

Correlations Between Visual Field Defects and Macular Thinning in Sickle Cell Disease

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PURPOSE. The purpose of this study was to investigate the correlation between defects in automatic perimetry and macular temporal thinning in optical coherent tomography (OCT) on patients with sickle cell disease (SCD) to define the impact of its maculopathy on visual function.

METHODS. This single site retrospective cross-sectional study was conducted in a referral center for rare disease from January to July 2020. Fifty-eight patients with SCD were referred for an ophthalmological examination including automatic perimetry and OCT. The correlation between macular thickness and visual field defect in each Early Treatment Diabetic Retinopathy Study (ETDRS) quadrants was calculated.

RESULTS. Visual acuity was normal in 104 eyes (94.5%). Thirty-three eyes (30.0%) had a defect of visual field in at least one ETDRS quadrant. There was a significant correlation between macular thinning on OCT and decrease of the mean defect in visual field in the temporal quadrant ($P < 0.001$). When comparing sickle cell genotype groups, macular thickness was significantly reduced in temporal outer quadrants in patients with the SS genotype, and in the inner and outer temporal quadrants in other genotypes.

CONCLUSIONS. Despite normal visual acuity, macular temporal thinning in patients with SCD is associated with visual field defects in SS genotypes. This points to a primitive vascular dysfunction rather than neurogenic mechanism in occurrence of SCD maculopathy.

Keywords: optical coherent tomography (OCT), sickle cell disease (SCD), sickle cell maculopathy, sickle cell retinopathy, visual field defect

Sickle cell disease (SCD) is a group of pathologies characterized by the production of sickle hemoglobin or hemoglobin S. This pathologic hemoglobin is the result of a single mutation on the hemoglobin B gene. Although the most common form of SCD is homozygous hemoglobin S (HbSS), other combinations of heterozygous alleles can be found with hemoglobin S, such as hemoglobin C (HbSC), beta+-thalassemia (HbS β +) or beta0-thalassemia (HbS β 0), or even more rarely, hemoglobin O_{Arab} (HbSO_{Arab}).¹ All of these variations cause intracellular sickling under hypoxic conditions, acidosis or inflammation, and vaso-occlusion, and therefore acute and chronic complications. Kidneys, bones, heart, and lungs are the most common organs involved in SCD, but the retina can be also affected. The main cause of vision loss is the proliferative sickle cell retinopathy (PSR), which is still commonly graded with Goldberg's classification from stages I to V.² The sickle cell maculopathy is another ocular complication of SCD. Although visual acuity can

be preserved for a long time, ischemic damage to the macula can be detected by fluorescein angiography and more recently with optical coherence tomography (OCT).³ An OCT shows retinal thinning in the temporal macular area, predominating along the median temporal raphe.⁴ The physio pathogenic mechanisms of this maculopathy is not clearly understood, although data are consistent with the role of anemia or hemolysis in cerebral vasculopathy and macular involvement.⁵ These areas of macular thinning are considered as asymptomatic because patients did not complain of visual decrease. But alterations of the visual field have been described in a small group of five selected patients.^{6,7}

The aim of this cross-sectional study was to confront macular thinning in OCT and automated perimetry to OCT and to analyze the relationships between these two parameters in patients with SCD. Our hypothesis is that the areas of retinal damage are responsible for a more or less significant localized decrease in retinal sensitivity.



METHODS

We analyzed retrospectively from January 2020 to July 2020 the data of consecutive adult patients with SCD in a single ophthalmological department. According to National legislation, patients were warned that their data could be used anonymously unless they oppose specifically to such use. Thus, there was no need to obtain a specific consent from participants. This retrospective study was approved by the ethical committee of the French Society of Ophthalmology (IRB 00008855 Société Française d'Ophtalmologie IRB#1) and was conducted ethically in accordance with the recommendations of the Helsinki Declaration.

All patients with SCD and followed in the SCD referral center for our institution reached the eligibility criteria and could be a candidate to enter this cohort study. We defined two exclusion criteria: (1) patients with glaucoma with IOP within range (whether by treatment or normal tension glaucoma) and/or enlargement of the optic disc excavation because they can have specific visual field deficits; and (2) patients with missing data or poor-quality data.

