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Research Article

Comparison between Ultra-Widefield and 7-Standard Field Angiography for Proliferative Sickle Cell Retinopathy Screening, Follow-up and Classification

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Abstract

Purpose: To date, there is no gold standard examination for the screening, classification and follow-up of Sickle Cell Retinopathy (SCR). A monocenter, observational, cross-sectional study was conducted to compare ultra-widefield angiography (UWFA) to ETDRS 7-field angiography in patients with or screened for SCR.

Methods: Fifty-nine eyes of 30 patients, who underwent UWFA (Optos©, Optos Inc., Scotland) for screening or follow-up between September 2016 and April 2018, were included. UWFA images were interpreted and then another analysis was performed by superimposing the ETDRS grid (Optos© software) over the UWF images. The stage of SCR was defined for each eye using the Goldberg classification.

Results: After analysis of UWFA images, the diagnosis of SCR was confirmed in 96.6% of eyes: 47.5% with stage 2 and 49.1% with stage 3. Fifty-two eyes (88.1%) showed differences between the UWF and the ETDRS 7-field snapshots.

Of these 52 images, 46.2% and 32.7% were classified as stage 2 and stage 3 SCR on UWFA, respectively but as normal on ETDRS 7-field angiography. Thus, 41 out of the 59 eyes (69.5%) had SCR on UWFA (stage 2 or 3) that was not diagnosed with ETDRS 7-field angiography. Twenty-four eyes (82.7%) classified as stage 3 SCR on UWFA were not diagnosed with the ETDRS images (p <0.0001).

Conclusion: This study clearly showed the superiority of the UWF imaging technique over ETDRS 7-field angiography for proliferative SCR screening and classification.

Key messages: There is currently no gold standard examination for the screening, classification and follow-up of sickle cell retinopathy. This study showed that 82.7% of sickle cell retinopathy classified as stage 3 on ultra-wide field angiography, and thus candidates for laser therapy, were not diagnosed with standard images. Ultra-wide field angiography, when available, should be a key examination for the screening of proliferative sickle cell retinopathy.

Precis: Using ultra wide field imaging for screening and follow-up of Sickle cell retinopathy allows an early detection and treatment of peripheral pre retinal neovascularization.

Keywords: Goldberg classification; Pre retinal neovascularization; Retina; Sickle cell retinopathy; Ultra wide field

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Introduction

Sickle Cell Disease (SCD) is a very common hemoglobinopathy in African, Mediterranean and Middle East populations. Retinopathy is the most common ophthalmologic complication [1] of this disease and can be potentially severe.

Retinopathy progresses insidiously and leads to serious complications (intravitreal hemorrhage, retinal detachment) [2,3]. It results in the occlusion of peripheral capillaries due to a reduction in red blood cell deformability and is more common in the heterozygous form of the disease (SC SCD).

The frequency of proliferative Sickle Cell Retinopathy (SCR) increases with age: in 1981, Hazes [4,5] has reported a prevalence of 14% for the SS form and 37-43% [6] for the SC form, but it increased to 68% in subjects over 45 years.

To date, there are no specific guidelines for the screening and monitoring of SCR. The recent introduction of Ultra-Widefield (UWF) imaging in clinical practice allows visualizing 200 degrees of the retina. This new device contributes to provide more information on the periphery than the repeated regular 30-50° color pictures or angiographs. This wider visualization might have a prognostic and therapeutic impact in SCR [7,8].

The aim of this study was to compare the use of UWF angiography and ETDRS 7-standard field imaging [9] in SCR screening, classification and follow-up.

Patients and Methods

A monocenter, cross-sectional study was conducted in Avicenne Hospital, Bobigny, France and all consecutive sickle cell patients who underwent UWF Angiography (UWFA) (Optos©, Optos Inc., Scotland) for screening or follow-up purposes between September 2016 and April 2018 were included.

We obtained the Federation France Macula Ethical Committee agreement for this study (number: 2017- 1107). Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination of our research.

Each patient underwent UWF photograph and Fluorescein Angiography (FA) after ophthalmological examination (visual acuity, slit lamp and fundus examination). For each patient, collected data were age, sex and genotype of SCD.

The inclusion criterion was any sickle cell patient consulting for SCR screening or follow-up.

