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Sickle cell maculopathy: microvascular analysis in OCTA and identification of genetic, systemic and biological risk factors

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THESE

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Antilles et examinée par les Enseignants de ladite Faculté

Le Mardi 30 Juin 2020

En vue d'obtenir le grade de **DOCTEUR EN MEDECINE**

Par

FARES Sélim

**MACULOPATHIE DREPANOCYTAIRE : ANALYSE
MICROVASCULAIRE EN OCTA ET
IDENTIFICATION DES FACTEURS DE RISQUES
GENETIQUES, SYSTEMIQUES ET BIOLOGIQUES**

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ABBREVIATIONS

SD-OCT :	Spectral Domain Optical Coherence Tomography
OCTA :	Optical Coherence Tomography Angiography
SCR :	Sickle Cell Retinopathy
SCM :	Sickle Cell Maculopathy
SCD :	Sickle Cell Disease
TP :	Temps de Prothrombine
PR :	Prothrombine Ratio
PSCR :	Proliferative Sickle Cell Retinopathy
FAZ :	Foveal Avascular Zone (ZAC)
ZAC :	Zone Avasculaire Centrale (FAZ)
HbS :	Hemoglobine S (Sickle)
HbF :	Hemoglobine Fœtale
SE :	Spherical Equivalent
BCVA :	Best Corrected Visual Acuity
LDH :	Lactate Dehydrogenase
GEE :	Generalized Estimating Equation
PMM :	Predictive Mean Matching
CRP :	C-Reactive Protein
ACS :	Acute Chest Syndrome
CVA :	Cerebrovascular accident
VOC :	Vaso-occlusive crisis
G6PD :	Glucose-6-phosphate dehydrogenase
GGT :	gamma-glutanyl transferase

RÉSUMÉ :

Objectifs :

Identifier les facteurs de risques génétiques, systémiques et biologiques de maculopathie dans la drépanocytose. Évaluer les anomalies microvasculaires maculaires dans la drépanocytose grâce à l'optical coherence tomography angiography (OCTA).

Méthodes :

Dans cette étude transversale observationnelle monocentrique, 151 yeux de 78 patients atteints de drépanocytose et 40 yeux de 20 sujets sains de même origine ethnique ont bénéficié des examens spectral domain optical coherence tomography (SD-OCT) et OCTA sur l'angiographe Spectralis (Heidelberg, Allemagne) pour évaluer 3 critères : la prévalence de maculopathie drépanocytaire, l'élargissement de la zone avasculaire centrale (ZAC) et la sévérité de l'ischémie maculaire. Nous avons aussi recueilli les données cliniques, génétiques, biologiques et avons fait une analyse multivariée en régression logistique pour identifier une association entre chaque facteur de risque potentiel et la maculopathie drépanocytaire, l'aire de la ZAC et l'ischémie maculaire.

Résultats :

Notre étude a inclu 43 patients HbSS, 30 HbSC, 4 HbS/ β^+ et 1 HbSLepore. La maculopathie drépanocytaire est survenue chez 66 yeux (44%), en particulier chez les patients HbSS (71%, $p = 0,004$). L'analyse multivariée a identifié le génotype HbSS et l'allongement du temps de prothrombine (TP) comme les facteurs de risques les plus significatifs de maculopathie ($p = 0,01$). La rétinopathie drépanocytaire proliférative a aussi été associée à la maculopathie ($p = 0,02$). L'augmentation du taux de lactate déshydrogénase a été significativement associée à l'élargissement de la ZAC ($p = 0,02$). L'ischémie maculaire a été plus sévère chez les patients avec un taux bas de base en hémoglobine ($p = 0,04$) et un TP allongé ($p = 0,01$). Les aires de non perfusion en OCTA ont été identifiées chez des patients sans amincissement rétinien (36 yeux, 42%) et sont survenues plus fréquemment dans la partie temporale supérieure de la macula. (36%). Des irrégularités de la ZAC et des boucles vasculaires périfovéales ont été retrouvées respectivement chez 70 yeux (46%) et 38 yeux (25%) en OCTA.

Conclusion :

Le génotype HbSS, une coagulation anormale et l'hémolyse sont associés à la maculopathie drépanocytaire. L'OCTA apporte de nouveaux critères pour identifier les facteurs de risque de maculopathie dans la drépanocytose. L'OCTA est utile pour détecter des anomalies microvasculaires avant même l'apparition d'un amincissement maculaire. La définition de la maculopathie drépanocytaire comme un amincissement maculaire à l'OCT n'est plus d'actualité et d'autres critères sont à définir afin d'identifier l'apparition précoce de la maculopathie et évaluer son évolution.

ABSTRACT :

Purpose:

To identify genetic, systemic and biologic risk factors of the occurrence and severity of maculopathy in sickle cell disease (SCD). To evaluate microvascular macular alterations in SCD using optical coherence tomography angiography (OCTA).

Methods:

In this cross-sectional monocentric study, 151 eyes of 78 adult patients with SCD and 40 eyes of 20 race-matched healthy controls underwent spectral domain optical coherence tomography (SD-OCT) and OCTA using Spectralis (Heidelberg Engineering, Heidelberg, Germany) to evaluate 3 criteria : the occurrence of sickle cell maculopathy (SCM), the foveal avascular zone (FAZ) enlargement and the severity of macular ischemia. We also collected clinical, genetic, systemic and biologic data and used multivariate logistic regression analysis to evaluate association between each potential risk factor and SCM, FAZ area and macular ischemia.

Results:

Our study included 43 HbSS, 30 HbSC, 4 HbS/ β^+ and 1 HbSLepore patients. SCM occurred in 66 eyes (44%), especially in HbSS patients (71%, $p = 0,004$). Multivariate analysis identified HbSS genotype and lower prothrombin ratio (PR) as the most predictive risk factors of SCM ($p = 0,01$). Proliferative sickle cell retinopathy was also associated with SCM ($p = 0,02$). FAZ enlargement was statistically associated with higher lactate dehydrogenase (LDH) level ($p = 0,02$). Macular ischemia was significantly more severe in patients with lower hemoglobin level ($p = 0,004$) and lower PR ($p = 0,01$). Areas of no flow were identified with OCTA even in eyes with no macular thinning (36 eyes, 42%) and happened more frequently in the temporal superior subfield (36%). Irregularities of the FAZ borders and perifoveal venular loops were found respectively in 70 eyes (46%) and in 38 eyes (25%) using OCTA.

Conclusion:

HbSS genotype, abnormal coagulation and hemolysis increase the risk of SCM. OCTA provides valuable criteria to identify potential risk factors of SCM. OCTA also proved to be useful tool in order to detect early microvascular changes before the onset of macular thinning. Maculopathy as defined as macular thinning on OCT is now outdated and we need to find other

valuable criteria in order to define when begins sickle cell maculopathy and determine its natural history.

Sickle Cell Maculopathy: microstructural analysis using OCTA and identification of genetic, systemic and biologic risk factors

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INTRODUCTION :

Sickle cell disease (SCD) is the most common genetic disease in the world affecting around 120 millions of people and about 6000 to 7000 patients in France.^{1,2} SCD is caused by a mutation of the β -globin gene resulting in the production of an abnormal hemoglobin called hemoglobin S (HbS). Hemoglobin S polymerizes under hypoxic conditions, which causes a mechanical distortion of red blood cells into a sickle-like shape. These sickled red blood cells are fragile and rigid, resulting in chronic hemolytic anemia and vaso-occlusive like complications in multiple organs, respectively, in particular in the eyes.³ SCD is a generic term encompassing different syndromes according to genotype: homozygotes HbSS or compound heterozygotes (HbSvariant).