We included all patients that were referred by the SCD center during the inclusion period for a regular routine ophthalmological examination looking for retinal SCD complications, as recommended by national guidelines. In the absence of data on the frequency of campimetric anomalies that could be observed in patients with SCD, it was not possible to calculate an optimal sample size. However, the possibility of including all patients with SCD, regardless of type, made it possible to obtain a series of sufficient size.

The type of sickle hemoglobinopathy was determined by hemoglobin electrophoresis (HPLC). Analyses of campimetry and OCT parameters were performed in subgroups constituted by the type of SCD. All patients underwent complete ophthalmological examination, including visual acuity assessment, slit-lamp examination, IOP measurement, dilated fundoscopy with Goldmann three mirror lens, OCT, and visual field assessment. Visual acuity was converted to logarithm of minimal angle of resolution (logMAR). Stage of PSR was determined according to the Goldberg's classification.²

OCT Analyses

These data were obtained using a Spectralis HRA – OCT2 (Heidelberg Engineering GmbH, Hamburg Germany) and were performed after pupil dilatation by a trained technician. Posterior pole volumes were recorded with 20 degrees or 30 degrees wide scans centered on the fovea. Automated retinal thickness color maps and measurements were obtained and positioned on the Early Treatment Diabetic Retinopathy Study (ETDRS) grid on macular thickness map. This grid is composed of 3 concentric circles of 1 mm, 3 mm, and 6 mm in diameter, crossed by 2 diagonal lines, and defining therefore 9 areas. Automated segmentation of the different layers were achieved by the software provided by the Spectralis HRA – OCT2. Mean thickness of each area was reported, as well as the presence of a possible subjective focal thinning using the color scale. OCT scans were excluded when the quality was poor due to parasitic movements during image acquisition and did not allow a correct analysis and measurement of the retinal thickness. We did not note any abnormalities of visual acuity or central visual field in these patients.

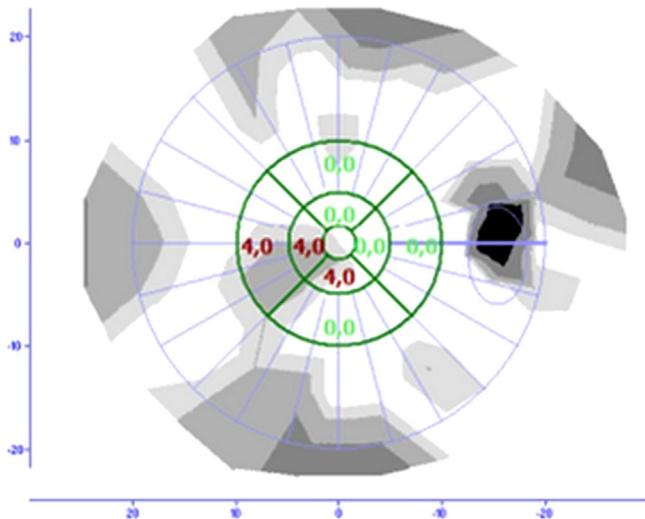


FIGURE 1. Value of mean deficit of the visual field in each ETDRS quadrant.

Automatic Campimetry

Automatic perimetries were obtained with a MonPack-One (Metrovision, Perenches, France) using the FAST-24 program comprising of 79 dots up to 24 degrees of eccentricity. All examinations were performed before pupil dilatation by a trained technician. We reported global mean defect (MD) and the MD in each ETDRS area with a specific software (Fig. 1). This software was developed by Metrovision to calculate the MD in each ETDRS quadrant in order to compare those value with usual OCT macular thickness software. Patients were excluded when fixation losses were above 25%, meaning poor examination quality.

Statistical Analyses

The statistical analyses were performed using Stata (version 17, StataCorp). A Student *t*-test was performed to compare continuous variables using a significant level at *P* values less than 0.05. The strength of association between the retinal thickness and a visual field defect was assessed using Pearson's correlation coefficient. A multivariate analysis of retinal thickness was also conducted using a multiple regression including visual field defect, Goldberg stage, and SCD genotype as explanatory variables or subgroups.

