Multifocal electroretinogram findings in sickle cell maculopathy

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Laurence Beral[1,2], Marc Romana[2,4], Nathalie Lemonne[3], Yoann Garnier[2,4], Marie Billaud[3], Malik Acomat[1], Coralie Zorobabel[1], Maryse Etienne-Julan[3], Thierry David[1,8] and Philippe Connes[2,4,6,7]

1 Service d'ophtalmologie, CHU de Pointe-à-Pitre/ Abymes, route de Chauvel, Pointe-à-Pitre, Guadeloupe, France

2 UMR Inserm 1134, Biologie Intégrée du Globule Rouge, INSERM/Université Paris Diderot - Université Sorbonne Paris Cité/INTS/Université des Antilles

3 Unité transversale de la Drépanocytose, CHU de Pointe-à-Pitre/ Abymes, route de Chauvel, Pointe-à-Pitre, Guadeloupe, France

4 Laboratoire d'Excellence GR-Ex « The red cell : from genesis to death », PRES Sorbonne Paris Cité, Paris, France

5 Unité Physiologie des Exercices et Activités en Conditions Extrêmes, Institut de Recherche Biomédicale des Armées, Brétigny-sur-Orge, France

6 Laboratoire Interuniversitaire de Biologie de la Motricité (LIBM), EA7424, Equipe Biologie Vasculaire et du Globule Rouge, Université Claude Bernard Lyon 1, COMUE Lyon, Villeurbanne, France

7 Institut Universitaire de France, Paris, France

8 Université des Antilles, Guadeloupe (FWI), France

Corresponding author: Philippe Connes (pconnes@yahoo.fr / philippe.connes@univ-lyon1.fr)

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ABSTRACT

BACKGROUND: The aim of the present work was to describe and compare multifocal electroretinogram findings (mfERG) in patients with sickle cell disease (SCD) without clinical sign of maculopathy according to the hemoglobin genotype.

METHODS: HbSS (homozygous SCD), HbSC (Hemoglobin SC disease) and HbAA (controls) individuals underwent a full ophthalmologic examination (with a fundoscopy), a spectral domain ocular coherence tomography (SD-OCT) and a mfERG.

RESULTS: A total of 86 subjects were included: 54 SCD patients (107 eyes) with 32 HbSS (63 eyes) and 22 HbSC (44 eyes) and 32 controls (64 eyes). None of the eyes showed retinal clinical abnormalities. SD-OCT analysis showed that macular thickness was statistically lower in SCD eyes than in controls. mfERG analysis demonstrated a significant reduction of N1 (initial negative deflection), P1 (positive peak) and N2 (second negative deflection) response amplitude densities of HbSS eyes compared to HbAA eyes from the center (<2°) to the periphery (>15°). Implicit time response was also reduced in the center (<2°). N1 and P1 response amplitude densities of HbSC eyes were significantly lower than those of HbAA eyes from the center (<2°) to the periphery (>15°). N2 response amplitude densities were also significantly reduced in the center (<2°) and in the periphery (>10°). N1 implicit time was statistically reduced in HbSC compared to HbSS eyes.

CONCLUSION: Our study is the first one to describe macular electrophysiological dysfunction in SCD patients. Moreover, we confirm that SCD maculopathy is equally frequent in HbSS and HbSC genotypes.

INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive disease caused by a single mutation of the β-globin gene leading to the production of an abnormal hemoglobin, named hemoglobin S (HbS). While HbS results from the substitution of glutamic acid by valine at the sixth codon of the β-globin gene, hemoglobin C (HbC) is caused by the substitution of glutamic acid by lysine at the same position of the β-globin gene (Ware, de Montalembert, Tshilolo, & Abboud, 2017). Upon deoxygenation, HbS polymerizes leading to red blood cell (RBC) sickling. These sickled RBCs are more fragile and rigid than healthy RBCs. Indeed, patients with homozygous SCD (HbSS genotype) are anemic, exhibit hemorheological abnormalities and may experience frequent vaso-occlusive events (Connes et al., 2018). In SCD patients with both HbS and HbC (HbSC genotype), HbC may form crystal upon oxygenation and promote RBC dehydration, increasing the ability of HbS to form polymers under deoxygenated condition (Brittenham, Schechter, & Noguchi, 1985; Bunn, 1997). HbSC patients are less anemic than HbSS patients but are also characterized by impaired RBC rheology (Nagel, Fabry, & Steinberg, 2003; Renoux et al., 2016). In addition, these sickled RBCs have increased adhesiveness to the vascular wall, leading to a broad range of acute and chronic clinical complications affecting various organs, including the eyes (Ballas, 2018). For instance, both retinopathy and maculopathy have been reported in HbSS and HbSC patients (Beral et al., 2018; Lu et al., 1999). It has been established that HbSC patients would be at higher risk to develop retinopathy than HbSS individuals (Elagouz, Jyothi, Gupta, & Sivaprasad, 2010a; Lemaire et al., 2013). While extensive literature is available on sickle retinopathy, very few studies focused on maculopathy.

