Ophthalmic Manifestations of Sickle Cell Disease: Update of the Latest Findings

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Structured Abstract:

Purpose of review: Recent developments in the diagnosis and management of sickle cell ocular manifestations are reviewed to enable the clinician to better manage the ophthalmic care of these patients.

Recent findings: Research over the past year has focused upon systemic and ocular clues to the presence of sickle cell retinopathy. In addition, newer imaging modalities, such as spectral domain optical coherence tomography (SD-OCT) and wide-field imaging, have resulted in the detection of subclinical retinopathy related to sickle cell disease. Decreased retinal function (via microperimetry testing) has also been detected in association with areas of retinal thinning. Identification of these ocular and systemic factors that are associated with sickle cell retinopathy will help identify those patients who most need to be screened for sickle cell retinopathy.

Summary: The awareness of subclinical disease as well as the identification of systemic factors associated with higher prevalence of sickle cell retinopathy will aid the clinician in identifying patients are at higher risk of retinopathy.

Keywords: spectral domain OCT, wide-field imaging, microperimetry, risk factors, sickle cell retinopathy

Introduction:

This review will focus upon the latest and most salient publications related to sickle cell disease in the ophthalmic literature. A pubmed search was utilized to find articles of ophthalmic interest over the last 12 months. The vast majority of these recent articles discuss findings of ocular and systemic associations with sickle cell retinopathy as well as newer imaging modalities that aid in the detection of sickle cell retinopathy. Some illustrative case reports are included that relay the positive impact of these modalities in the care of the sickle cell patient. An attempt was made to find articles that show the effect of sickle cell disease on the various structures, anterior and posterior, of the eye.

Sickle cell disease results in localized ischemia and sometimes infarction of local tissues in the area of vascular sickling of erythrocytes. Triggers for this sickling include cold weather, dehydration and hypoxia. These triggers cause vasoconstriction, increased viscosity and hypoxia, which further causes erythrocytes to sickle. The sickle cells in turn result in further impaired Bloodflow, increased viscosity and further hypoxia. This process can result in a variety of ocular abnormalities; all structures can be affected, ranging from orbital tissues to the retina. The following review presents information published in the past year.

Orbital Findings

During vaso-occlusive crises, infarction of the orbital bones can occur. It is well accepted that sickle cell patients are predisposed to orbital wall infarction and to orbital cellulitis. Both processes present with symptoms of orbital compression and inflammation. This may result in acute proptosis and restricted extraocular motility. Magnetic resonance imaging (MRI) is indicated in these patients with empiric antibiotics. Prompt recognition of orbital wall infarction is required so that appropriate management can be promptly administered and serious sequellae averted.[1]

Anterior Segment Findings

The anterior segment of sickle cell patients frequently shows abnormalities in the conjunctiva. In addition, the anterior chamber, iris and lens may also be affected. It is important to carefully examine the anterior segment in these patients in addition to the retina. Recently, several groups have focused upon this region.

Conjunctival Abnormalities

The classic conjunctival abnormality in sickle cell patients is that of “comma-shaped” vessels. However, there are other more subtle findings that also affect these vessels. These abnormalities have been found to be more severe in adults compared with pediatric patients. In a recent study of 8 adult and 14 children with sickle cell disease, Cheung et al noted that although both children and adults showed a blanched appearance consistent with decreased vascularity, the conjunctival vasculopathy severity varied between adults and children.[2] Vessel morphology, tortuosity and flow

were analyzed in their study. Abnormal vessel morphometry was seen in 3 of 8 adult patients (38%), but not seen in any of the pediatric patients. Vessel tortuosity was observed in 7 out of 8 adult patients (88%) compared with only 3 out of 14 pediatric patients (21%). The OR (95% CI) for the difference in prevalence was 25.7 (1.7, 1258) (p=0.006). However, both adults and children exhibited high prevalence rates of sludged flow (71 % children, 88 % adults), abnormal vessel distribution (57 % children, 88 % adult), abnormal A:V ratio (71 % children, 100 % adult), and boxcar flow (70 % children, 75 % adult). Evaluation of the conjunctiva and finding more advanced changes may be indicative of more severe effects of sickle cell disease. The conjunctival vessels may be a useful biomarker of disease and may be helpful in managing patients. The clinician should carefully examine the conjunctiva for these more subtle findings and refer more severe patients for prompt retinal examinations.