RESULTS

We enrolled 122 eyes of 61 consecutive patients with SCD in this study. Due to poor visual field quality, we excluded both eyes of two patients and one eye of six other patients. One patient withdrew his consent for using his data after inclusion (Fig. 2). However, we included all patients for whom a macular retinal thickness measurement could be obtained in more than six ETDRS quadrants out of the eight tested. Therefore, we analyzed 110 eyes from 58 patients (29 women and 29 men). The mean age of the patients was 29.9 years (from 18 to 61 years). According to the hemoglobin electrophoresis, we considered 3 subgroups: 87 eyes had HbSS SCD (79.1%), 17 eyes had HbSC (15.5%), and 6 eyes had less frequent phenotype of SCD, which we regrouped in one category due to the small frequency of cases (2 HbS β +, 2 HbS β 0, and 2 HbSO_{Arab}; Table 1). The mean visual acuity

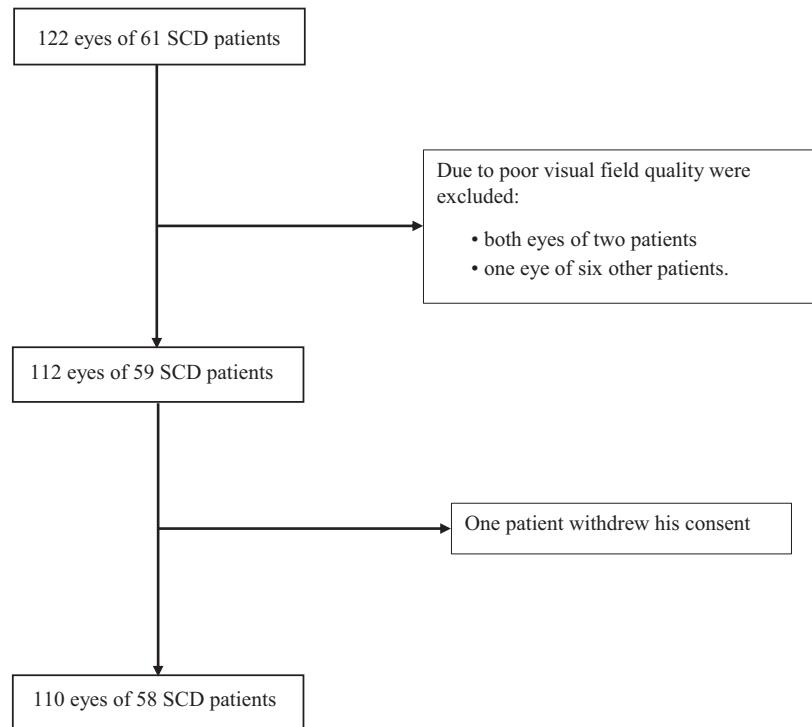


FIGURE 2. Flow chart of patient's inclusions.

TABLE 1. Demographic Characteristics

SCD Genotype	HbSS	HbSC	Other	Whole Series
Patient Characteristics				
Patients, number (% of all)	46 (79.3)	9 (15.5)	3 (5.1)	58 (100)
Male, number (% of type)	21 (45.7)	5 (55.5)	3 (100)	29 (50)
Age, mean, y (SD)	28.7	35.2	31.7	29.9 (9)
Maculopathy (% of type)	31 (67.4)	5 (55.5)	1 (33.3)	37 (63.8)
Visual field defect (% of maculopathy)	20 (64.1)	3 (60.0)	1 (100.0)	24 (64.9)
Eyes Characteristics				
Eyes, number	87	17	6	110
Visual acuity, mean (SD)	0.003	0	0	0.002 (0.03)
Maculopathy (% of type)	43 (49.4)	9 (52.9)	2 (33.3)	54 (49.1)
Unilateral (% of type)	19 (21.8)	1 (5.9)	0 (0.0)	20 (18.9)
Bilateral (% of type)	24 (27.6)	8 (47.0)	2 (33.3)	34 (31.0)
Visual field defect (% of maculopathy)	27 (64.3)	4 (44.4)	2 (100.0)	33 (61.1)
Superior 3 mm	1	1	0	2
Superior 6 mm	3	2	0	5
Temporal 3 mm	5	3	2	10
Temporal 6 mm	7	3	2	12
Inferior 3 mm	4	2	1	7
Inferior 6 mm	3	0	0	3
Nasal 3 mm	2	0	0	2
Nasal 6 mm	4	2	0	6
Stage Goldberg Classification				
0, number (% of type)	48 (55.1)	6 (35.2)	4 (66.7)	58 (52.7)
1, number (% of type)	26 (29.9)	3 (17.6)	0 (0)	29 (26.3)
2, number (% of type)	2 (2.3)	0 (0)	0 (0)	2 (1.8)
3, number (% of type)	11 (14.9)	8 (47.0)	2 (33.3)	21 (19.1)
4, number (% of type)	0 (0)	0 (0)	0 (0)	0 (0)
5, number (% of type)	0 (0)	0 (0)	0 (0)	0 (0)