Recent spectral domain optical coherence tomography (SD-OCT) findings suggest retinal thinning of the temporal zone of the macula in SCD patients. On the OCT angiography (OCTA), this thinning corresponds to microvascular abnormalities with loss of vascular density in the superficial and deep macular vascular plexuses (Do & Rodger, 2017; Ghasemi Falavarjani et al., 2016; Han, Tadarati, Pacheco, & Scott, 2017; Mathew et al., 2015). In most of these reports, SCD maculopathy was asymptomatic, suggesting that OCT can display macular atrophy without any

decrease in visual acuity (Lee et al., 1987; Leveziel et al., 2005). The etiology of asymptomatic macular thinning without apparent perfusion reduction remains unclear. Parafoveal acute middle maculopathy has been described in SCD patients (Hussnain, Coady, & Stoessel, 2017; Ilginis, Keane, & Tufail, 2015). In addition, it has been shown that even when the macula appears to be normal on clinical examination, angiography can reveal microvascular abnormabilities (Minvielle et al., 2016). Therefore, in absence of clinical macular abnormalities, we could suspect electrophysiological dysfunction.

To our knowledge, no study has been performed using multifocal electroretinogram (mfERG) to explore the electrophysiological macular function in SCD. We therefore investigated and compared inner macular function in asymptomatic HbSS and HbSC patients and AA subjects.

PATIENTS AND METHODS

Study design

This prospective monocentric study was performed in the ophthalmology department of the Pointe-à-Pitre university Hospital of Guadeloupe (FWI) between February 2014 and April 2018. All SCD patients were referred to the department for their annual fundoscopy by the sickle cell unit of the academic hospital of Guadeloupe. We included 54 SCD patients (107 eyes): 32 HbSS (63 eyes), 22 HbSC (44 eyes), and 32 HbAA healthy subjects (64 eyes). All SCD patients were at steady state at the time of the study (i.e. without vaso-occlusive crisis, acute medical complication or blood transfusion/phlebotomies within the last 3 months). Any condition causing a peripheral proliferative retinopathy (i.e., diabetes, central retinal vein or artery occlusion) was exclusion criteria. Blood was sampled in EDTA tubes for hematological measurements. The study was approved by the local ethics committee of the Hospital.

Ophthalmic examinations

Best corrected visual acuity (BCVA), slit lamp microscopy and biomicroscopy were performed for all patients by two independent ophthalmologists. They used a non-contact slip lamp lens (super-field, Volk Optical, Mentor, OH, USA). BCVA was measured using the Monoyer scale and vision results were quantified in logMar (Holladay & Msee, 2004).

Spectral Domain Ocular coherence tomography (SD-OCT)

SD-OCT data were acquired using a Copernicus SD-OCT (Copernicus, Optopol Technologies, Zawierci, Poland) in 83 SCD eyes (47 HbSS eyes and 36 HbSC eyes). We also examined 52 HbAA eyes.

Multifocal electroretinography (mfERG)

Because of the limited availability of the equipment, only 29 SCD patients (38 HbSS and 20 HbSC eyes) also underwent an mfERG test. The ERG is a diagnostic test ,which measures the electric signal of neural and non-neural cells in the retina in response to a light stimulus. This light stimulus induces changes in the flux of trans-retinal ions (sodium and potassium in particular), generating an electrical response.