Exclusion criteria were the presence of retinal detachment (stage 5 of Goldberg classification [3]) or another associated retinal pathology.

The images were then analyzed independently. UWF images were interpreted collegially by two examiners (FF and FA) and then a second analysis was performed after superimposing the ETDRS grid (Optos© software) over the UWF retinographs and removing the periphery. The examiner of the second set of images had not seen (AGA) the periphery outside the grid. The stage of SCR was defined for each eye using the Goldberg classification.

The primary endpoint of the study was the Goldberg classification stage based on UWF imaging.

The Goldberg classification of proliferative SCR is the most commonly used and includes 5 stages [3]. Stages are defined as follows: presence of peripheral arteriolar occlusions for stage 1, presence of arteriovenous anastomoses for stage 2, presence of peripheral retinal neovascularization (Seafan) for stage 3, presence of intravitreal hemorrhages for stage 4 and presence of retinal detachment for stage 5.

Statistical analysis: Statistical analyzes were performed using PRISM 7 software, and results were compared using the Fisher's exact test. Statistical significance was set at $p < 0.05$ for all analyses.

Results

Fifty-nine eyes of 30 patients were assessed: 21 men and 9 women aged 18-55 years. Mean age was 36.3 years. Among them, 46% had the heterozygous form, 40% had the homozygous form, and 14% had another form (S-beta thalassemic, AS and S-Beta O forms in respectively 2, 1 and 1 patients).

Only one eye (1/60) was excluded from the study because of a prior retinal detachment secondary to stage 5 proliferative SCR.

After analysis of UWF images, the diagnosis of SCR was confirmed in 96.6% of eyes: 47.5% with stage 2 and 49.1% with stage 3. Only 2 eyes (3.4%) did not show any SCR lesion on both UWF and ETDRS 7-field imaging. The interpretation of ETDRS 7-field and UWF images was similar in 7 eyes (11.9%) (Figure 1). The remaining 52 eyes (88.1%) showed differences in stages between UWF and ETDRS 7-field imaging (Table 1).

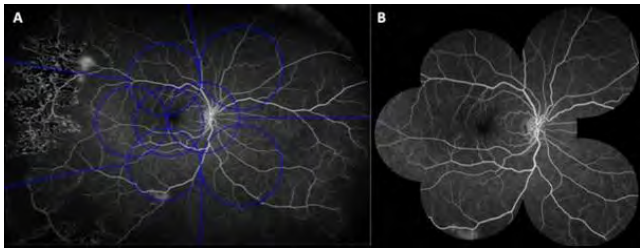

Figure 1: Stage 3 sickle cell retinopathy (SCR) on ultra-widefield angiography (A) and on ETDRS 7-field angiography (B).

Stage based on EDTRS 7-field angiography	Stage based on UWF angiography	Percentage of eyes
Normal	Stage 2	46.2%
Normal	Stage 3	32.7%
Stage 1	Stage 2	7.7%
Stage 1	Stage 3	5.7%
Stage 2	Stage 3	7.7%

Table 1: Differences in staging between Ultra-Widefield (UWF) angiography and ETDRS 7-field angiography for the classification of sickle cell retinopathy, (n = 52 eyes).

Of these 52 images, 46.2% and 32.7% were respectively classified as stage 2 and stage 3 SCR based on UWF images but as normal based on ETDRS 7-field images (Figures 2 & 3, respectively). Also, 7.7% of images were classified as stage 3 based on UWF images, and as stage 2 based on ETDRS 7-field images (Figure 4), and 7.7% of images were classified as stage 2 based on UWF images and as stage 1 based on ETDRS 7-field images. Finally, 5.7% of eyes were classified as stage 3 based on UWF images and as stage 1 based on ETDRS 7-field images (Figure 5).

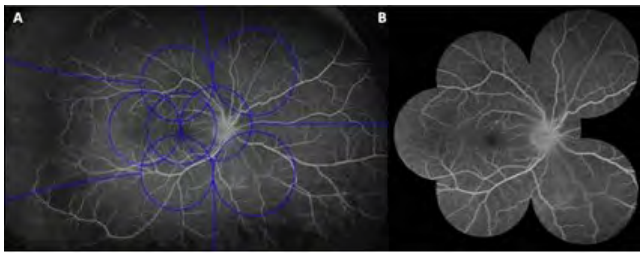

Figure 2: Stage 2 SCR on ultra-widefield angiography (A) and normal angiography on the ETDRS 7-field image (B).

