Retinal Imaging in Sickle Cell Retinopathy: A Literature Review

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Introduction

SCD is an inherited haemoglobinopathy that carries the risk of significant ocular co-morbidity through the development of sickle cell retinopathy. The ischemia brought on by the sickled red blood cells may trigger sea-fan neovascularization which can then be complicated by vitreous hemorrhage or retinal detachment. In addition, SCM is a newly recognized complication of the disease. Management involves regular screening to prevent such complications from occurring. Disease is classified as non-proliferative or proliferative, with proliferative disease staged using the Goldberg staging system. Current standard of care involves annual funduscopic examination and to offer prophylactic treatment if development of proliferative disease is suspected [1]. There is variation in practice and ancillary forms of imaging (UWFP, FA, UWFA, OCT, OCT-A) may be offered to some patients. Ophthalmic imaging offers insight into the pathophysiology of SCR and may be a tool for predicting the development of proliferative disease.

Objectives

To conduct a literature review that highlights the current imaging findings and practices in sickle cell retinopathy.

Methodology

A PubMed search was conducted using the terms 'sickle cell retinopathy imaging' and results were sorted by most recent. Articles were selected based on their relevancy to the objective of the literature review. Articles published in 2020-21 were included.

The Utility of OCT

Yilmaz et al [2] evaluated RNFL and choroidal thickness in SCD patients vs healthy controls. They found both RNFL and choroidal thickness to be statistically significantly reduced in all quadrants. No correlation was found between the incidence of annual crises and thickness measurements. RNFL and choroidal thickness may be used as a marker for subclinical progression of disease.

Fares et al [3] utilized OCTA to evaluate the microstructural changes at the macula in SCD. They found that areas of reduced vascular flow were present in several eyes with no signs of maculopathy. In addition, the FAZ area was increased, and the border found to be irregular in cases of SCD as compared to age- and race-matched controls. Figure 1 demonstrates the grading of macular ischaemia. The reduction in vascular flow may be a precedent for the development of SCM.

Grego et al [4] evaluated the utility of OCT and OCTA to identify early signs of SCM. Using those imaging modalities, they found signs of SCM on 13 out of the 18 examined eyes that were not present on fundoscopy. In addition, OCTA revealed filling defects in the deep vascular plexus of all eyes, with retinal thinning correlating to the level of flow void. The finding of filling defects affecting the deep plexus more so than the superficial is further supported by Mokrane et al [5]. OCTA has provided us with valuable insight into the vascular changes at the macula as a result of SCD.

Zhou et al [6] used OCTA to compare interocular asymmetry of the FAZ and parafoveal vessels in SCD disease vs controls. They demonstrated significant interocular asymmetry with the size of the FAZ and parafoveal capillary density, with the left eye significantly more affected than the right in SCD eyes vs controls.

The Utility of Ultra-Widefield Imaging

Sevgi et al [7] evaluated the natural history of SCR using angiographic and vascular features derived from UWFA. Two UWFA images taken with a mean interval of 23 months taken and ischemic index, vessel area, vessel length, and geodesic distance were calculated. The study found that the ischemic index increased significantly whereas the mean vessel area and geodesic area decreased significantly. In addition, baseline Goldberg stage and ischemic index were correlated with faster progression. Prospective studies can demonstrate how these biomarkers can be used to predict progression to proliferative disease.

Bunod et al [8] sought to compare the sensitivity and specificity of UWFA vs UWFP in staging SCR. Although UWFA is considered the gold standard for detecting retinal vasculature complications, UWFP is less invasive. They found that at varying levels of expertise, UWFP is 100% sensitive and specific in staging SCR and detecting proliferative disease when using UWFA as a reference. Figure 2 demonstrates the appearance of sea-fan neovascularization on both modalities. This is an important finding as UWFP may replace the more invasive UWFP.