Sickle cell retinopathy (SCR) has been well described, proliferative sickle cell retinopathy (PSR) being a major sight-threatening complication.⁴ Since the development of Spectral Domain Optical Coherence Tomography (SD-OCT), macular vascular abnormalities in SCD are now commonly detected.⁵ Sickle cell maculopathy (SCM) is defined as patchy areas of severe retinal thinning in the temporal macula. The exact etiology of macular thinning remains unclear but it may be related to the temporal macula ending along the horizontal raphe making it a watershed zone between the vascular arcades of the retinal circulation and thus more susceptible to vascular occlusions.⁶ By allowing depth-resolved visualization of macular vascular network with high resolution, Optical Coherence Tomography Angiography (OCTA) recently detected much more macular vascular changes than previously and provided additional features, including enlargement and irregularities of the foveal avascular zone (FAZ), hairpin venular loops and areas of flow loss responsible for irreversible macular thinning.^{7,8}

Previous studies showed that HbSC genotype, male gender, lower fetal hemoglobin (HbF), higher hemoglobin levels and higher blood viscosity (particularly in HbSS genotype) are associated with severe PSR.⁹⁻¹¹ But the clinical staging for SCR does not correspond to macular involvement. Little is known about the impact of genetic, biologic and systemic factors on the occurrence and severity of SCM. The question is to know if the systemic severity of SCD can be correlated in any way to ocular damage and to findings reported on OCTA. Identifying risk factors could lead to reliable prediction models for SCM management and to

minimize the onset of irreversible macular scotoma, decreased retinal sensitivity or vision loss described in eyes with severe macular thinning.^{12,13}

The primary purpose of this study was to identify the systemic, biologic and genetic risk factors of SCM on OCT. The secondary purpose was to analyze macular microvascular network using OCTA and test if FAZ area and macular ischemia could be useful to identify more specific risk factors of SCM.

MATERIALS AND METHODS :

Patients:

This study received the ethical approval of the Regional Ethics Committee (CPP Sud-Ouest Outre-Mer III, Bordeaux, France) and adhered to the principles set by the Declaration of Helsinki. Written informed consent was obtained from each participant. This cross-sectional monocentric study concerned 117 patients with confirmed SCD diagnosis using standard methods and undergoing regular ophthalmological evaluation at the Ophthalmology Department of the University Hospital of Guadeloupe, French West Indies, between January 1st, 2019 and January 1st, 2020. Exclusion criteria were age under 18, history of other confounding retinal vascular disease such as hypertension, diabetes or retinal vein occlusion, prior retinal surgery, spherical equivalent (SE) $> \pm 1D$, retinal involvement such as vitreomacular traction syndrome, epiretinal membrane or druses, poor quality images or ocular media opacities preventing detailed imaging. Sixty-nine eyes of 37 patients met these criteria and were excluded, so that 151 eyes of 78 patients were analyzed. An ethnic-matched control group of 20 healthy African Caribbean subjects was also recruited and underwent the same ocular procedures.

Multimodal imaging:

Ophthalmic examination included best corrected visual acuity (BCVA) measured with Snellen chart, slit-lamp evaluation, dilated fundus examination. SCR was graded according to the Goldberg classification including peripheral arteriolar occlusions (stage I), peripheral arteriovenous anastomoses (stage II), preretinal neovascularization (stage III), vitreous hemorrhage (stage IV) and retinal detachment (stage V).¹⁴ Eyes with no retinopathy were graded as Goldberg stage 0. Patients with previously performed focal laser photocoagulation for peripheral neovascularization were classified as stage III. Analyses were performed using three categories of retinopathy: no retinopathy (stage 0), non-proliferative retinopathy (stage I and II) and proliferative retinopathy (stage III, IV and V).

All patients and control group underwent a macular SD-OCT and OCTA using the Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany). For each eye, the standard scanning protocol included an automated « posterior pole » 30x25° cuboid volume scan of 61 high resolution OCT scans and 10° and 20° OCTA scans centered on the fovea.

Multiple scans were acquired as needed to secure adequate quality criteria and the best quality scans were selected by the lead grader for analysis. Images were anonymized and analyzed by two independent retina fellowship trained graders in a blinded fashion. In case of disagreement, scans were reviewed and arbitrary graded together. Sick cell maculopathy was identified as patchy retinal thinning areas on OCT (i.e., blue areas of markedly decreased thickness on retinal thickness color-coded map). The first step involved manual delineation of the full thickness retina FAZ border taken from 10° OCTA scans using the « area » function of the software (*Figure 1*). Scans were then qualitatively graded by the investigators for macular ischemia from no (0) to severe (3) macular ischemia (including extension of flow loss areas, vessel density, enlargement of the FAZ, presence of perifoveal venular loops and focal disruption of the perifoveal anastomotic capillary arcade). *Figure 2* illustrates our macular ischemia graduation.

