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OCT-Angiography and Ultra-Widefield Fluorescein Angiography for Early Detection of Adolescent Sickle Retinopathy

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Abstract

Purpose—Using standard screening techniques, sickle retinopathy reportedly occurs in 10% of adolescents with sickle cell disease (SCD). We performed a prospective, observational clinical study to determine if ultra-widefield fluorescein angiography (UWFA), spectral-domain optical coherence tomography (SD-OCT) and optical coherence tomography angiography (OCT-A) detect more frequent retinopathy in adolescents with SCD.

Design—Cross-sectional study.

Setting—Institutional.

Subjects—Sixteen adolescents with SCD, ages 10–19 years, (mean age 14.9 years) and 5 age-equivalent controls (mean age 17.4 years).

Observation Procedures—Examinations including acuity, standard slit-lamp biomicroscopy, UWFA, SD-OCT and OCT-A were performed.

Main Outcome Measures—Sickle retinopathy defined by biomicroscopic changes, Goldberg stages I–V, Penman scale, flow void on OCT-A, or macular thinning on SD-OCT.

Results—While 22/32 SCD eyes (68.8%) had retinopathy on biomicroscopy, by UWFA 4/24 (16.7%) SCD eyes had peripheral arterial occlusion (Goldberg I), and 20/24 eyes (83.3%) had peripheral arteriovenous anastomoses (Goldberg II) in addition. No patients had Goldberg stages III–V. By SD-OCT and OCT-A, thinning of the macula and flow voids in both the superficial and deep retinal capillary plexus were found in 6/30 (20%) eyes.

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Conclusions—All 24 eyes with adequate UWFA studies demonstrated sickle retinopathy. SD-OCT and OCT-A, which have not been previously reported in the adolescent population, detected abnormal macular thinning and flow abnormalities undetected by biomicroscopy. These findings suggest that pediatric sickle retinopathy may be more prevalent than previously suspected. If these findings are confirmed with larger cross-sectional and prospective analyses, these approaches may enhance early screening for sickle retinopathy.

INTRODUCTION

Sickle cell disease results from a single amino acid substitution in the hemoglobin (Hb) gene, leading to abnormal red blood cells. Interactions between sickled red blood cells and vascular endothelium often lead to vaso-occlusion and tissue ischemia. As a result, blood vessels can become damaged, a pathology referred to as “sickle vasculopathy.”¹

The effect of sickle vasculopathy on the retinal vasculature results in sickle retinopathy. Childhood screening for retinopathy, recommended to begin at age 10 years,² is important in order to identify proliferative changes and prevent the long-term consequences of untreated proliferative sickle retinopathy, including vitreous hemorrhage, retinal detachment, and visual loss.^{3–5} Proliferative retinopathy can be graded and defined based on the degree of pathology with both Goldberg scale Stages I–V⁶ and Penman border classification.⁷ The prevalence of proliferative sickle retinopathy in pediatric populations has been estimated to be anywhere between 0 and 40%.^{8,9} This wide range is due to several confounding factors, including differing definitions of proliferative retinopathy, standardization, and differing retinal imaging techniques performed. Many of these prevalence studies perform only standard biomicroscopic evaluation.^{10–12}

More modern retinal imaging techniques of ultra-widefield fluorescein angiography (UWFA), spectral-domain optical coherence tomography (SD-OCT), and optical coherence tomography angiography (OCT-A) have been shown to reveal sub-clinical macular and peripheral vascular changes in asymptomatic adult sickle populations not observed with traditional imaging technologies.^{13–17} Recent reports have shown that UWFA, which captures up to twice as much retinal area as conventional fluorescein angiography (FA)¹⁸, is more sensitive than traditional FA in identifying peripheral vascular changes in sickle retinopathy.¹⁴ Additionally, proliferative sickle retinopathy has been found to be more prevalent in patients with macular thinning identified on SD-OCT suggesting the utility of SD-OCT in identifying patients at higher risk for proliferative disease.^{16,19} Finally, OCT-A has been found to provide a more accurate visualization of the macular vasculature than traditional FA.^{20,21}

The goals of this study were to assess sickle retinopathy in an adolescent SCD sample using more sensitive modes of ocular examination than has previously been done. We hypothesized that peripheral vascular changes may be more prevalent than previously reported using more sensitive imaging modalities. Additionally, we hypothesized that the macular changes undetectable on clinical exam and observed in adult SCD populations could be observed in pediatric SCD populations by SD-OCT and OCT-A.^{13,15,20} These

pilot data assessed the utility of UWFA, SD-OCT, and OCT-A in screening for pediatric sickle retinopathy.