Patients and eyes characteristics. The "Other" column gathered one patient with HbS β +, one patient with HbS β 0, and one patient with HbSO_{Arab}.

of the entire series of 110 eyes was 0.002 logMAR (-0.08 to 0.15) and 104 eyes (94.5%) had a visual acuity of 0 logMAR or better.

Sickle cell maculopathy due to SCD was assessed qualitatively and quantitatively by strictly localized thickness reduction. Such sickle cell maculopathy was observed in 54 eyes (49.1%) of 37 patients (63.8%). This abnormality was more frequent in patients with HbSC (52.9%) than in patients with HbSS (49.4%). There is no significant difference between these two groups of patients according to the type of SCD ($P = 0.72$). The low prevalence in other groups (33.3%) was probably due to the small number of patients. Sickle cell maculopathy was present in both eyes in 63% of our cohort. Bilateral forms were more frequent in patients with HbSC (88.9%) versus patients with HbSS (55.8% of eyes with maculopathy). However, the difference is not significative ($P = 0.06$).

Thirty-three eyes (30.0%) had a localized defect of visual field sensitivity as proved by an abnormal MD. Due to the mean age of the patient, MD over 1.5 decibel (dB) were considered as abnormal. The repartitions according to the localization of the ETDRS grid applied to visual field is reported in Table 1. This defect could be extended over several sectors.

Mean macular thickness were notably $314 \pm 26 \mu\text{m}$ for the inner temporal quadrant and $277 \pm 22 \mu\text{m}$ for the outer temporal quadrant. When a visual field defect was present, it was always a relative deficit and none of the eyes had a complete visual field defect. For each ETDRS quadrant, we compared the retinal thickness in the absence or presence of a deficit on the visual field (Table 2). We observe a significant difference of retinal thickness according to the aspect of the visual field only in the nasal inner, the temporal inner, and the outer quadrants. In addition, we compared the mean visual field defect according to the presence or absence of sickle cell maculopathy (Supplementary Table S1).

We must point out the existence of false-positive results (visual field defect without macular thinning) and false-negative results (macular thinning without visual field damage). The analysis of the correlation between macular thickness and visual field defect for each ETDRS quadrants allows us to account for the importance of the rate of these false-positive results and false-negative results. We have studied this correlation for each ETDRS quadrants (see Table 2). A significant association was observed in the nasal inner quadrant (Pearson's coefficient -0.242 , $P = 0.011$), the temporal inner (-0.641 , $P < 0.001$), and the outer (-0.569 , $P < 0.001$). It did not show significant correlation in the superior inner and outer quadrants, the inferior inner and outer quadrants, and the nasal outer quadrant.

When comparing the retinal thickness between patients with or without visual defect according to the subgroups (Table 3), a significant difference was observed in patients with HbSS genotype in the outer temporal quadrant ($P = 0.005$). Such a significant difference was observed in the inner temporal ($P = 0.033$) and outer temporal quadrants ($P = 0.036$) in patients with other genotypes (HbS β +, HbS β 0, and HbSO_{Arab}). No difference was observed for the other quadrants in these two genotypes. No significant difference was observed in patients with the HbSC genotype whatever the quadrant being considered.