Figure 1 : Manual delineation of FAZ area

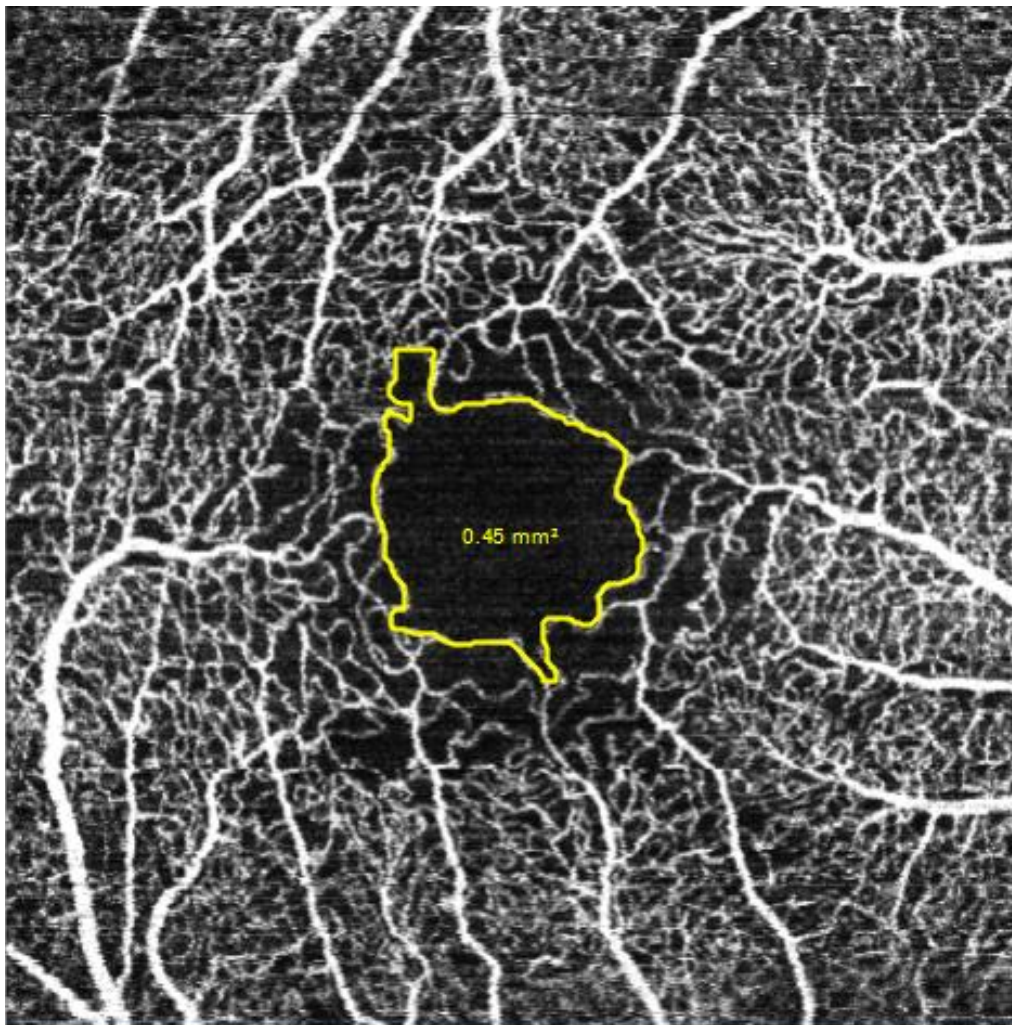
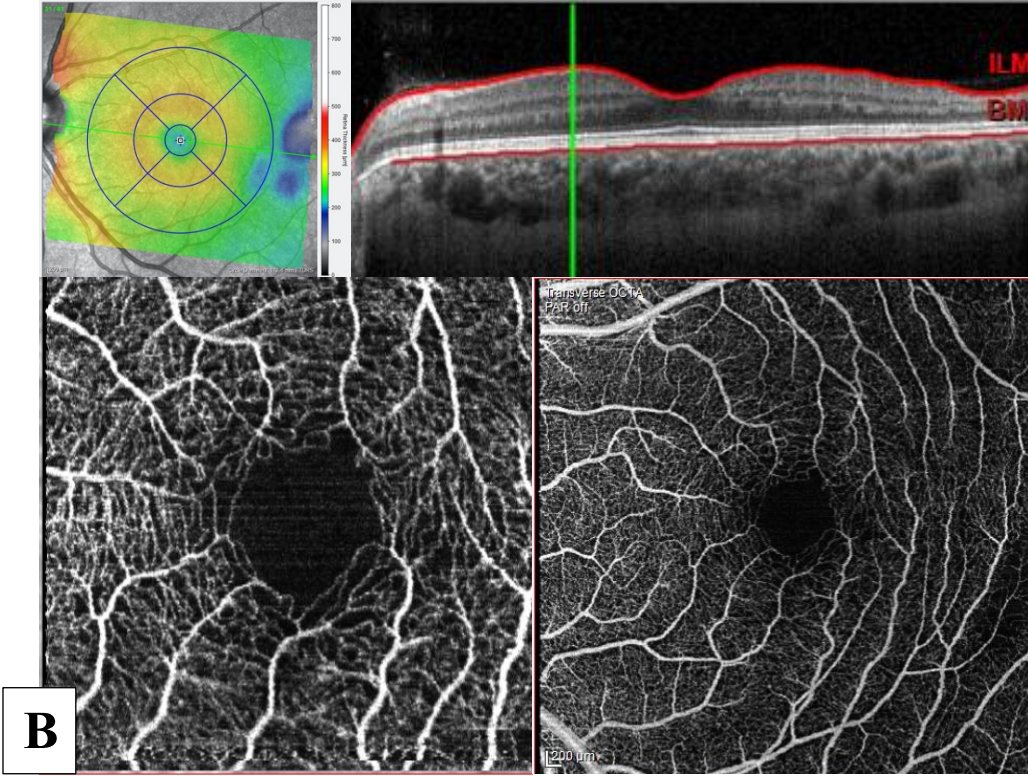
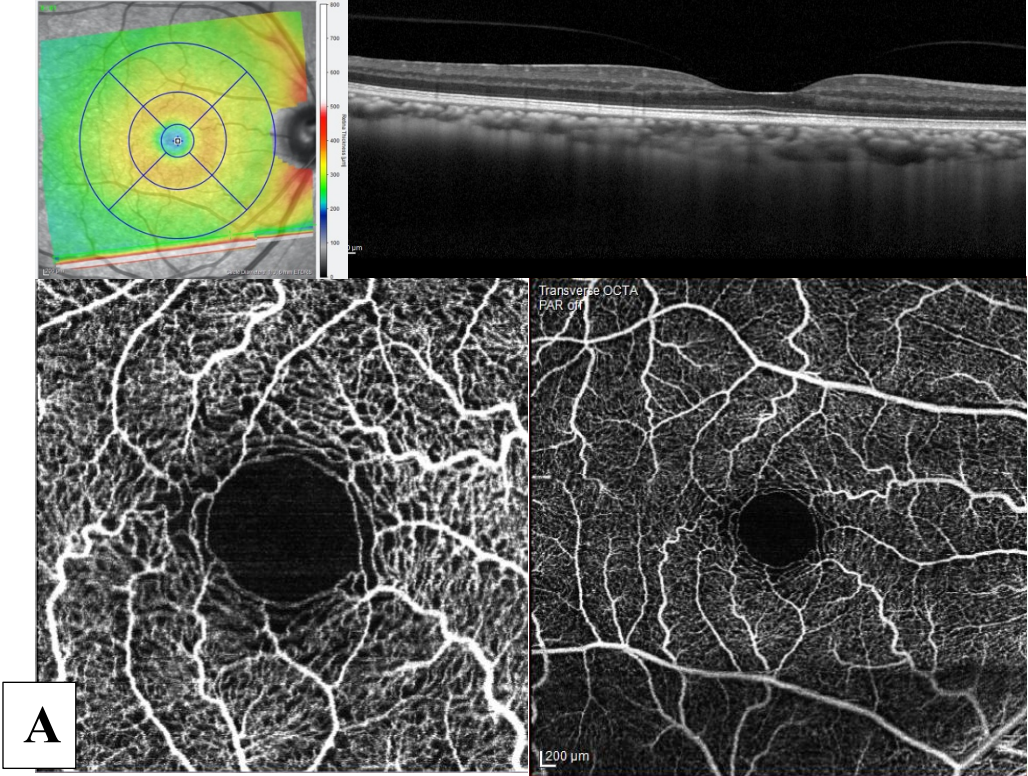
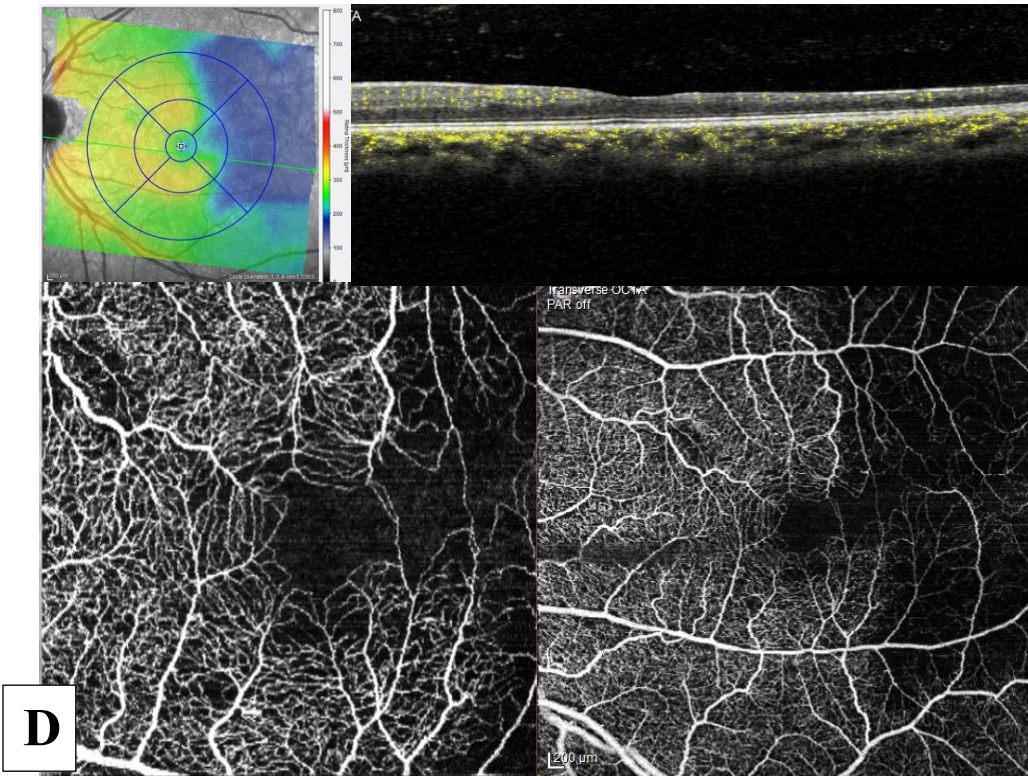
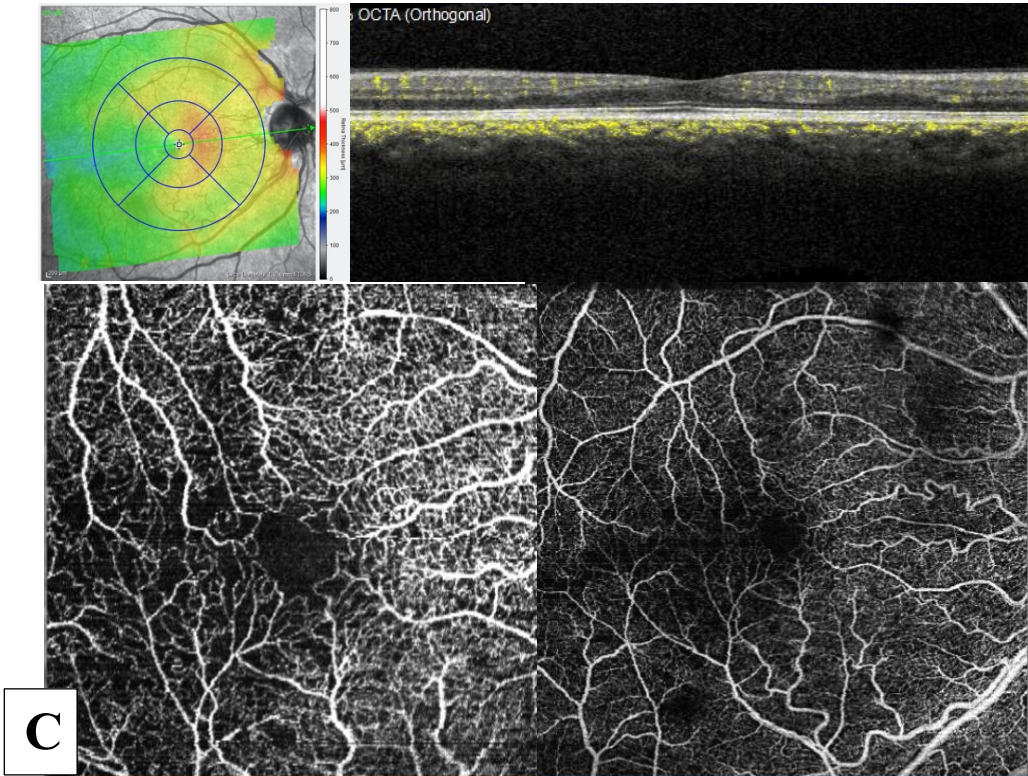