Anterior Uveitis

Anterior uveitis can present as a masquerade syndrome and results from sickle cell ischemic disease. A 15 year old boy presented with fine keratic precipitates, iritis, vitritis and subretinal posterior pole infiltrates. A fluorescein angiogram showed areas of retinal ischemia, which led to the suspicion of sickle cell disease. A sickle work-up was positive. Unfortunately, this patient progressed to macular infarction. One should consider the possibility of sickle cell disease when evaluating ischemic ocular disease.[3]

Hyphema and Associated Elevated Intraocular Pressure (IOP)

The presence of a hyphema from trauma in a sickle cell patient warrants serious attention. A hyphema may be associated with elevated intraocular pressure (IOP). Sickle cell patients exhibit poor tolerance of elevated IOP, with optic nerve damage resulting from milder elevations of IOP. Because of this, the classic teaching is to perform an anterior chamber washout procedure if the IOP cannot be lowered from 24 mmHg with mediations after 24 hours. A recent report by Pandey and Sung report on the use of gonioaspiration.[4] In contrast to an anterior chamber washout procedure, this procedure utilizes a Lewicky anterior chamber maintainer cannula at the superior limbus and direct visualization of the anterior chamber angle via a Koeppe goniotomy lens. A 23-gauge single-port cannula is used to aspirate and evacuate the hyphema from the anterior chamber angle until the angle is free of blood. The authors found IOP normalized 2 hours after the procedure in all 3 patients; there were no reported intraoperative complications. Patients with sickle cell disease require more aggressive management of IOP. This procedure presents an effective, alternative method to evacuate the hyphema and normalize IOP.

Prior work on hyphema management in sickle cell disease patients has shown that re-bleed rates can be lowered with the use of epsilon amino-caproic acid (amicar). A recent study analyzed visual acuity results based upon various interventions in patients with hyphema without IOP elevation.[5] This Cochrane group study showed that systemic aminocaproic acid did reduce the rate of recurrent hemorrhage in patients with

hyphema. Rebleeds can lead to complications in sickle cell patients. Hence one should consider use of systemic aminocaproic acid in these patients even though it will take longer for the hyphema to resorb.

Posterior Segment

The classic severity scale of sickle cell retinopathy scale was developed by Goldberg. This system encompasses 5 stages of sickle retinopathy, ranging from non-proliferative to proliferative changes. In stage 1, only arterial occlusions are noted. In stage 2, the classic finding is arterio-venous anastamoses. In stage 3, neovascularization is seen, described as the classic seafan. In stage 4, vitreous hemorrhage is present. In a stage 5, there is a retinal detachment. Associations of stage of retinopathy with systemic findings has recently been evaluated. In addition, new imaging modalities have been applied to eyes with sickle cell retinopathy to further define retinal abnormalities.

Systemic associations with sickle cell retinopathy

A recent study in pediatric sickle cell patients of 10 years of age or older, noted that several systemic factors were associated with sickle cell retinopathy. In a retrospective review of 258 children with sickle cell disease, 54 children with sickle cell retinopathy were identified and compared with age matched controls. Rosenberg and colleagues noted the following factors significantly correlated with retinopathy: pain crisis (odds ratio (OR) = 5; p=0.011), male gender (OR 4.20; p=0.004), splenic sequestration (OR 4.00; p=0.013). The glucose- 6-phosphate dehydrogenase deficiency was more

common in retinopathy but did not reach statistical significance. These eye findings included any type of sickle retinopathy and not necessarily proliferative sickle cell retinopathy. Thus, the authors suggest that patients with the above findings be considered for earlier ophthalmic screening examinations.[6]