MfERG is a non-invasive objective technique that detects functional changes in the central retina. The standard ISCEV mfERG evaluates cone system function over 103 discrete hexagonal retinal areas, within the central 40-50° of the posterior pole centered on the macula (Robson et al., 2018). MfERG values were also measured in 64 controlled eyes using a Metrovision Monpack One mfERG according to the International Society of Clinical Electrophysiology of Vision (ISCEV) guidelines (Donald C. Hood et al., 2012). Full pupil dilation was obtained using 1% tropicamide and 2.5% phenilephrine hydrochloride. The visual stimulator generated a matrix of 16×217 hexagones that were stimulated with independent sequences of flashes. The global ERG was recorded via a unique electrode. Local responses were obtained by computing the inverse correlation between this global ERG response and the stimulation sequence. The typical mfERG response was a biphasic waveform with an initial negative deflection (N1) followed by a positive peak (P1), and then a second negative deflection (N2) (Donald C. Hood et al., 2012). During the examination, we recorded the local responses in real time with an automated identification of the N1, P1 and N2 peaks for each response. 2D and 3D interpolated maps of the amplitude and implicit time of the N1, P1 and N2 peaks of the local responses were obtained. Topographic (3D) response density plots displayed the overall signal strength per unit of area of retina.

Statistical analysis

Statistical analysis was performed using GraphPad Prism (version 6.0 c). The three groups (HbSS, HbSC and HbAA) were compared using a one-way analysis of variance (and Tukey post-hoc tests) or Kruskal-Wallis tests (and Dunn post-hoc tests). Significance level was defined as $p<0.05$. Results are displayed as mean ± SD.

RESULTS.

Among the SCD patients, there were 27 males and 27 females. As expected, Hemoglobin level, red blood cell count (RBC), mean cell volume (MCV) and hematocrit were lower in HbSS than in HbSC patients (Table 1). BVCA of HbSS eyes was statistically lower than that of HbAA eyes (0.04 ± 0.1 log Mar vs 0.0 ± 0.0 log Mar). BVCA of HbSC eyes (0.08±0.4 Log Mar) was not statistically different from HbAA eyes. At slip examination, no patient had retinopathy, nor maculopathy. On the OCT, the mean central macular thickness was lower in HbSS and HbSC eyes than in HbAA eyes (Table 2). Temporal, nasal inner and superior inner were statistically thinner in SCD groups compared to HbAA eyes (Table 2).

Serial changes in mfERG

Tables 2 to 4 illustrate the changes in mfERG amplitudes densities and implicit times from the foveola (<2°) to the periphery. There was a significantly reduction of N1, P1 and N2 response amplitude densities of HbSS eyes compared to HbAA eyes from <2° to >15°. Implicit time response was reduced in the center (<2°).

N1 and P1 response amplitude densities of HbSC eyes were significantly lower than those of HbAA eyes from <2° to >15°. N2 response amplitude densities were also significantly reduced in the center (<2°) and in the periphery (>10°). Responses in implicit time were not reduced in the center (Tables 3-5). N1 implicit time was statistically reduced in HbSC than in HbSS eyes (table 3).

We found no difference between HbSS and HbSC eyes concerning the posterior pole of the retina.

DISCUSSION

Several authors have reported global ERG alterations at the early stages of SCD retinopathy (Bottin et al., 2017; Jung, Chen, Frambach, Rofagha, & Lee, 2016; Peachey et al., 1987). Our study is the first to explore the electrophysiological function of the macula in SCD eyes. It has been previously established that SCD eyes can be affected by maculopathy, which can be demonstrated by OCT (Hoang, Chau, Shahidi, & Lim, 2011; Mathew et al., 2015). However, up to now, no information was available about the electrophysiological function of the macular cells in SCD patients with no ocular anatomical abnormalities or complications.

In the present study, BVCA was significantly reduced in HbSS eyes compared to HbAA eyes but no difference was found between HbSC and HbAA eyes. Macular thickness was lower in both HbSS and HbSC eyes compared to HbAA eyes. Therefore, in contrast to SCD retinopathy which occurs more likely in HbSC eyes, maculopathy seems to be equally frequent in both SCD genotype (Elagouz, Jyothi, Gupta, & Sivaprasad, 2010b; Fox, Dunn, Morris, & Serjeant, 1990). In addition, our study confirms that SCD maculopathy is mainly localized in the temporal areas of the macula on the OCT as it has already been reported (Sanfilippo, Klufas, Sarraf, & Tsui, 2015).