Figure 2 : Subjective graduation of macular ischemia based on SD-OCT and OCTA using the following criteria: extension of blue area in retinal thickness map, the areas of flow loss in OCTA 10° and 20°, the irregularity and enlargement of the FAZ. a) no ischemia, b) mild ischemia, c) moderate ischemia, d) severe ischemia.





Clinical data collection:

Clinical data were retrospectively collected from patient's charts at the last on-site consultation to the Sickle cell disease center of Guadeloupe and included : SCD type (genotype, α thalassemia status), medical and surgery history (other systemic condition, spleen status, cholecystectomy), current treatment (hydroxyurea, chelation therapy, chronic transfusion, anticoagulants) and history of SCD systemic complications (acute chest syndrome, cerebrovascular accident, severe vaso-occlusive crisis frequency, osteonecrosis). Frequency of severe vaso-occlusive crises was defined using Duan et al's method, i.e. as rare if once a year or less, occasional if twice a year and frequent if three times a year or more, averaged over the two years prior to the index ocular examination.¹⁰ Severe vaso-occlusive crises were defined as requiring acute Emergency Department visit or inpatient admission.

We also collected laboratory results including fetal hemoglobin (HbF) level, baseline hemoglobin level, hematocrit, C-reactive protein (CRP), prothrombin ratio (PR), reticulocytes, leucocytes, neutrophils and platelets count, lactate dehydrogenase (LDH), total bilirubin, serum ferritin and fibrinogen levels and G6PD deficiency.

Statistical analysis:

To analyze demographic, clinical and ocular characteristics of the population and to compare with the occurrence of maculopathy and FAZ enlargement, a Mann-Whitney test was used. P-value < 0.05 was considered as significant. Three ocular criteria were included in the analysis: the occurrence of maculopathy, the FAZ enlargement and the severity of the macular ischemia. Because simple comparison of the distribution of systemic and biologic factors between patients can be misleading as certain factors are interdependent or age related, we used multiple logistic regression analysis, adjusted by genders, genotypes and factors showing a p-value < 0.1 in univariate analysis to identify risk factors independently associated with sickle cell maculopathy, FAZ enlargement and macular ischemia in an ordinal Generalized Estimating Equations (GEE) model.

Complete data were not available for all patients, so we used a simple imputation with a predictive mean matching (PMM) method for the missing data. Matched controls were used to compare FAZ measures with SCD patients using a Mann-Whitney test. Statistical analyses were performed using R statistical software.

RESULTS:

Demographic results:

Table 1 summarizes patients' demographical and clinical characteristics. All participants were of African origin. 151 eyes of 78 patients (25 men and 53 women) with a mean age of 37 years (range 18 – 61 years old) were enrolled in this study. Five eyes were excluded due to unilateral high myopia (1 eye), phthisis bulbi (1 eye), poor acquisition due to no fixation (2 eyes) and a large foveal vascular pigmentary epithelium drusen (1 eye). Several sickle cell syndromes were analyzed including homozygotes HbSS (43 patients, 55%) and compound heterozygotes HbSvariant (35 patients, 45%) including HbSC (30 patients), HbS/ β^+ (4 patients) and HbSLepore (1 patient). Visual acuity ranged from 20/25 to 20/20 for all patients. The most frequently systemic events in our population were painful vaso occlusive crisis (49%), acute chest syndrome (42%) and osteonecrosis (31%). There was no statistical difference in age, gender, functional α -globin gene number, vaso-occlusive crisis, osteonecrosis, anticoagulant medication and chronic transfusion between HbSS and HbSvariant groups. However, HbSS patients used more hydroxyurea ($p < 0.001$), exhibited more ulcers ($p = 0.019$), more acute chest syndrome ($p < 0.01$) and more cerebrovascular accidents ($p < 0.01$). HbSS patients are more hemolytic: lower hemoglobin and hematocrit ($p < 0.001$), higher LDH and total bilirubin levels ($p < 0.001$). Finally, HbSS patients seemed to exhibit a pro-inflammatory state: higher leucocytes and neutrophils levels ($p < 0.001$ et <0.02 , respectively) and a trend through higher level of CRP ($p=0.087$).

Table 1: Baseline demographic characteristics of the sickle cell disease population of this study.

	Total	Hb SS	Hb Svariant	P values
Patients, n (eyes)	78 (151)	43 (85)	35 (66)	-
Age in years, mean +- SD (range)	37 ± 11 (18-61)	35 ± 10	38 ± 12	0.21
Female, n (%)	53 (68)	29 (6)	24 (69)	0.92
SYSTEMIC CHARACTERISTICS				
Hydroxyurea use, n (%)	27 (34.6)	27 (63)	0 (0)	<0.001
Anticoagulation, n (%)	12 (15.4)	9 (21)	3 (8,6)	0.13
Acetylsalicylic acid, n (%)	7 (9)	5 (12)	2 (5.7)	-
Apixaban, n (%)	1 (1.3)	1 (2.3)	0 (0)	-
Clopidogrel, n (%)	1 (1.3)	1 (2.3)	0 (0)	-
Fluindione, n (%)	1 (1.3)	1 (2.3)	0 (0)	-
Rivaroxaban, n (%)	2 (2.6)	1 (2.3)	1 (2.9)	-
Regular phlebotomy, n (%)	24 (31)	7 (16)	17 (49)	<0.01
Chronic transfusion, n (%)	6 (7.7)	5 (12)	1 (3)	0.22
Osteonecrosis, n (%)	24 (30.8)	16 (37)	8 (23)	0.17
Ulcers, n (%)	11 (14)	10 (23)	1 (3)	0.019
ACS* / 2 years, n (%)	12 (15.4)	10 (23.3)	2 (5.7)	0.033
ACS* history, n (%)	33 (42.3)	26 (60.5)	7 (20.0)	<0.001
VOC* frequency/2 years, n (%)	38 (49)	25 (58)	13 (37)	0.065
VOC* frequency/2 years, n (%)				
Rare, n (%)	62 (79)	33 (77)	29 (83)	0.51
Occasional, n (%)	6 (7.7)	4 (9.3)	2 (5.7)	0.69
Frequent, n (%)	10 (13)	6 (14)	4 (11)	1
CVA*, n (%)	10 (13)	10 (23)	0 (0)	<0.01
Cholecystectomy, n (%)	34 (44)	26 (60)	8 (23)	<0.001
BIOLOGICAL CRITERIA				
Baseline hemoglobin (g/dL), mean ± SD (range)	9.2 ± 1.7 (6-13)	8.1 ± 1.2	10.7 ± 1.0	<0.001
Baseline HbF* (%), mean ± SD (range)	6.4 ± 7.0 (0-27.7)	9.0 ± 7.6	2.7 ± 3.9	<0.001
Hematocrit (%), mean ± SD (range)	28 ± 5 (16-41)	24 ± 4	32 ± 3	<0.001
Platelets (G/L), mean ± SD (range)	336 ± 155 (60-786)	388 ± 155	273 ± 130	<0.001
Reticulocytes (G/L), mean ± SD (range)	198 ± 117 (7-582)	258 ± 120	124 ± 54	<0.001
Leucocytes (G/L), mean ± SD (range)	8.1 ± 2.9 (3.9-16.2)	9.1 ± 3.0	6.8 ± 2.0	<0.001
Neutrophils (G/L), mean ± SD (range)	4.4 ± 2.1 (1.0-12.0)	4.8 ± 2.5	3.8 ± 1.4	<0.02
CRP* (mg/L), mean ± SD (range)	5.27 ± 6.05 (0-32)	6.28 ± 6.98	3.97 ± 4.35	0.087
PR* (%), mean ± SD (range)	83 ± 14 (23-100)	78 ± 14	88 ± 13	<0.01
LDH* (U/L), mean ± SD (range)	395 ± 178 (138-928)	507 ± 162	257 ± 60	<0.001
Total bilirubin (µmol/L), mean ± SD (range)	36.4 ± 29.2 (6-184)	49.5 ± 32.9	20.6 ± 11.1	<0.001
GGT* (U/L), mean ± SD (range)	59 +- 52 (10-248)	74 ± 60	40 ± 33	<0.01