Most eyes (58 eyes, 52.7%) had no sign of PSR on fundus examination and were stage 0 of the Goldberg classification. Respectively, 29 eyes (26.4%), 2 eyes (1.8%), and 21 eyes

TABLE 2. Comparison of Retinal Thickness and Visual Field Defect in the Different ETDRS Quadrants According to the Presence or Absence Visual Field Defects and Correlation Between Retinal Thickness and Visual Field Defect in the Different ETDRS Quadrants

ETDRS Grid Quadrant	No Visual Field Defect			Visual Field Defect			Pearson's Coefficient	<i>P</i> Value
	Number of Eyes	Mean Thickness, Microns	Mean MD, dB	Number of Eyes	Mean Thickness, Microns	Mean MD, dB		
Nasal 3 mm	108	336.15 \pm 17.92	0	2	299.00 \pm 7.07	22.90 \pm 11.45	0.004	-0.242 0.011
Nasal 6 mm	92	314.32 \pm 18.41	0	7	313.42 \pm 10.45	9.47 \pm 11.26	0.843	0.045 0.656
Superior 3 mm	108	333.87 \pm 24.78	0	2	344.50 \pm 9.19	5.00 \pm 1.41	0.547	0.064 0.507
Superior 6 mm	94	2980.9 \pm 17.49	0	5	300.80 \pm 13.08	11.00 \pm 11.35	0.735	-0.034 0.736
Temporal 3 mm	100	317.81 \pm 18.40	0	10	274.20 \pm 51.55	12.77 \pm 9.04	<0.001	-0.641 <0.001
Temporal 6 mm	89	280.00 \pm 17.70	0	10	246.50 \pm 37.30	12.75 \pm 9.76	<0.001	-0.569 <0.001
Inferior 3 mm	103	332.20 \pm 20.60	0	7	334.42 \pm 6.29	6.84 \pm 4.74	0.777	0.033 0.733
Inferior 6 mm	96	289.11 \pm 15.60	0	3	286.67 \pm 9.29	11.80 \pm 6.79	0.788	0.004 0.966

The numbers in bold represent statistical significance.

TABLE 3. Comparison of Retinal Thickness and Visual Field Defect According to SCD Genotype

ETDRS Grid Quadrant	No Visual Field Defect			Visual Field Defect			P Value OCT Mean Thickness, Microns
	Number of Eyes	Mean Thickness, Microns	Mean MD, dB	Number of Eyes	Mean Thickness, Microns	Mean MD (dB)	
SS							
Temporal 3 mm	82	317.31 ± 16.35	0	5	273.6 ± 46.21	15.06 ± 10.37	0.10
Temporal 6 mm	69	281.00 ± 17.82	0	7	241.6 ± 16.62	13.14 ± 9.60	<0.001
SC							
Temporal 3 mm	14	315.36 ± 18.35	0	3	317.67 ± 25.32	5.13 ± 1.96	0.85
Temporal 6 mm	14	274.00 ± 14.87	0	3	289.33 ± 9.07	5.00 ± 1.73	0.11
(HbS β +, HbS β 0, and HbSO $_{\text{Arab}}$)							
Temporal 3 mm	4	336.75 ± 10.53	0	2	210.50 ± 17.68	18.50 ± 5.66	<0.001
Temporal 6 mm	4	305.00 ± 5.66		2	194.50 ± 14.85	23.00 ± 9.90	<0.001

Association between retinal thickness and visual field defect in temporal inner and outer quadrant according to the sickle cell disease genotype.

The numbers in bold represent statistical significance.

TABLE 4. Multivariate Analysis of OCT Macular Thickness

ETDRS Grid Quadrant	Goldberg's Stage	Visual Field Deficit	Genotype	Age
Temporal 3 mm	0.786 (1.824/2.044)	<0.001 (1.400/2.307)	<0.001 (0.649/1.188)	0.65 (27.622/32.454)
Temporal 6 mm	0.017 (0.777/1.218)	0.09 (0.630/2.711)	0.05 (1.850/2.026)	0.049 (283376/33.234)

Multivariate analysis of OCT macular thickness in each temporal quadrant: multiple regression of retinal thickness on the Goldberg's classification stage of retinopathy, visual field defect, and SCD genotype (SS, SC, and Others). Results are expressed as *P* value and lower and upper limits.