METHODS

This non-interventional, cross-sectional study was performed under Institutional Review Board approval at Columbia University. Informed consent was obtained from parents and participants 18 years or older. The study is HIPAA-compliant and adhered to the tenets of the Declaration of Helsinki.

Study procedures were conducted at the Edward S. Harkness Eye Institute at Columbia University between May 2016 and December 2016. Patients with SCD were referred from Columbia's Pediatric Sickle Cell Clinic and Stem Cell Transplantation team. Adolescents were selected as subjects to maximize the findings within a small pediatric sample. Adolescents age 10–19 years with SCD (10 HbSS, 5 HbSC, 1 HbS/beta thal) were offered opportunity for study enrollment. This age range was chosen based on current recommendations for retinopathy screening in patients with SCD starting at age 10 from the American Academy of Pediatrics.²² A total of 9 patients declined participation due to scheduling issues or lack of interest. For SCD patients undergoing stem cell transplantation, study participation was offered in lieu of standard clinical ophthalmologic evaluation. Five control patients age 12–19 were recruited. Aged-matched controls were healthy volunteers without SCD.

All patients underwent standard clinical examination, including best-corrected Snellen visual acuity, intraocular pressure and slit-lamp examination. Ocular examinations were performed by RWSC, a fellowship-trained vitreoretinal specialist. Refraction was performed in adolescents without 20/20 vision. Pupil dilation of both eyes was performed using Tropicamide 1% and Phenylephrine 2.5% drops. Following dilation, all patients were examined by slit lamp biomicroscopy and indirect ophthalmoscopy noting the presence of both non-proliferative changes (salmon patch hemorrhage, iridescent spots, black sunburst lesions, vascular tortuosity) and proliferative changes.

Following clinical examination, SD-OCT and OCT-A scans were obtained for each patient on the Cirrus HD-OCT 5000 with Angioplex OCT Angiography, software v 9.5 (Carl Zeiss Meditec, Dublin, CA). The Cirrus OCT uses an 840-nm wavelength superluminescent diode as optical source and acquires 68,000 A-scans per second with axial resolution of 5 μ m in tissue. 6 mm macular cube scans centered on the fovea were obtained in all patients. The Cirrus Angioplex OCT-A system uses an algorithm entitled OMAGc, which uses phase and amplitude OCT data signal to detect differences in light reflectivity in repeated scans. For each patient, 3 mm $\times$ 3 mm, 6 mm $\times$ 6 mm, and 8 mm $\times$ 8 mm OCT-A scans centered on the fovea were performed.

UWFA was performed in all patients using the Spectralis S3300 HRA-OCT with ultra-widefield angiography module (Heidelberg Engineering, Heidelberg, Germany). This device captures images with up to 102 degrees of view. 1–2 mL of a fluorescein sodium solution was injected into a peripheral vein with a 25-gauge butterfly needle for UWFA. Fluorescein

angiograms centered on the posterior pole were captured, followed by superior, inferior, temporal, and nasal sweeps. UWFA images were steered in order to best capture the vascular periphery.

SD-OCT and OCT-Angiography Analysis

SD-OCT images were assessed qualitatively for macular thinning. For each eye, the 128 individual line scans from the macular scan protocol were reviewed to assess for abnormal retinal thinning defined as an irregular retinal contour accompanied by abrupt thinning observed by two fellowship-trained vitreoretinal experts (RWSC, JSC). OCT-A images were qualitatively assessed for areas of non-perfusion defined as decreased vessel density in both the superficial and deep capillary plexuses. Images were excluded if there were too many motion artifacts to permit adequate grading.

Ultra-Widefield Fluorescein Angiography Analysis

UWFA images were reviewed by two experts (RWSC, JSC) and graded based on the Goldberg scale for proliferative retinopathy: Stage I: peripheral arteriolar occlusions; Stage II: arteriovenous anastomoses; Stage III: neovascularization; Stage IV: vitreous hemorrhage; Stage V: Retinal detachment. Additionally, UWFA images were graded on the Penman scale based on the morphological and qualitative characteristics of the peripheral vascular border (type I: qualitatively normal with smooth vascular borders; type IIa: qualitatively abnormal with capillary buds or stumps extending into the nonperfused retina; type IIb: qualitatively abnormal with capillary buds or stumps without extension into the nonperfused retina). For each eye, the image with the most advanced stage of pathology was used for grading purposes. In situations in which the expert's grading of the UWFA images differed, their consensus was reached after discussion.