Serum ferritin (ng/ml), mean ± SD (range)	222 +- 354 (7-2282)	335 ± 452	102 ± 132	<0.01
Fibrinogen (g/L), mean ± SD (range)	3.2 +- 0.8 (1.6-6.5)	3.21 ± 0.8	3.13 ± 0.8	0.67
G6PD* deficiency, n (%)	4 (5.3)	3 (7,.3)	1 (2.9)	0.62
α globin gene number, n (%)	-	-	-	0.47
2	2 (2.6)	2 (5.3)	0 (0)	-
3	20 (25.6)	12 (32)	8 (26)	-
4	47 (60.3)	24 (63)	23 (74)	-

* ACS = acute chest syndrome; CVA = cerebrovascular accident; VOC = vaso-occlusive crisis; PR = Prothrombin ratio; HbF = hemoglobin F; CRP = C-reactive protein; LDH = lactate dehydrogenase; G6PD = Glucose-6-phosphate dehydrogenase; GGT = gamma-glutamyl transferase

Sickle cell maculopathy:

SCM, defined as patchy areas of macular thinning on SD-OCT, was present in 66 eyes (43.7%), especially in HbSS patients (71.2%, p=0.004). Univariate analysis (*Table 2*) showed that patients with SCM had lower hemoglobin (p = 0.001), lower hematocrit (p = 0.01), lower PR (p = 0.038) and higher LDH levels (p = 0.007) than those without. Multivariate regression analysis revealed that HbSS genotype and lower prothrombin ratio (PR) were the most predictive risk factors of SCM (p = 0.01). In addition, we observed higher occurrence of SCM in eyes with proliferative sickle cell retinopathy (p = 0.04) with an odd ratio of 3.86. Chronic transfusion also tended to be associated with the occurrence of SCM even without reaching statistical significance (p = 0.073). As expected, maculopathy was associated with FAZ enlargement (p = 0.021) and more severe macular ischemia (p < 0.001). A level of HbF > 15% based on the prior studies about sickle cell retinopathy did not show any association with maculopathy.¹⁵

Table 2: Univariate analysis for occurrence of sickle cell maculopathy

	Maculopathy	No maculopathy	P value
Number of eyes (%)	66 (43.7)	85 (56.3)	-
Female, n (%)	42 (63.6)	60 (70.6)	0.45
Age (years), mean \pm SD	36.1 \pm 9.5	36.8 \pm 11.4	0.63
SYSTEMIC CHARACTERISTICS			
HbSS genotype	47 (71.2)	38 (44.7)	0.004
Hydroxyurea use, n (%)	28 (42.4)	26 (30.6)	0.19
Anticoagulation, n (%)	12 (18.2)	11 (12.9)	0.45
Regular phlebotomy, n (%)	15 (22.7)	30 (35.3)	0.15
Chronic transfusion, n (%)	8 (12.1)	3 (3.5)	0.073
ACS* history, eyes (%)	33 (50)	31 (36.5)	0.17
ACS*/2 years, eyes (%)	11 (16.7)	13 (15.3)	0.81
VOC* frequency/2 years, eyes (%)	38 (58)	36 (42)	0.063
VOC* frequency/2 years, eyes (%)			
Rare	51 (77)	68 (80)	0.68
Occasional	5 (8.2)	7 (7.6)	0.88
Frequent	10 (15)	10 (12)	0.54
Osteonecrosis	20 (30.3)	26 (30.6)	0.95
OCULAR CHARACTERISTICS			
FAZ* area, mean in μm^2	0.56 \pm 0.18	0.49 \pm 0.13	0.021
Macular ischemia index, eyes (%)			
0	0 (0)	49 (58)	<0.001
1	18 (27)	34 (40)	-
2	33 (50)	2 (2)	-
3	15 (23)	0	-
Sickle cell retinopathy, eyes (%)			
Proliferative	20 (30.3)	14 (16.5)	0.04
Non-proliferative	46 (69.7)	71 (83.5)	-
BIOLOGICAL CRITERIA			
Baseline hemoglobin (g/dL), mean \pm SD	8.8 \pm 1.6	9.6 \pm 1.7	0.001
HbF* > 15%, n (%)	10 (15.2)	13 (15.3)	0.97
Hematocrit (%), mean \pm SD	26.1 \pm 5.3	28.9 \pm 5.0	0.01
Platelets (G/L), mean \pm SD	373.0 \pm 153.8	305.7 \pm 147.9	0.02
Leucocytes (G/L), mean \pm SD	8.3 \pm 2.9	7.9 \pm 2.9	0.40
Neutrophils (G/L), mean \pm SD	4.3 \pm 2.3	4.4 \pm 2.1	0.97
CRP* (mg/L), mean \pm SD	5.4 \pm 4.9	6.2 \pm 6.9	0.45
PR* (%), mean \pm SD	79.2 \pm 15.0	84.4 \pm 12.9	0.038
Fibrinogen (g/L), mean \pm SD	3.2 \pm 0.7	3.2 \pm 0.9	0.78
LDH* (U/L), mean \pm SD	449.7 \pm 183.6	355.7 \pm 161.0	0.007
Total bilirubin ($\mu\text{mol/L}$), mean \pm SD	42.3 \pm 30.6	32.9 \pm 28.2	0.12
GGT* (U/L), mean \pm SD	57 \pm 52.6	59.6 \pm 51.8	0.79
Serum Ferritin (ng/ml), mean \pm SD	249.2 \pm 415.2	204.6 \pm 270.6	0.332
α globin gene number, n (%)	-	-	0.85
2	3 (4.5)	2 (2.4)	-
3	19 (28.8)	26 (30.6)	-
4	44 (66.7)	57 (67.1)	-

* ACS = acute chest syndrome; VOC = vaso-occlusive crisis; HbF = hemoglobin F; PR = prothrombin ratio; FAZ = foveal avascular zone; CRP = C-reactive protein; LDH = lactate dehydrogenase; GGT = gamma-glutamyl transferase

Faz area:

On OCTA, FAZ was measured in 142 eyes (94%) of SCD patients and in all healthy control eyes. In 9 eyes, it was not detectable by the software related to extensive macular ischemia (*Figure 3*) due to central arterial occlusion (4 eyes) and extensive perifoveal capillary remodeling with a poorly defined FAZ (5 eyes). For these 9 eyes, the quantitative value of their surely enlarged FAZ could be misleading in the analysis. Accordingly, we used a censored statistical model that assigned 1.0 to larger FAZ area than 1.0. Univariate analysis (*Table 3*) showed that FAZ enlargement was associated with HbSS genotype ($p = 0.04$), hydroxyurea use ($p = 0.04$), anticoagulant medication ($p = 0.05$), acute chest syndrome history ($p = 0.02$), occasional vaso-occlusive crises ($p = 0.01$), lower hematocrit and hemoglobin levels ($p = 0.01$) and higher LDH level ($p = 0.02$). Unexpectedly, we also found that male SCD patients had a smaller FAZ size ($p = 0.01$). In multivariate analysis only high LDH level was independently associated with FAZ enlargement (a rise of $0.03 \mu\text{m}^2$ for every 100 units of LDH, $p = 0.02$). Interestingly, positive history for acute chest syndrome was marginally associated with FAZ enlargement ($p = 0.07$). Even if not statistically significant, chronic transfusion and frequent vaso occlusive crisis also tended to enlarge the FAZ size ($p = 0.06$ and $p = 0.08$, respectively). Comparison between SCD patients with or without SCM and age, ethnic and sex – matched controls revealed that the FAZ area was larger in our patients than controls (respectively 0.52 ± 0.19 vs 0.38 ± 0.17 , $p < 0.01$).

