal, 11 HbS/Beta-thal0)	5 to 13	**1** **2** **3**	Direct Ophthalmoscopy Indirect Ophthalmoscopy Fluorescein for age 6+	PSR - 0.3%	Cohort	Peripheral arteriolar closure – 90% of HbSS and HbSC by age 12
Tantawy et al. (2013) [78]	60 (28 HbSS, 32 HbS/ Beta-thal)	3 to 18	**1** **2**	Indirect Ophthalmoscopy Fluorescein for all	Any retinopathy – 17% (25% of HbSS and 9.4% of HbS/ Beta-thal) PSR - 0%	Cohort	

Study	Number of patients	Age Range	Retina Exams Done	Prevalence	Study Type	Additional Findings
				NPR- 17% (25% of HbSS and 9.4% of HbS/Beta-thal)		

NPR- non-proliferative retinopathy; PSR - proliferative sickle retinopathy

Table 2

Definitions of major ophthalmological findings in sickle cell retinopathy

Finding	Definition [27-29, 69]
Salmon Patch Hemorrhage	Oval-shaped, orange, well-defined area of bleeding on the retina surface
Black Sunburst Lesion	Circular, black, stellate and spiculate lesion from the migration of retinal pigment epithelium
Iridescent Spot	Small retinal cavity with yellow spots containing hemosiderin-laden macrophages resulting from a resorbed salmon patch hemorrhage
Disc Sign	Dark red spots on the optic disc due to plugs of deoxygenated, sickled erythrocytes
Posterior Vessel Tortuosity	Vessels that make a twisted rather than normal straight path
Angioid Streaks	Gray, bilateral, irregular lines emanating from the optic disc representing small breaks in Bruch's membrane (membrane that separates the retina and choroid)
Retinal depression sign	Abnormal light reflex from the retina due to ischemia of the macula causing atrophy
Retinoschisis	Splitting of the retina's neurosensory layers
Sea Fan	Neovascular growth in PSR that resembles the marine species *Gorgonia flabellum*