The numbers in bold represent statistical significance.

(19.1%) were stage 1, 2, and 3. No patients were stage 4 or 5. The PSR was significantly more severe in patients with sickle cell maculopathy in the inner temporal quadrant (Supplementary Table S2). But no difference can be detected in the outer quadrant. When detailing the analysis by SCD phenotype, stage 0 of the Goldberg classification was prominent in patients with HbSS or in other genotypes (HbS β +, HbS β 0, and HbSO $_{\text{Arab}}$; respectively, 48 eyes for HbSS 55.2% and 4 eyes for the other, 66.7%), but less frequent in patients with the HbSC genotype (6 eyes, 35.3%). Stage 3 of the Goldberg classification was present in 11 eyes (12.6%) the in HbSS genotype, 8 eyes (47.1%) in the HbSC genotype, and 2 eyes (33.3%) in other genotypes.

In multivariate analysis including age, Goldberg stage, and visual field defect, we observed a significant effect of genotype and visual field defect on OCT retinal thickness in the inner temporal quadrant, whereas the Goldberg stage of peripheral retinopathy, genotype, and age were significantly associated with OCT retinal thickness in the temporal outer quadrant (Table 4).

DISCUSSION

To our knowledge, this is the first study that compared visual field defects and OCT retinal thickness in a large series of patients with SCD with different PSR status. In a previous study, Martin et al. reported three cases of patients with asymptomatic SCD with normal visual acuity and no PSR. This author found visual field defect and temporal macular atrophy.⁸ SCD is mostly seen as a peripheral retinopathy, however, SCD maculopathy comes along with either temporal thinning, or anomalies in the foveal avascular zone (FAZ).⁹

The frequency of macular maculopathy seems to be identical in whatever the type of SCD. The prevalence we observed is able conform to previous publications.¹⁰ This author also found a higher frequency in patients with HbSC (62.5%) as in our series. However, the difference is not significant in this study. In the opposite, Lim et al. or Fared et al. showed that patients with HbSS are more likely to have macular thinning, particularly temporally, compared with those with HbSC.^{11,12} There is no clear explanation for such difference. But risk factors and physio pathogeny of this macular thickness are not clearly identified. Thus, it is difficult to confirm the homogeneity of the series. Fares reported that macular thinning was more frequent in the superior temporal sector.¹² In our study, we preferred to use the ETDRS macular grid. We observed a mean temporal thickness of 277 ± 22 μm for the outer quadrant and 314 ± 26 μm for the inner quadrant, which is consistent with previously published data of SCD maculopathy observed by macular OCT examination.¹³

In 33 eyes of our series (30%), we observed a deficit in at least one quadrant of the ETDRS grid applied to the visual field. This deficit usually affects the temporal quadrant of the visual field and predominantly the temporal peripheral region of this quadrant when looking at OCT data. In addition, the mean MD was lower than normal but there was never a full defect. Because the best corrected visual acuity is based on foveolar vision, it explained that most of our patients (95%) had logMar 0 or better best corrected visual acuity, as was reported by other studies.^{8,10} Such measurement is not sufficient to characterize the visual function of patients with SCD. This argues for a more complete ophthalmological screening for the sickle cell maculopathy. We do not know which is the evolution of such a defect. In a study of three patients, including two children, similar macular

thinning was found in OCT angiography (OCT-A), associated with campimetric deficits, highlighting the precocity of this retinal damage during SCD.⁸ However, the evolution of these damages according to the age of the patients has not yet been studied. It is therefore necessary to consider carrying out additional longitudinal studies.