The mfERG analysis demonstrated a reduction of N1, P1 and N2 in the central areas of HbSS and HbSC eyes when compared to controls, which may reflect a cone system dysfunction. Therefore, macular atrophy demonstrated by the OCT may correspond to electrophysiological dysfunctions. The N1 and P1 mfERG may originate from the outer and the inner retinal layer, respectively (D C Hood, 2000; Donald C. Hood et al., 2012; Donald C Hood, Odel, Chen, & Winn, 2003). Our data suggest that SCD macular dysfunction may be a global disorder as both of these peaks were reduced in SCD eyes. We also detected macular electrophysiological alterations in SCD eyes without any OCT alteration (and indeed loss of BVCA) but larger cohorts are needed to confirm this finding.

It has been reported that even though the macular seems to be normal at fundoscopy, angiography may demonstrate microvascular abnormabilities. Indeed, parafoveal acute middle maculopathy has been described in SCD patients (Hussnain et al.,

2017; Ilginis et al., 2015). This abnormality is characterized by an hyper-reflective band at the level of the inner nuclear layer on the SD-OCT, which could reflect ischemia in the deep capillary plexuses (Chen et al., 2015; Ilginis et al., 2015).
Nevertherless, Minvielle et al showed that even if the macula appears to be normal on clinical examination, angiography can reveal microvascular abnormabilities. OCTA results of the present study demonstrated microvascular changes such as rarified and dilated capillaries, foveal avascular zone enlargement, areas of capillary nonperfusion, disruption of the perifoveal anastomotic capillary arcade in all the patients. Most of the abnormalities were observed in the temporal juxtafoveal area, located in the deep capillary plexus (Minvielle et al., 2016). Therefore, in absence of clinical macular abnormalities, we could suspect that the electrophysiological dysfunction observed would reflect perifoveal microvascular changes. Further OCTA studies are warranted to assess this hypothesis.

CONCLUSION

To our knowledge, our study is the first one to describe macular electrophysiological dysfunction in SCD patients. Moreover, we confirm that SCD maculopathy is equally frequent in HbSS and HbSC genotypes.

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TABLES

Table 1: Haematological and haemorheological parameters in our SCD patients.

	HbSS (n=32)	**HbSC(n=22)**
Age(years)	36.6 ± 2.3	42.9 ± 2.8
WBC (10^9 /L)	10.84 ± 2.36	14.34 ± 4.87
RCBs (10^{12} /L)	2.95 ± 0.15	4.21 ± 0.13**
Hb (g/100ml)	8.42 ± 0.22	10.76 ± 0.20**
MCV (fl)	85.5 ± 3.05	69.5 ± 3.5*
Platelets count (10^9/L)	337.1 ± 25.1	285.5 ± 41.5
Lactate dehydrogenase (UI/l)	511.2 ± 28.1	337.6 ± 29.2*
Hct (%)	24.9 ± 0.7	31.5 ± 0.6**

Statistical Difference between the two groups: *p < 0.05; **p < 0.01.

WBC: white blood cell count; RBC: red blood cell count; PLT: platelet count; Hb: haemoglobin concentration; MCV: mean cell volume; Hb: haemoglobin; LDH: lactate dehydrogenase

Table 2: Comparison of macular thickness between HbSS, HbSC and HbAA eyes.

	HbSS (n=47)	HbSC (n=36)	HbAA (n=52)
Fovea (μm)	207.4 ± 45.1**	208.2 ± 46.3**	245.6 ± 68.9
Temporal inner (μm)	267.6 ± 47.3**	267 ± 48.3**	292.9 ± 44.3
Superior inner (μm)	284 ± 43.8**	283.3 ± 44.7**	308.1 ± 3 4.7
Nasal inner (μm)	278.5 ± 41.2**	278.6 ± 41.2**	303.6 ± 32.8
Inferior inner (μm)	278.8 ± 45.8	278 ± 46.6*	297.3 ± 25.1
Temporal outer (μm)	266.8 ± 57.3*	267.2 ± 57.2*	300.9 ± 41.3
Superior outer (μm)	296.7 ± 23.2	297 ± 23.5	308.6 ± 28.7
Nasal outer (μm)	307.8 ± 21.9	308.2 ± 22.42	304.6 ± 20.8
Inferior outer (μm)	300.4 ± 17.2	300.4 ± 17.4	301.3 ± 24.7

Values are expressed as mean ± SD. Statistically different from HbAA (*p<0.05; **p<0.01).

Table 3: Comparison of N1 amplitude densities and implicit times between HbSS, HbSC and HbAA eyes.