Figure 3 : Exemple of difficulty in FAZ delineation on OCTA scan from a patient with severe (3) macular ischemia.

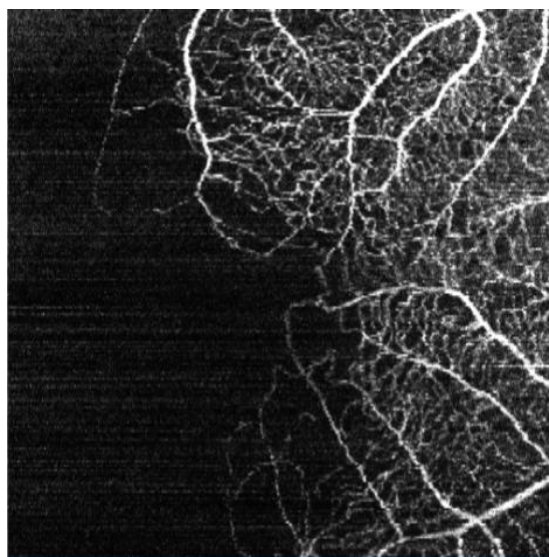


Table 3: Univariate analysis of FAZ area

	FAZ area			
	Estimator	Std error	t	P value
SYSTEMIC CHARACTERISTICS				
Male	-0.09	0.03	7.30	0.01
HbSS Genotype	0.07	0.03	2.07	0.04
Hydroxyurea use	0.07	0.03	2.05	0.04
Anticoagulation	0.09	0.04	1.97	0.05
Chronic transfusion	0.12	0.06	1.91	0.06
Regular phlebotomy	-0.12	0.03	-3.53	<0.01
Osteonecrosis	0.04	0.04	1.28	0.20
CVA*	0.00	0.06	0.00	0.98
Ulcers	0.05	0.06	0.69	0.41
ACS* history	0.08	0.03	5.83	0.02
VOC* frequency /2 years				
Rare	-0.01	0.03	0.10	0.75
Occasional	0.09	0.03	6.75	0.01
Frequent	0.06	0.04	3.14	0.08
OCULAR CHARACTERISTICS				
Macular ischemia index				
1	0.00122	0.01761	0.00	0.94
2	0.02777	0.02651	1.10	0.29
3	0.03558	0.03679	0.94	0.33
Proliferative retinopathy	-0.03	0.02	1.24	0.27
BIOLOGICAL CRITERIA				
Baseline Hemoglobin	-0.03	0.01	- 2.73	0.01
HbF* < 15%	-0.03	0.03	0.99	0.32
Hematocrit	-0.01	0.00	6.84	0.01
Platelets	0.00	0.00	2.03	0.15
Leucocytes	0.01	0.01	0.80	0.37
Neutrophils	0.00	0.01	0.27	0.60
PR*	-0.0004	0.00	0.24	0.62
Fibrinogen	0.02	0.02	0.87	0.35
LDH*	0.0003	0.00	5.85	0.02
GGT*	0.00	0.00	2.11	0.15
α globin gene number	-0.01	0.03	- 0.21	0.83

* ACS = acute chest syndrome; CVA = cerebrovascular accident; VOC = vaso-occlusive crisis; HbF = hemoglobin F; PR = prothrombin ratio; LDH = lactate dehydrogenase; GGT = gamma-glutamyl transferase

Macular ischemia:

Macular ischemia was subjectively identified using SD-OCT and OCTA with quantitative and qualitative criteria: irregularity of the FAZ, the extension of no flow areas and the general vascular density. We graded ischemia from no (0) to severe (3) for all 151 eyes of the study. The size of the grade 3 (severe) group of macular ischemia was not large enough and was regrouped with the grade 2 (moderate) group for the analysis. Thus, we had 49 eyes (32.5%) with no ischemia, 52 with mild ischemia (34.4%) and 50 with moderate or severe ischemia (33.1%). Areas of no flow were more frequent in the temporal superior (36%) subfield than the temporal inferior (27%), nasal superior (9%) and nasal inferior (5%) subfields. Seventy eyes had irregularities of the FAZ borders (46%). Thirty-eight eyes had perifoveal venular loops (25%). Abnormal macular flow loss was visible even in SCD eyes with no macular thinning on OCT (36 eyes, 42%). Univariate analysis (*Table 4*) revealed that 80% of the eyes with moderate and severe macular ischemia are from HbSS patients ($p < 0.001$). We also showed a significant association between the severity of macular ischemia and the severity of anemia ($p < 0.001$), lower hematocrit and PR ($p = 0.01$ and < 0.001 , respectively), higher platelet level ($p = 0.01$) and increased LDH ($p = 0.003$). In multivariate analysis, the severity of anemia ($p = 0.004$) and lower PR ($p = 0.01$) remained independently associated with macular ischemia severity.

Table 4: Univariate analysis of risk factors in macular ischemia

	No ischemia	Mild ischemia	Moderate or severe ischemia	P value
Number of eyes (%)	49 (32.5)	52 (34.4)	50 (33.1)	-
Female, eyes (%)	33 (67.3)	41 (78.8)	28 (56.0)	0.40
HbSS genotype, eyes (%)	17 (34.7)	28 (53.9)	40 (80.0)	<0.001
Age, mean \pm SD	34.2 \pm 11.2	41.0 \pm 10.2	34.0 \pm 9.0	0.912
SYSTEMIC CHARACTERISTICS				
Hydroxyurea use, eyes (%)	11 (22.4)	21 (40.4)	22 (44.0)	0.055
Regular phlebotomy, eyes (%)	17 (34.7)	18 (34.6)	10 (20.0)	0.16
Chronic transfusion, eyes (%)	2 (4.1)	1 (1.9)	8 (16.0)	0.09
Anticoagulant, eyes (%)	5 (10.2)	7 (13.5)	11 (22.0)	0.25
Osteonecrosis, eyes (%)	11 (22.4)	22 (42.3)	13 (26.0)	0.66
ACS* history, eyes (%)	17 (34.7)	21 (40.4)	26 (52.0)	0.16
OCULAR CHARACTERISTICS				
Occurrence of maculopathy, eyes				
No maculopathy	49 (100)	34 (65)	2 (4)	< 0.001
Maculopathy	0 (0)	18 (35)	48 (96)	-
Proliferative retinopathy, eyes (%)	24 (49.0)	28 (53.9)	37 (74.0)	0.53
Photocoagulation, eyes (%)	12 (24.5)	19 (36.5)	21 (42.0)	0.123
BIOLOGICAL CRITERIA				
Baseline hemoglobin (g/dL), mean \pm SD	10.2 \pm 1.7	9.0 \pm 1.4	8.6 \pm 1.6	<0.001
HbF* > 15%, eyes (%)	5 (10.2)	10 (19.2)	8 (16.0)	0.42
Hematocrit, mean \pm SD	30.2 \pm 5.1	27.3 \pm 4.2	25.6 \pm 5.6	0.01
Platelets (G/L), mean \pm SD	298.8 \pm 140.1	311.4 \pm 141.4	395.3 \pm 163.4	0.01
Leucocytes (G/L), mean \pm SD	7.7 \pm 3.0	7.7 \pm 2.6	8.8 \pm 2.9	0.2077
Neutrophils (G/L), mean \pm SD	4.1 \pm 2.1	4.4 \pm 2.0	4.5 \pm 2.4	0.471
CRP* (mg/L), mean \pm SD	5.9 \pm 6.1	6.0 \pm 7.0	5.6 \pm 5.2	0.842
PR* (%), mean \pm SD	86.2 \pm 8.9	82.7 \pm 17.1	77.6 \pm 13.5	<0.001
Fibrinogen (g/L), mean \pm SD	3.2 \pm 0.7	3.3 \pm 0.9	3.2 \pm 0.7	0.847
LDH* (U/L), mean \pm SD	323.4 \pm 140.5	399.8 \pm 183.5	465.5 \pm 176.9	0.003
Total bilirubin (μ mol/L), mean \pm SD	30.7 \pm 27.1	33.4 \pm 25.0	47.1 \pm 33.7	0.156
GGT* (U/L), mean \pm SD	50.8 \pm 46.5	68.7 \pm 60.8	55.4 \pm 46.2	0.597
Serum ferritin (ng/ml), mean \pm SD	174.3 \pm 249.6	221.4 \pm 245.7	275.5 \pm 476.1	0.19