We did not find any significant association between the visual field and the macular thickness in the nasal, the superior, and the inferior quadrants, either in the outer or in the inner circles, which is consistent with previous studies.⁶ Both the outer and inner temporal quadrants were significantly associated with a reduced macular thickness. Pearson's coefficient was -0.550 for the temporal peripheral quadrant ($P < 0.001$), -0.569 for the temporal outer quadrant ($P < 0.001$), and -0.641 for the temporal inner quadrant ($P < 0.001$), which indicates a moderate correlation. Despite a significant result in the nasal inner quadrant, Parson's coefficient showed a negligible correlation.

Physiopathologies of sickle cell maculopathy are not yet fully explained. Due to the localization of this maculopathy in the temporal quadrant, near the horizontal raphe, primitive vascular, or neurogenic mechanisms were suspected.⁶ In addition, some studies showed contradictory results of the layers of the retina affected, whether inner, outer, or global thinning.^{14–16} Even if it is not known whether it is a pre- or post-receptor. The aim of this study was not to investigate the origin of this macular temporal thinning, or the retinal layers affected, but it suggests a primary vascular dysfunction. A neurogenic dysfunction would have led to cell loss and visual field deficit without initially too pronounced thinning of the parafoveal retina as observed in glaucoma. Neither can this study show if this macular thinning or the visual field deficit are fixed or evolutive as there is no follow-up examinations.

We found more frequent proliferative retinopathy in the HbSC genotype than in the HbSS genotype, which had already been shown in previous studies. Saif Aldeen AlRyalat et al. observed a similar frequency of PSR in HbSS and HbS β + and even less in HbS β 0,¹⁷ and there is only a few case reports of HbSO_{Arab} but it seems to be similar to HbSS retinopathy.¹⁴ We have too small a number of patients with HbS β +, HbS β 0, and HbSO_{Arab} to corroborate these findings.

We did not find any relation between such visual field defect or retinal thinning in the macular region (3 and 6 mm) and the peripheral SCD retinopathy, whereas it was significant for the more peripheral quadrant. Such finding is also consistent with previous data.^{10,18} Such absence of correlation is an argument to propose that those two types of retinal pathologies did not share the same physio pathological mechanisms. Moreover, we observed no difference in macular thickness in the HbSC genotype, which is consistent with previous studies. Lim et al. showed that the patients with HbSS are more likely to have macular thinning, particularly temporally, compared with those with HbSC.¹¹ This can be explained because HbSC retinopathy could be associated with blood hyperviscosity, whereas HbSS genotype retinopathy is not.^{18,19}

The main strength of our study is the recruitment of consecutive patients systematically referred by a referral center for SCD, with the realization of the full examination. Its result is important as it confirms that the temporal macular thinning in an OCT scan in patients with SCD is associated with detected visual field deficit in asymptomatic patients, at least in the HbSS genotypes, and should alert the ophthalmologist. These deficits can have consequences

in the visual abilities of these patients and can also prohibit certain activities or regulated professions.

In addition, this retrospective study also provides physio pathogenic elements. Because we did not find those scotomas in all patients with macular thinning, these data point to a primitive vascular dysfunction rather than neurogenic mechanism.

We also acknowledge a number of limitations. First of all, we assessed the macular thickness using standard OCT scans, but Martin et al. demonstrated that macular thinning occurred usually in an area of 7 to 100 μ m from the fovea.²⁰ The ETDRS grid corresponds to scope of 15 degrees of visual field. We observed visual deficit in the area included between the 15th and the 24th degree of the FAST-24 program, which is consistent with a temporal macular thinning beyond the 15th degree of the macula. OCT scans extended to this area would be needed to fully understand the visual field and the macular thickness correlation.

Moreover, we only assessed the visual field to study the functional parameters of the retina. Other tests could be performed to study the impact of macular thinning, such as electroretinogram, which can be affected in early-stage sickle cell retinopathy, contrast sensibility, or the color vision test.²¹ Another limitation is the small number of patients in the subgroups' analysis, especially for SC, HbS β +, HbS β 0, and HbSO_{Arab} genotypes, which induces a lack of power to detect any statistical association in these subgroups of patients.

It would be interesting to perform a longitudinal study of these patients to see what the evolution of the SCD maculopathy and of the visual field defects will be. But we first wanted to confirm the existence of a correlation between the damage found in OCT and the visual field before considering a longitudinal study.

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