	HbSS (n=38)	HbSC (n=20)	HbAA (n=64)
N1<2° (amplitude)	794.3 ± 270.9**	840.3 ± 2942**	1121 ± 413.6
N1 2-5° (amplitude)	497 ± 71.04*	558.6 ± 136.4	636.5 ± 168.3
N1 5-10° (amplitude)	468.1 ± 80.9**	496.9 ± 110.3**	576.7 ± 145.7
N1 10-15°(amplitude)	470.2 ± 83.75**	477.8 ± 100.7*	552.4 ± 124.6
N1>15°(amplitude)	482.7 ± 74.94*	517.6 ± 139	566.9 ± 118.1
N1 <2° (implicit time)	26.41 ± 2.249*	26.85 ± 3.129	27.92 ± 2.438
N1 2-5° (implicit time)	27.2 ± 1.7	27.6 ± 1.1	27.41 ± 1.4
N1 5-10° (implicit time)	27.2 ± 1.1	27.4 ± 0.9	26.8 ± 1.1
N1 10-15° (implicit time)	29.8 ± 7.5	38.5 ± 23.3**$^{\delta}$	28.8 ± 6.3
N1 >15° (implicit time)	27.3 ± 1.8	27.6 ± 1.8	26.9 ± 1.2

Values are expressed as mean ± SD. Statistically different from HbAA (*p<0.05; **p<0.01). Statistically different from HbSS ($^{\delta}$p<0.05)

Table 4: Comparison of P1 amplitude densities and implicit times between HbSS, HbSC and HbAA eyes.

	HbSS (n=38)	HbSC (n=20)	HbAA (n=64)
P1<2° (amplitude)	1337 ± 273.8**	1472 ± 602.8*	1991 ± 646.3
P1 2-5° (amplitude)	1013 ± 183.3**	1093 ± 253.3**	1306 ± 317.3
P1 5-10° (amplitude)	932.3 ± 155.2**	1000 ± 238.4*	1193 ± 259.6
P1 10-15°(amplitude)	969.3 ± 165**	1017 ± 234.5*	1202 ± 251.5
P1>15°(amplitude)	1071 ± 182.7**	1105 ± 321.4	1254 ± 331.1
P1 <2° (implicit time)	50.6 ± 3.1	45.4 ± 5.3	39.7 ± 48.7
P1 2-5° (implicit time)	46.8 ± 1.2	47.4 ± 1.9	46.8 ± 1.8
P1 5-10° (implicit time)	45.5 ± 1.1	45.9 ± 1.4*	45.1 ± 1.4
P1 10-15° (implicit time)	45.3 ± 1.1	45.8 ± 1.5*	44.9 ± 1.4
P1 >15° (implicit time)	45.3 ± 1.2	45.9 ± 1.5*	45 ± 1.5

Values are expressed as mean ± SD. Statistically different from HbAA (*p<0.05; **p<0.01).

Table 5: Comparison of N2 amplitude densities and implicit times between HbSS, HbSC and HbAA eyes.

	HbSS (n=38)	HbSC (n=20)	HbAA (n=64)
N2<2° (amplitude)	1431 ± 378.1**	1657 ± 699.3*	2108 ± 662.3
N2 2-5° (amplitude)	943.9 ± 179**	1020 ± 227	1166 ± 397
N2 5-10° (amplitude)	842.9 ± 17.3*	897.7 ± 210.1	1048 ± 342.4
N2 10-15°(amplitude)	897.5 ± 174.9**	933.3 ± 256.1**	1116 ± 241.9
N2 >15°(amplitude)	994.2 ± 212.7**	988.6 ± 321.5*	1193 ± 311.6
N2 <2° (implicit time)	70.9 ± 2.8	73 ± 4.9	70.8 ± 3.4
N2 2-5° (implicit time)	65.8 ± 1.9	66.2 ± 3.4	65.6 ± 2.6
N2 5-10° (implicit time)	63.1 ± 1.3	64.3 ± 3.1	63.2 ± 1.8
N2 10-15° (implicit time)	63.6 ± 3.5	64.2 ± 3.03	71.9 ± 73.2
N2 >15° (implicit time)	62.8 ± 1.4	64.02 ± 2.9	62.6 ± 1.7

Values are expressed as mean ± SD. Statistically different from HbAA (*p<0.05; **p<0.01).