Finally, patient charts were reviewed for age, hemoglobin type, years on transfusions, years on hydroxyurea therapy, and indications for transplant.

RESULTS

Thirty-two eyes of 16 adolescent patients with SCD (mean age 14.9 years; 10 HbSS, 5 HbSC, 1 HbS-Beta thalassemia⁰) were evaluated for both peripheral and central evidence of retinopathy. Nine were on hydroxyurea therapy, 1 on chronic transfusion, 0 on both, and 6 on no therapy. 10 eyes of five age-equivalent adolescent controls (mean age 17.4 years) were evaluated. Patient demographics are summarized in Table 1. The small sample precluded the use of hydroxyurea-based biomarkers (e.g. fetal hemoglobin) for risk stratification. No patient had vision disturbance at the time of examination. One patient had anisometropic amblyopia in the right eye with vision of 20/100 at the time of examination.

Biomicroscopic examination revealed conjunctival comma vessels in all sickle eyes. On dilated fundus examination, 10/32 eyes (31.3%) had evidence of salmon patch hemorrhages. 10/32 eyes (31.3%) demonstrated vessel tortuosity, and sunburst lesions were observed in 10/32 eyes (31.3%). In total, 22/32 SCD eyes (68.8%) had evidence of retinopathy on biomicroscopy. No controls showed evidence of vascular changes on biomicroscopic evaluation (0/10 eyes, Table 2).

Sixteen SCD patients were offered analysis by UWFA. Two adolescents were not able/ refused to undergo UWFA testing, and two UWFA tests (4 eyes) were considered inadequate due to motion artifact or poor fluorescein uptake. Of the remaining 12 patients, UWFA detected peripheral arteriolar occlusion (Goldberg Stage I) alone in 4/24 eyes (16.7%); 20/24 eyes (83.3%) had peripheral arteriovenous anastomoses (Goldberg Stage II) in addition to arteriolar occlusions. No patient had Goldberg Stages III–V. One UWFA study (1 eye) that was considered adequate for Goldberg staging, was considered inadequate for Penman classification. Twelve of 23 eyes (52.2%) were classified as Penman type I border, 5/23 eyes (21.7%) as type IIa, and 6/23 eyes (26.1%) as type IIb. Only three out of the five controls underwent UWFA testing. No vascular abnormalities were observed by UWFA in control eyes (0/6 eyes, Figure 1).

In evaluation of SD-OCT and OCT-A images for thinning and flow voids, one patient (2 eyes) was excluded due to excessive motion artifact. SD-OCT demonstrated qualitative thinning of the temporal macula in 6/30 eyes (20%): 3 eyes of 2 patients with SC disease, and 3 eyes of 3 patients with SS disease. OCT-A of the same 6/30 eyes (20%) revealed flow voids in both the superficial and deep retinal capillary plexuses in the area of thinned retina found on SD-OCT (Figure 2). The flow voids were typically more prominent in the deep plexus than in the superficial in OCT-A images (Figure 3). Twenty-four of 30 eyes (80%) had no significant findings on OCT-A or SD-OCT. No control eyes demonstrated thinning or flow abnormalities (0/10 eyes). Both the SD-OCT and OCT-A abnormalities were undetectable with standard biomicroscopy. There was 100% agreement between graders on the presence of retinal thinning and flow abnormalities in patient and control eyes.

DISCUSSION

The goals of this study were to assess the frequency and severity of sickle retinopathy in a pediatric sample using more sensitive modes of ocular examination than has previously been done. To our knowledge, this is the first study demonstrating the characteristics of pediatric sickle retinopathy based on the sensitive imaging modalities of UWFA, SD-OCT, and OCT-A. All 16 adolescents with SCD in this case series demonstrated evidence of sickle retinopathy using the combination of standard biomicroscopy, UWFA, SD-OCT, and OCT-A imaging. No vascular pathology was seen in controls.

While 69% of eyes had evidence of retinopathy on biomicroscopy, UWFA was far more sensitive and revealed at least Goldberg Stage I in 100% of SCD eyes. Interestingly, macular changes were also detected in this pediatric population, as 20% of eyes (3 SC, 3 SS) showed both retinal thinning on SD-OCT and corresponding flow voids on OCT-A studies. The areas of SD-OCT thinning and OCT-A flow voids were not detected on biomicroscopy. A recent study reported flow voids present in 37.8% of an adult population with SCD.²² The 20% of eyes in our study with flow voids and thinning suggests two conclusions in relation to the adult study: 1. Ischemic macular events occur in adolescent populations, and 2. The prevalence of these events likely increases with age. We were unable to determine if there was an effect of hemoglobin type on likelihood of flow abnormalities due to the relatively small sample size in this study.