* ACS = acute chest syndrome; HbF = hemoglobin F; PR = Prothrombin ratio; CRP = C-reactive protein; LDH = lactate dehydrogenase; GGT = gamma-glutamyl transferase

DISCUSSION :

The current study is the largest study to date evaluating SCD patients with OCTA findings. The analysis revealed that HbSS genotype, lower PR and proliferative sickle cell retinopathy are independently associated with sickle cell maculopathy. Correlation between proliferative sickle cell retinopathy and maculopathy is an expected outcome. An association between genotype and sickle cell maculopathy is less apparent, especially since it is well accepted that sickle cell retinopathy is more common and more severe in SC patients than in HbSS.^{14,16} Mathew et al reported a higher rate of retinal thinning in HbSS patients than in HbSC patients (48% vs 35%),⁵ whereas other studies found no statistical difference.^{8,17} Our study demonstrated that retinal thinning occurs more frequently in HbSS eyes compared to the other form of SCD (HbSC, HbS/β+, HbSlepore). This result can easily be explained. Indeed, prior studies proposed that a higher rate of vaso-occlusive crisis in HbSS patients could lead to repeated ischemic episodes in the eyes and thus the development of extensive retinal atrophy.^{9,18,19} On the other hand, milder degree of retinal ischemia in HbSC genotype would be not enough to infarct the retina but could result in the production of angiogenic factors and a higher risk of peripheral neovascularization.^{20,21} Natural history of sickle cell retinopathy is unique because peripheral neovessels can infarct itself over time.¹⁶ In this study, we graded as PSR the few eyes with focal photocoagulation for a prior neovascularization, so PSR eyes may have been overrepresented in the analysis. However, our results suggest a strong relationship between maculopathy and retinopathy. This relationship may be explained by the fact that the temporal macular area and the retinal periphery are both supplied by small caliber terminal arterioles, therefore vascular occlusion can easily damage these areas.⁵ Interestingly, PR was found significantly lower in patients with maculopathy. Low PR means a prolonged prothrombin time which is common in SCD even if the reason is not well established.^{22,23} It is likely that prolonged prothrombin time is a marker of chronic vascular inflammation among others like platelets and adhesion molecules. Prolonged PR could be related to several conditions such as liver dysfunction that decreases the synthesis of clotting factors or dysfunctional coagulation factors on vitamin K deficiency due to cholestasis for example.

OCTA enabled us to determine valuable findings of maculopathy and to identify or confirm specific risk factors for macular damages in SCD. FAZ area and macular ischemia were correlated with several biologic factors. Indeed, high serum LDH level was significantly associated with FAZ area enlargement in multivariate analysis with a rise of 0.03 μm^2 for every

100 units of LDH. Also, lower hemoglobin level was significantly associated with more severe macular ischemia in multivariate analysis with a rise of $0.36 \mu\text{m}^2$ for every unit of hemoglobin. It is noteworthy that lower hemoglobin, lower hematocrit and higher serum LDH levels, which are good markers of chronic intravascular hemolytic state,²⁴ were statistically associated with the occurrence of maculopathy even if they did not remain in multivariate regression analysis. These results are consistent with hemolytic severity, so we can hypothesize on hemolysis as the onset factor of sickle cell maculopathy. Indeed, two mechanisms are involved in the pathophysiology of SCD. Kato et al suggests a model that associates clinical events (vaso occlusive crises, acute chest syndrome or osteonecrosis for example) reflecting hyperviscosity and vaso occlusion phenotype, versus other clinical events (leg ulcers, pulmonary hypertension, priapism) mainly associated with hemolytic phenotype.²⁴ By analogy, few studies found that severe sickle cell retinopathy is more frequent in patients with higher hemoglobin and hematocrit levels, suggesting blood viscosity as a potential risk factor.^{9,25} These studies comforted in the capacity of phlebotomy to treat blood viscosity and to prevent retinopathy and maybe even maculopathy. In our study, we failed to find any statistical association between SCM and evident complications of hyperviscosity, apart from acute chest syndrome. Yet, we can not formally conclude if SCM belongs to one phenotype or the other.

Another potential risk factor barely failed the multivariate analysis: chronic transfusion. SCD patients have chronic anemia which is corrected by occasional or regular transfusion. By reducing the HbS level, chronic transfusion prevents hemolysis and hemolytic complications.³ We could not conclude to the capacity of blood transfusion to prevent macular damages, especially since our study is transversal.

Concerning hydroxyurea use, it induces an increase of HbF preventing HbS polymerization and red blood cells deformation.²⁴ We suggest that it is efficient against vascular occlusion causing macular and peripheral ischemia like it is reported to reduce the frequency of sickling crises in SCD patients.²¹ Similar studies concurred in the same direction.^{15,25} A previous study conducted on 123 HbSS children showed a protective effect of HbF on retinopathy when superior at 15%.¹⁵ Dell 'Arti showed a correlation between lower HbF and sickle cell maculopathy but their analyses did not reach significance.¹⁷ The current study failed to show any association with hydroxyurea use. Analyzing hydroxyurea use as a binary variable was problematic because it did not account for age of initiation or cumulative dosage to really establish a correlation with the FAZ area, the occurrence or the severity of SCM.

On OCT, sickle cell maculopathy is defined as a macular thinning. In our study, the occurrence of maculopathy in patients with SCD was 43.7% which confirms prior studies where maculopathy frequency varied from 44% to 60%.^{5,26,27} A great advantage of OCTA is to detect microvascular abnormalities before retinal thinning occurs. For instance, Minvielle et al already detected perifoveal abnormalities in fluorescence angiography in only 50% of eyes whereas OCTA detected in 100% of cases.⁷ Our results confirm prior studies.^{5,28} Areas of no flow on OCTA were present in 36/85 eyes without maculopathy on OCT. This data suggests that OCTA may detect early signs of macular changes in patients and can likely be considered as a clinically useful marker in the screening and the evaluation of SCD progression or even for preventive treatment.

As expected, FAZ area was found larger in SCD patients than controls. This finding should be read with caution because loss of capillaries may have been the result of blood flow velocity below the detection threshold of the OCTA rather than no perfusion. In addition, it is important to acknowledge that FAZ area can vary with ethnicities.²⁹ An enlarged FAZ area is not specific of patients with SCD but also a physiological variation for healthy subjects from African origin. To avoid any bias related to ethnicity effect, the control group was selected in the same population. We also noticed a substantial variability in FAZ area and irregularity between patients and controls. Some studies in healthy eyes support that this parameter can be ambiguous and thus may be insufficient for discriminating occurrence and severity of maculopathy in SCD.^{30,31} Because of the clinical implication of significant disruption of the FAZ extending beyond the borders of the OCTA scans and, even if a quantitative value could be misleading in the 9 concerned eyes, we did not exclude them from analysis but used a censored statistical model instead. As such, eyes with more severe macular vascular pathology could be represented in this study in order to establish association with potential risk factors. In our study, there was no statistical difference between male and female in the occurrence of maculopathy and the macular ischemia, but men had a lower FAZ area than women. Interestingly, some studies have questioned a protective female effect in SCR. Indeed, Fox found that HbSS men had a 2.5-fold higher risk of developing severe SCR than women.⁹ They attributed the female protective effect to estrogen levels through a vascular protective effect by increasing endothelial nitric oxide synthase activity. Further studies are warranted to address this issue.