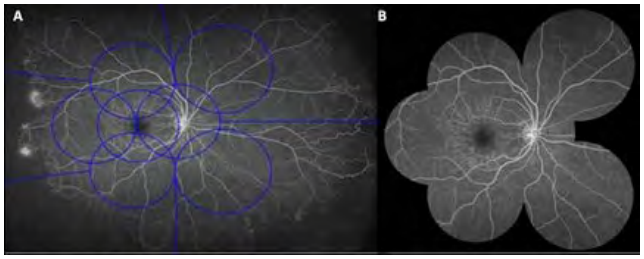

Figure 3: Stage 3 proliferative SCR on ultra-widefield angiography (A) and normal angiography on the ETDRS 7-field image (B).

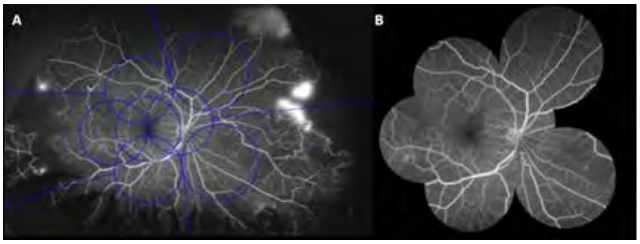

Figure 4: Stage 3 SCR on ultra-widefield angiography (A) and stage 2 SCR on the ETDRS 7-field image (B).

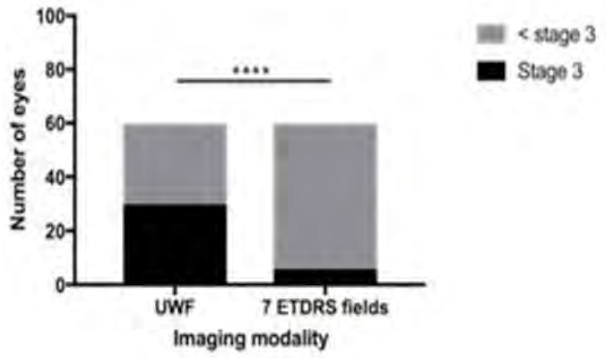

Figure 5: Graph showing the number of patients diagnosed with stage 3 SCR (black), versus minor stages based on UWF versus ETDRS 7-field images.

Thus, 41 out of the 59 eyes (69.5%) had stage 2 or 3 SCR based on UWF images while SCR was undiagnosed based on ETDRS 7-field images.

Finally, of the 29 eyes diagnosed with stage 3 SCR based on UWF, only 5 were also diagnosed based on ETDRS images and therefore 24 cases (82.7%) were missed when ETDRS 7-field images were used ($p < 0.0001$).

Discussion

This study showed the benefit and superiority of UWFA over classical ETDRS 7-field imaging for detecting peripheral abnormalities in SCR.

UWF imaging has already been shown to provide a wider visualization of the retina and to reveal more retinal abnormalities than ETDRS 7-field imaging in diabetic retinopathy. Moreover, it is an easy to use device providing a 200° visualization of the retina with a single snapshot [7,8]. Compared to EDTRS 7-field imaging, Wessel et al., [8] have shown that UWFA allows studying a 3.2-time larger retinal surface. As for diabetes, the high value of UWFA in SCR has already been suggested, because of the frequent involvement of the extreme periphery in the first stages of the disease [10,11].

However, it should be noted that the ETDRS 7-field technique, although being the gold standard for diabetic retinopathy staging, is certainly not the best evaluation and is usually not used in the current clinical practice for SCR screening. Indeed, most teams use angiographs that allow, based on 10 snapshots, a 120-130° view of the retina, and not a 75° visualization as with ETDRS 7-field imaging. In our study, we chose to use ETDRS 7-field imaging as a control examination because of the grid surface reproducibility provided by Optos software. Conversely, classical angiography with 9 peripheric images, although larger, depends on the operator, patient cooperation and pupil dilation. The comparison to ETDRS 7-field imaging thus allowed having a reproducible control set of pictures.