Similar work in the adult sickle cell population has been performed. Leveziel and colleagues in France have recently explored the clinical and laboratory factors associated with PSR in patients with hemoglobin SC and SS disease. They noted that proliferative sickle cell retinopathy stages 3 to 5 were associated with older age, pulmonary disease, deafness, or tinnitus and no history of osteomyelitis in patients with SC disease. Older age, male gender and history of acute pyelonephritis were associated with SS patients. These authors suggest that knowledge of these associations may contribute to improved preventive strategies. [7]

Imaging Studies of the posterior segment in sickle cell eyes

The foveal depression sign was described many years ago as a manifestation of sickle cell retinopathy. More recently, our group and others have studied the macular and peripheral retina with SDOCT imaging in order to investigate the presence of subclinical macular thinning which may occur as a result of macular ischemia. Our group has also utilized functional tests of vision such as microperimetry to determine whether thinning is associated with decreased function.

Ocular Coherence Tomography Imaging

Using SD-OCT and microperimetry (MP), asymptomatic sickle cell patients were frequently found to have macular thinning, described as macular splaying. [8] Thus, although patients are asymptomatic, many adult sickle patients do harbor findings of sickle cell retinopathy. These findings precede the clinical detection of a foveal depression sign. Further work is needed to determine whether these patients are also at higher risk of progression to more severe forms of sickle cell retinopathy. The use of SDOCT has identified a group of patients with the earliest levels of sickle cell retinopathy. One could envision a new classification system that includes these subclinical stages of sickle cell retinopathy.

Other groups have also used SD-OCT imaging studies in adults with sickle cell disease. They have shown temporal thinning in addition to areas of macular splaying and focal thinning. The presence of temporal thinning was associated with PSR and was asymptomatic in two of three patients. All patients showed peripheral ischemia and PSR. The authors suggest further studies are needed to correlate the temporal macular thinning with peripheral ischemia. [9]

Wide-field Imaging

Recently, wide-field imaging has been applied to the detection of manifestations of sickle cell disease. [10] In this retrospective case series of 12 eyes in 6 patients, wide-field fundus photography and fluorescein angiography imaging using the Optomap scanning laser ophthalmoscope (Optos, Marlborough, MA) were compared with seven field fundus photography. The Optomap captured findings that were missed in all but one eye by standard seven field photography. The authors suggest that this modality

may help to better identify the peripheral vascular remodeling that occurs in sickle cell eyes. Perhaps in the future, Optomap imaging may be used to screen for sickle cell retinopathy.

Microperimetry

MP-1 evaluation has shown significantly decreased function in the areas of retinal thinning as compared to sickle cell eyes without thinning.[11] This study showed that compared to age matched non-sickle cell control patients, patients with sickle cell disease and macular thinning had decreased function. In contrast, patients without macular thinning did not differ from control eyes. Microperimetry is a sensitive measure of macular function in sickle cell disease patients.

Conclusion:

Recent work has identified ocular, systemic and imaging findings that are correlated with higher rates of sickle cell retinopathy. Dissemination of this information to those caring for sickle cell disease patients is important. Identification and prompt referral of these patients for screening for sickle cell retinopathy may identify earlier stages of the disease and limit visual loss. In addition, newer imaging modalities have increased the ability of clinicians to detect subclinical disease states. It remains to be determined whether these subclinical findings are associated with disease states that will translate to higher rates of visual loss. These modalities, however, currently help to identify patients with the earliest stages of sickle cell retinopathy.

Key points:

- Systemic associations with higher rates of sickle cell retinopathy have been identified in both the adult and pediatric population.
- Spectral domain imaging and microperimetry testing have documented retinal thinning with associated decreased retinal function in asymptomatic patients.
- Temporal retinal thinning and macular splaying are common findings in patients with sickle cell disease.
- Prompt referral of patients with known associations with sickle cell retinopathy is important in limiting visual acuity loss.

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Conflict of Interest:

None

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