Findings from these sensitive imaging modalities suggest that pediatric sickle retinopathy is more prevalent than previously suspected. Most studies assessing sickle retinopathy in pediatric populations utilize FA only when indicated on clinical exam skewing results towards a lower prevalence of retinopathy than in fact exists.^{10–12, 23, 24} One retrospective analysis of 258 adolescents with SCD aged 10–18 conducted over a 10 year period found a 20.9% prevalence of SR,¹¹ while another analysis in children with SCD aged 1 to 18 found an 18.7% prevalence of any retinopathy.¹² Our findings of Goldberg Stage I or II retinopathy in the eyes of all adolescents with SCD aged 10–19 are more consistent with Talbot et al. which utilized FA studies in all patients and demonstrated peripheral arteriolar closure (Goldberg Stage I) in 90% of HbSS and HbSC adolescents by age 12.²⁵ Similarly, Condon et al. found a 94% prevalence of retinopathy in adolescents with HbSC disease ages 2 to 15.²⁶ As opposed to conventional FA, UWFA allows the examiner to more easily examine areas of the peripheral retina where vascular changes in SCD most often occur.²⁷ The usage of UWFA compared to conventional FA has been shown to improve detection of peripheral vascular changes in adult SCD populations.¹⁴ This difference may also likely account for the high frequency of retinopathy detected in this study.

Variation exists regarding the proper classification of proliferative sickle retinopathy. Some studies have reported prevalence rates based on dilated exam alone, while others have employed diagnostic tests, including fluorescein angiography. This variety of detection methods may have contributed to the range of reported prevalence rates of sickle retinopathy in both the adult and pediatric population. Goldberg Stage I and Stage II have historically been classified as proliferative stages of retinopathy. The more sensitive examination provided by UWFA revealed in our small sample that the majority of adolescents have peripheral retinal changes that can be classified as either Goldberg Stage I or II. Based on historical data,^{3, 28} many of these adolescents will not go on to develop visually debilitating retinopathy that more likely occurs with more severe proliferative disease. In light of our findings, a more appropriate approach may be to classify proliferative retinopathy as restricted to Goldberg Stage III–V, stages in which true retinal neovascularization has developed.

Our novel findings of macular thinning detected by SD-OCT in pediatric SCD patients are consistent with similar findings in adult SCD populations. Goldbaum et al. first described the “retinal depression sign” in 1978, which was believed to represent focal areas of retinal thinning due to infarction.²⁹ SD-OCT and OCT-A allow for more sensitive visualization of retinal thickness and blood flow through the deep and superficial plexuses in the macular region compared to FA. Additionally, in contrast to UWFA, which requires dye injection and produces a 2D image, OCT-A is non-invasive and allows visualization of all three major capillary networks (superficial retinal, deep retinal, and choriocapillaris).³⁰

SD-OCT and OCT-A studies in adult SCD populations have found discrete areas of macular thinning and flow void in asymptomatic patients. These OCT findings are consistent with histopathologic findings of inner retinal layer thinning in patients with SCD.³¹ Han et al. demonstrated that areas of decreased blood flow in the deep capillary plexus correlated to areas of macular thinning.²⁰ Furthermore, the presence of discrete areas of macular thinning on OCT-A has been shown to be correlated with the presence of proliferative sickle

retinopathy.¹⁶ This has been corroborated by additional studies including a 2016 retrospective, case-controlled analysis that found temporal macular atrophy to have a positive predictive value of 83% and a negative predictive value of 13% for identifying neovascularization and proliferative sickle retinopathy.¹⁹ Finally, a recent retrospective case series found areas of macular thinning on SD-OCT correlated to the degree of peripheral ischemia observed on UWFA.³² These findings taken together suggest the potential utility of OCT-A as a non-invasive tool for screening and identifying SCD patients at a higher risk for proliferative disease.¹⁶ The six eyes in this study that had flow voids on OCT-A and macular thinning on SD-OCT did not have corresponding neovascularization in the periphery. These patients may be at higher risk for the development of more severe peripheral ischemia. Penman et al. described an increased risk of proliferative sickle retinopathy in patients with type II borders.⁷ 11/23 eyes in this study were classified as having a type IIa or IIb border by Penman classification. A natural follow-up question would be whether a relationship existed between flow voids on OCT-A and type II border, as the presence of each finding has been demonstrated to increase risk of proliferative retinopathy. In the present study, no relationship was found between OCT-A flow voids and presence of type II border. It is possible that these findings are both independent risk factors for the development of proliferative sickle retinopathy.