To date, there is no recommendation for SCR follow-up regarding the type of imaging to be used or its frequency, but FA is part of the baseline assessment in any sickle cell patient. Indeed, FA facilitates the detection of early stages of SCR by detecting peripheral ischemic retina.

In 1987, Stephens RF, Magargal LE [12] have aimed to develop a technique for the evaluation of SCR, with 9 images (8 peripheral, 1 of the posterior pole), allowing a visualization of about 130° of the retina. However, they have shown that only a trained photographer could manage to capture 130° with a traditional angiograph.

In 2011, Cho M et al., [10] has shown that UWFA allowed a very good visualization of peripheral changes in retinal vasculature related to SCR.

Similarly, in 2017, Pahl DA et al., [11] has shown the interest of UWFA, coupled with Spectral Domain OCT and OCT-angiography, in SCR screening in an adolescent population.

To the best of our knowledge, our study is the first study to compare the use of UWFA and ETDRS 7-field angiography for the determination of the SCR stage. We demonstrated the superiority of UWFA in the detection of SCR lesions with a more severe Goldberg classification in 88.1% of cases, and 82.7% of cases of preretinal neovascularization (stage 3) were only detectable on UWF imaging. The detection of this stage is crucial because, despite the absence of consensus, stage 3 is usually the threshold for laser treatment [13]. Although traditional angiography performed by a retina specialist for SCR screening and classification provides larger views than classical ETDRS 7-field angiography, the total field surface varies from one photographer to another and from one patient to another, and it can thus not be compared to UWFA. Therefore, UWFA, when available, is a good alternative to classical angiography for SCR screening and monitoring. Moreover, this is a time-saving technique for both patients and caregivers, the patient is less dazzled at the end of the examination, and pupil dilation is not mandatory. In our study, all patients underwent angiography with dilated pupils because the fundus examination was performed at the same time, however, UWF imaging could also be used in non-dilated [14], low-compliant patients.

We also noted that in all patients with SCR, no stage 1 of the Goldberg classification was diagnosed based on UWF images, but only stage 2 or higher. On the other hand, in some of these patients, stage 1 was diagnosed based on ETDRS 7-field images. Thus, we could assume that stage 1 was described from images of smaller field angiographs revealing ischemic areas in the middle periphery, but which actually corresponded to stage ≥2 when the large periphery was visualized. Other larger prospective studies are needed to confirm this hypothesis and also to show that an earlier detection of peripheral abnormalities may change patient prognosis.

Nowadays, sectoral retinal photocoagulation is recommended when stage ≥3 SCR is detected, in order to prevent any complication, although spontaneous lesion regression has been described in about

32-39% of cases [6,15]. However, the determination of a new classification based on UWF imaging could help to precise the follow-up modalities in patients with SCR based on the stage and maybe to understand why neovascularization sometimes evolves to complications or to spontaneous regression.

Finally, we noted in our series that the incidence of SCR (96.4%) was significantly higher than that reported in the literature where the prevalence ranges from 14-68% [4-6]. This could be explained by a selection bias since we selected all consecutive patients with SCD in our department regardless of whether they already had SCR.

However, the study was not designed for assessing disease prevalence.

The main limitation of this study is the control imaging system used (ETDRS 7-field angiography) that is probably inferior to classic angiography performed by a retina specialist. However, UWF images remain larger than images of classical angiography and they are thus difficult to compare due to the variability of the retina surface captured.

Conclusion

This cross-sectional study clearly showed the superiority of the UWF imaging technique over ETDRS 7-field angiography in the screening and classification of proliferative SCR: two-thirds of SCR cases would not have been diagnosed with ETDRS 7-field angiography, and 82.7% of stage 3 SCR would have been missed. Wide-field angiography could therefore become the technique of choice for SCR screening and follow-up.

Conflict of Interest:

F Fajnkuchen and A Giocanti-Auregan are consultants for Novartis, Bayer, Allergan, Optos Plc. No conflict of interest for the other authors.

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Authors Contribution

GD: acquisition of data, drafting the work

FA: acquisition of data and analysis, revising the work critically for important intellectual content

BB: conception and design of the work, revising the work critically for important intellectual content

AGA: conception and design of the work, revising the work critically for important intellectual content

FF: conception and design of the work, revising the work critically for important intellectual content

All: Final approval of the version to be published; AND

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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