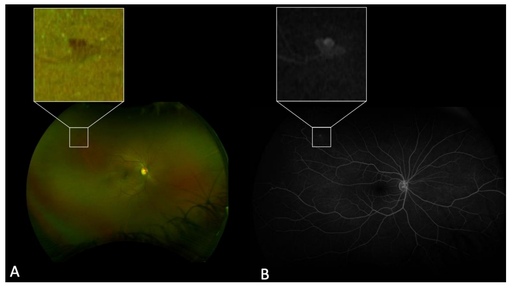


Figure 2. Appearance of sea-fan neovascularization on UWFP (A) and UWFA (B). [8]

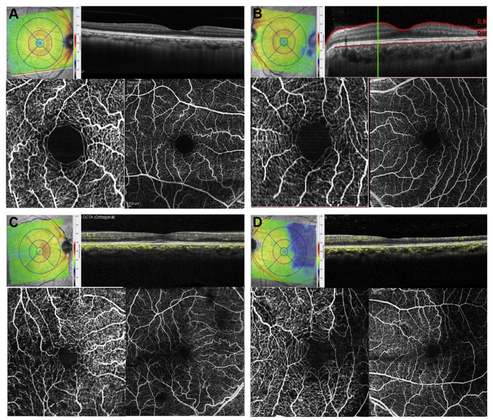


Figure 1. Grading of macular ischemia based on OCTA. No ischemia (A), mild ischemia (B), moderate ischemia (C), and severe ischemia (D). [3]

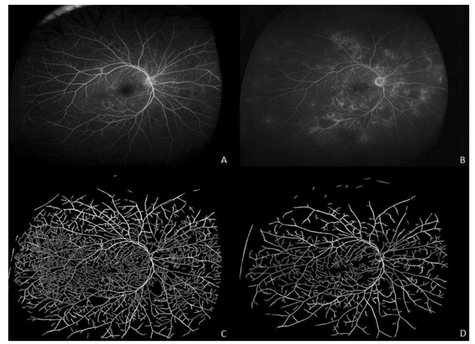


Figure 3. Automatically selected early (A) and late (B) phase UWFA images and their corresponding (C and D, respectively) retinal vessel masks. [9]

The Utility of Artificial Intelligence

Sevgi et al [9] analyzed the use of deep learning algorithm to select UWFA images that show maximum cumulative retinal vessel areas. The aim was to reduce practice variability in selecting UWFA images in the arteriovenous and late phases. The study included eyes with diabetic retinopathy and SCR. The study found the deep learning algorithm to be 85% accurate in selecting the correct image for both phases. Figure 3 demonstrates an example of a selected image, and the retinal vessel mask used by the deep learning algorithm to select the correct image. In SCR, the average timestamp to reach maximal retinal vessel detection after injection of dye was 47 seconds. The use of this deep learning algorithm can increase clinical efficiency by eliminating the need for the clinician to review the entire UWFA sequence and minimize bias in image selection.

Cai et al [10] developed and evaluated the use of a deep learning algorithm in detecting sea-fan neovascularization in UWFP. Images were graded by retina specialists for the presence or absence of sea-fan neovascularization and detection rates were compared against the deep learning algorithm. They found the deep learning algorithm to be 97% accurate with 97.4% sensitivity and 97% specificity. The use of a deep learning algorithm may improve outcomes by improving patient adherence and increasing detection rates in areas where access to a retinal specialist is difficult.

Abbreviations

SCD = Sickle Cell Disease

SCR = Sickle Cell Retinopathy

SCM = Sickle Cell Maculopathy

UWFA = Ultra Wide-Field Fluorescein Angiography

UWFP = Ultra Wide-Field Fundus Photograph

OCT/A = Optical Coherence Tomography / Angiography

FAZ = Foveal Avascular Zone

Summary and Clinical Applications

In summary, a review of the recently published literature has revealed several notable advances and observations in SCR. OCT studies have demonstrated that RNFL and choroidal thinning are central to the pathophysiology of non-proliferative disease. In addition, OCTA has provided us with insight into the filling defects that precede and predispose to the development of SCM. Numerical biomarkers derived from UWFA images show changes that correlate to Goldberg clinical stages. In addition, UWFP are just as sensitive as UWFA but less invasive and time consuming. Deep learning may be utilized to select the most optimal UWFA image, thereby improving efficiency and reducing selection bias of images. Finally, in cases of poor adherence or in resource-poor areas, deep learning may be of use in detecting cases of sea-fan neovascularization and referring patients onwards.

Future Works

- How do pre-proliferative changes on OCT and OCTA predict progression to proliferative disease?
- How do macular filling defects on OCTA correlate to the patient's clinical status?
- How can we use UWFA derived angiographic markers to predict progression to proliferative disease?
- The feasibility of deep learning in screening for sea-fan neovascularization in resource-poor areas.

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