Study limitations include its small sample size, lack of younger SCD patients, a mix of SCD phenotypes with heterogeneous risk for sickle retinopathy, single site, and modest number of controls. Normal historical findings in healthy adults modulated the use of a larger control group. Multi-site studies will be needed to assess protective factors for sickle retinopathy in larger pediatric patient populations, including use of hydroxyurea. Another limitation is the dependence on a single examiner for biomicroscopic evaluation. Additionally, despite the improved ability to capture both UWFA, SD-OCT, and OCT-A images, some studies were still inadequate for analysis due to patient movement resulting in imaging artifacts. Specifically, 8 eyes did not have appropriate UWFA imaging for analysis, and 2 eyes were deemed inadequate for SD-OCT/OCT-A analysis. Finally, assessing the lower age limit of retinopathy in these patients would be an important application of the methods used.

Screening for early detection and treatment remains the mainstay of prevention of retinopathy. The current recommendation by the American Academy of Pediatrics is to perform dilated fundoscopic exam beginning at age 10 years.² If findings from this case series are confirmed in larger and prospective studies, these more sensitive imaging approaches may enhance early screening for patients at higher risk of sickle retinopathy and visually threatening proliferative disease. Further, clinical factors such as use of hydroxyurea and fetal hemoglobin levels should be examined for utility in risk stratification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Ultra-widefield fluorescein angiograms in control eyes vs eyes with sickle retinopathy. (Top, left and right) Normal appearance of the vascular border in control eyes. As the vessels extend toward the ora serrata, there is a gradual reduction in vascular density, and some venous-venous loops are present. (Bottom left) Goldberg Stage II, Penman Type IIa border in a patient with SC disease. Note arteriovenous anastomoses and abrupt capillary dropout with arterial stumps extending into the avascular retina. (Bottom right) Goldberg Stage II, Penman Type IIa border in a patient with SS disease.

FIGURE 2.

Optical coherence tomography-angiography (OCT-A) (Left, top and bottom) and corresponding spectral-domain OCT (SD-OCT) (Right, top and bottom) images of two sickle cell patients. Yellow arrows demonstrate temporal macular flow voids in OCT-A images, and SD-OCT images show a compressed appearance of the inner retina in the temporal macula corresponding to OCT-A flow voids. The underlying outer plexiform layer reflective line is irregularly wavy in the area of the thinned retina.

FIGURE 3.

SD-OCT with purple segmentation lines for superficial plexus (Top left) and deep plexus (Bottom left), OCT-A superficial plexus (Center), and OCT-A deep plexus (Right), of a 12 year-old patient with SC disease. The flow voids corresponding to macular thinning are more prominent in the deep plexus than in the superficial plexus (yellow arrows).

Table 1

Patient Demographics

	Mean Age (Range)	Hemoglobin Type	Treatment Regimen
Sickle Cell (N=16)	14.9 years (10–19)	HbSS: 10 (63%) HbSC: 5 (31%) HbS-Beta thal ⁰ : 1 (6%)	Hydroxyurea: 9 (56%) Chronic transfusions: 1 (6%)
Control (N=5)	17.4 years (12–19)	N/A	N/A

Table 2**Fundus Features and Retinal Imaging Findings**

	Sickle Cell Disease (32 eyes)	Control (10 eyes)
Salmon Patch Hemorrhages	10/32 eyes (31%)	0/10 eyes (0%)
Vessel Tortuosity	10/32 eyes (31%)	0/10 eyes (0%)
Sunburst Lesions	10/32 eyes (31%)	0/10 eyes (0%)
SD-OCT (eyes with temporal macular thinning)	6/30 eyes (20%)	0/10 eyes (0%)
OCT-A (eyes with flow void)	6/30 eyes (20%)	0/10 eyes (0%)
UWFA (Goldberg Stages)	Stage I: 4/24 eyes (17%)	Stage I/II: 0/6 eyes (0%)
	Stage II: 20/24 eyes (83%)	Stage I/II: 0/6 eyes (0%)
UWFA (Penman Grading)	I: 12/23 eyes (52%)	I: 0/6 eyes (0%)
	IIA: 5/23 eyes (22%)	IIA: 0/6 eyes (0%)
	IIB: 6/23 eyes (26%)	IIB: 0/6 eyes (0%)