Finally, our analysis also revealed that the occurrence of the maculopathy or the severity of macular ischemia can vary significantly between 2 eyes of the same patient. Future prospective studies may elucidate the ocular risk factors that may predispose the injury of one eye compared to the other.

Our study had several limitations. First, it was a cross-sectional study, so we could not estimate the incidence and the evolution of the sickle cell maculopathy. Further studies are warranted to evaluate macular microvascular changes with OCTA in the same patients over time in a longitudinal manner. Secondly, we had strict inclusion and exclusion criteria resulting in a modest cohort of patients, which limited the multivariate analysis for potential risk factors. Yet, we did not exclude patients with prior photocoagulation because we think that it reflects a real-life situation and their exclusion can underestimate a number of severe patients in the analysis. Another limitation concerned image acquisition and the software used. OCTA has the advantage to be a non-invasive dye-free technique and to provide structural microvascular information. However, it requires a precise and stable ocular fixation from the patients for several seconds. Furthermore, the software we used could not provide any vascular density, so we could not have any quantitative criteria for ischemia. For this reason, we subjectively graded macular ischemia because we suspect that OCTA is a better tool to reveal maculopathy than OCT. However, the study may underestimate the frequency of macular abnormalities in patients with more severe systemic events.

In conclusion, the identification of systemic, genetic and biologic factors associated with the occurrence and the severity of maculopathy confirms the complexity of this disease. Association between sickle cell maculopathy and other organ damages in SCD is a significant question. OCTA is a highly sensitive method to detect microvascular macular abnormalities before the onset of macular thinning that commonly define the maculopathy status. Avoiding the occurrence of these abnormalities is critical to minimize and to manage the functional implication of retinal thinning in these young patients. Prospective studies are needed to determine the natural history of SCM and its relevance regarding preventive strategies for SCD patients. Furthermore, the emergence of novel technology such as OCTA could provide valuable information to contribute in a public health screening and follow up of patients with SCD.

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APPENDIX

Annex 1: Goldberg 's classification of Sickle Cell Retinopathy

<i>Stage 1</i>	Peripheral arteriolar vascular stops
<i>Stage 2</i>	Peripheral arteriolo-veinular anastomosis
<i>Stage 3</i>	Fibrovascular proliferations
<i>Stage 4</i>	Intravitreal hemorrhages
<i>Stage 5</i>	Retinal detachment

LISTE DES TABLEAUX ET FIGURES :

Table 1: Baseline demographic characteristics of the sickle cell disease population of this study.

Table 2: Univariate analysis for occurrence of sickle cell maculopathy

Table 3: Univariate analysis of FAZ area

Table 4: Univariate analysis of risk factors in macular ischemia

Figure 3 : Manual delineation of FAZ area

Figure 4 : Subjective graduation of macular ischemia based on SD-OCT and OCTA using the following criteria: extension of blue area in retinal thickness map, the areas of flow loss in OCTA 10° and 20°, the irregularity and enlargement of the FAZ. a) no ischemia, b) mild ischemia, c) moderate ischemia, d) severe ischemia.

Figure 3 : Exemple of difficulty in FAZ delineation on OCTA scan from a patient with severe (3) macular ischemia.

SERMENT D'HIPPOCRATE

Au moment d'être admis à exercer la médecine, en présence des maîtres de cette école et de mes condisciples, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité qui la régissent.

Mon premier souci sera, de rétablir, de préserver ou de promouvoir la santé dans tous les éléments physiques et mentaux, individuels collectifs et sociaux. Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.

J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou dignité.

Même sous la contrainte, je ne ferai usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients de décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer leurs consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera.

Je ne me laisserai influencer ni par la recherche du gain ni par la recherche de la gloire.

Admis dans l'intimité des personnes, je tairai les secrets qui me sont confiés.

Reçu à l'intérieur des maisons, je respecterai les secrets des foyers.

Et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances, sans acharnement.

Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission.

Que je sois modéré en tout, mais insatiable de mon amour de la science.

Je n'entreprendrai rien qui ne dépasse mes compétences ; je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses,

Que je sois déshonoré et méprisé si j'y manque.

**UNIVERSITE DES ANTILLES
FACULTE DE MEDECINE HYACINTHE BASTARAUD**

DEMANDE D'IMPRIMATUR

NOM ET PRÉNOM : FARES Sélim

SUJET DE LA THÈSE : Maculopathie drépanocytaire : Analyse microvasculaire en OCTA et identification des facteurs de risques génétiques, systémiques et biologiques

THÈSE : MEDECINE

Qualification : Médecine Spécialisée

ANNEE : 2020

NUMERO D'IDENTIFICATION : 2020ANTI0505

MOTS CLEFS : drépanocytose, maculopathie drépanocytaire, facteurs de risques, OCTA

RÉSUMÉ :

Objectifs : Identifier les facteurs de risques génétiques, systémiques et biologiques de maculopathie dans la drépanocytose. Évaluer les anomalies microvasculaires maculaires dans la drépanocytose grâce à l'optical coherence tomography angiography (OCTA).

Méthodes : Dans cette étude transversale observationnelle monocentrique, 151 yeux de 78 patients atteints de drépanocytose et 40 yeux de 20 sujets sains de même origine ethnique ont bénéficiés des examens spectral domain optical coherence tomography (SD-OCT) et OCTA sur l'angiographe Spectralis (Heidelberg, Allemagne) pour évaluer 3 critères : la prévalence de maculopathie drépanocytaire, l'élargissement de la zone avasculaire centrale (ZAC) et la sévérité de l'ischémie maculaire. Nous avons aussi recueilli les données cliniques, génétiques, biologiques et avons fait une analyse multivariée en régression logistique pour identifier une association entre chaque facteurs de risques potentiels et la maculopathie drépanocytaire, l'aire de la ZAC et l'ischémie maculaire.

Résultats : Notre étude a inclus 43 patients HbSS, 30 HbSC, 4 HbS/β+ et 1 HbSLepore. La maculopathie drépanocytaire est survenue chez 66 yeux (44%), en particulier chez les patients HbSS (71%, $p = 0,004$). L'analyse multivariée a identifié le génotype HbSS et l'allongement du temps de prothrombine (TP) comme les facteurs de risques les plus significatifs de maculopathie ($p = 0,01$). La rétinopathie drépanocytaire proliférative a aussi été associée à la maculopathie ($p = 0,02$). L'augmentation du taux de lactate déshydrogénase a été significativement associée à l'élargissement de la ZAC ($p = 0,02$). L'ischémie maculaire a été plus sévère chez les patients avec un taux bas de base en hémoglobine ($p = 0,04$) et un TP allongé ($p = 0,01$). Les aires de non perfusion en OCTA ont été identifiées chez des patients sans amincissement rétinien (36 yeux, 42%) et sont survenues plus fréquemment dans la partie temporale supérieure de la macula. (36%). Des irrégularités de la ZAC et des boucles vasculaires périfovéales ont été retrouvées respectivement chez 70 yeux (46%) et 38 yeux (25%) en OCTA.

Conclusion : Le génotype HbSS, une coagulation anormale et l'hémolyse sont associés à la maculopathie drépanocytaire. L'OCTA apporte de nouveaux critères pour identifier les facteurs de risque de maculopathie dans la drépanocytose. L'OCTA est utile pour détecter des anomalies microvasculaires avant même l'apparition d'un amincissement maculaire. La définition de la maculopathie drépanocytaire comme un amincissement maculaire à l'OCT n'est plus d'actualité et d'autres critères sont à définir afin d'identifier l'apparition précoce de la maculopathie et évaluer son évolution.

JURY : Président : Professeur Thierry DAVID

Juges : Professeur Harold MERLE

: Professeur Maturin TABUE TEGUO

: Docteure Laurence BERAL
