Electroretinogram Findings in Early-Stage Sickle Cell Retinopathy According to Hemoglobin Type

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Purpose. Although extensive clinical research has been performed on structural analysis of sickle cell (SC) retinopathy, functional aspects have been poorly investigated. Our purpose was to report full-field electroretinogram (ffERG) findings in patients with early SC retinopathy according to the following hemoglobin types: HbSS or HbSC (homozygous or heterozygous mutations, respectively).

Methods. In this monocentric retrospective observational study, patients affected by nonproliferative SC retinopathy were included from November 2014 to April 2016. Patients were separated into one of the following three groups: HbSS, HbSC, and control. All groups underwent full ophthalmologic examination (fundus examination) and ffERG. For SC patients, additional imaging testing was also performed (fluorescein angiography and spectral domain optical coherence tomography).

Results. A total of 24 eyes from 12 patients (6 HbSS and 6 HbSC) and 12 eyes from 6 controls were included. The HbSS group exhibited a dramatic decrease of the b-wave amplitudes for all dark-adapted (DA) ffERG responses when compared with the control group ($P = 0.02$, $P = 0.003$, $P = 0.005$, respectively, after DA 0.01, DA 3.0, and DA 10.0 cd.s.m^{-2} stimulations) and decreased a-wave amplitudes for light-adapted responses ($P = 0.03$ after light-adapted 3.0 cd.s.m^{-2} stimulations). The a-Wave amplitudes were significantly reduced for all dark-adapted and light-adapted responses in HbSC group compared to the control group ($P = 0.03$, $P = 0.01$, $P = 0.03$, respectively, after DA 3.0, DA 10.0, and light-adapted 3.0 cd.s.m^{-2} stimulations). The HbSS+HbSC groups presented decreased a-wave amplitudes for DA and light-adapted responses and decreased b-wave amplitude after DA 0.01 and 10.0 cd.s.m^{-2} stimulations when compared to the control group.

Conclusions. These results could suggest an early involvement of the inner retinal cells in the disease process in HbSS patients and of the outer retinal cells in HbSC patients. This could provide new insights on the pathophysiology of the retinal affection in HbSS/HbSC SC disease.

Keywords: sickle cell retinopathy, full-field ERG, ISCEV protocol, dark-adapted ERG, inner retina

Sickle cell disease is an autosomal recessive affection with mutation of the β gene of the hemoglobin on chromosome 11, leading to abnormal hemoglobin (Hb). The type A is the wild β allelic isoform. The following two main mutations are known: type S (HbS) is secondary to substitution of glutamic acid by valine, and type C (HbC) is secondary to substitution of glutamic acid by lysine.[1] Clinical manifestations occur with homozygous HbSS and double heterozygous HbSC patients. Heterozygous HbAS patients are usually asymptomatic and do not need any ophthalmologic screening. In the SS and SC types, modified sickled red blood cells interact with vascular endothelium, vasoactive factors, and other blood cells, leading to acute vaso-occlusion and chronic tissue ischemia, affecting various organs.[2] All ocular structures may be involved by the process,[3–5] but the most common complication is the sickle cell retinopathy.[6,7] Sickle cell peripheral retinopathy classification contains five stages. It was established in 1971 by Goldberg et al. based on fundus and fluorescein angiography (FA)

findings;[7–11] it describes the peripheral vascular modifications and their neovascular consequences.[12,13]

FA detects early retinal abnormalities, such as capillary loss secondary to capillary occlusions in the peripheral retina and in the foveal zone.[14,15] Many cases of capillary reperfusion have been described and provide arguments for the aggregation of erythrocytes rather than thrombosis. This vascular modification occurs in the peripheral retina but also in the macular capillaries. HbSC forms are associated with more severe retinopathy including neovascularization,[16–19] whereas HbSS forms are associated with more severe systemic complications.[16,19,20] Recent optical coherence tomography findings demonstrate retinal thinning of the temporal zone of the macula, predominantly in the inner retina layers in patients affected with early sickle cell retinopathy stages.[21,22] To our knowledge, only one study in 1987 evaluates the inner retinal function in sickle cell patients and finds global retinal dysfunction in proliferative sickle cell retinopathy, as it is observed in other chronic retinal ischemic diseases.[23] The present study investigated if full-field electroretinogram (ffERG) could be affected in the early stages of sickle cell retinopathy in HbSS and HbSC patients.

Methods

Study Design

This retrospective observational monocentric study was performed at the ophthalmology department of the Intercommunal Hospital of Creteil, France, between November 2014 and April 2016. All patients were referred for an annual ocular fundus examination due to their sickle cell disease.

Inclusion and Exclusion Criteria

Inclusion criteria for the for HbSS and HbSC groups were the following: 18 years old or older, lack of visual complaints, and best-corrected visual acuity better or equal to 20/25 with sickle cell retinopathy stage 0 (normal fundus and FA), stage 1 (peripheral arterial occlusions), or stage 2 (peripheral arteriovenous anastomosis) according to the Goldberg classification. Exclusion criteria were the following: visual acuity worse than 20/25, proliferative sickle cell retinopathy (stages 3, 4, or 5), previous treatment with vitreoretinal surgery, intra-vitreal injection or laser treatment, cloudy ocular media, other occlusive retinopathies (e.g., diabetic retinopathy and venous occlusions), and other ocular diseases such as retinal and macular dystrophies.

Inclusion criteria for the control group were the following: 18 years old or older, visual acuity better or equal to 20/25, and normal ophthalmologic examination. Exclusion criteria were sickle cell disease, diabetes, any retinal disorders, and any previous treatment with vitreoretinal surgery, intra-vitreal injection, or laser treatment.

Visual Acuity

Visual acuity was measured with the Monoyer chart by an independent observer[24] and was converted into Snellen acuity.[25]

Full-Field Electroretinogram

The ffERGs were performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) 2015 standards.[26] Accordingly, ffERGs were recorded using scleral monopolar disposable active electrodes (Laboratoire Dencott, Paris, France) under topical anesthesia (oxybuprocaine), two reference gold cup electrodes were placed at the lateral canthi and a ground gold cup electrode was placed on the forehead after proper face cleaning. The full-field white stimulation (light-emitting diode flash) was generated by METROVISION Pack Mon Color (Metrovision, Lille, France). The dark-adapted 0.01 ERG (DA 0.01), 3.0 ERG (DA 3.0), and 10.0 ERG (DA 10.0) were recorded after 20 minutes of dark adaptation with a flash luminance of 0.01, 3.0, and 10.0 cd.s.m^{-2}, respectively. Immediately after recording the dark-adapted ERGs, the patients were light adapted for 10 minutes to a background of 30 cd.s.m^{-2}. The light-adapted 3.0 ERG (LA 3.0) was then recorded with a flash luminance of 3.0 cd.s.m^{-2}, and light-adapted Flicker 30 Hertz (Fl30 Hz) was finally tested after the high-frequency stimulation (30/s) of 3.0 cd.s.m^{-2}. The amplitudes and the peak times of the a- and b-waves were measured for each response. The ffERGs measurements were all recorded between 9:30 AM and 11:30 AM to avoid circadian variations.

Table 1. Clinical Characteristics of the Patients

Patient	Sex	Age	Hb Type	Eye	Side	Snellen VA	Stage of Retinopathy
1	F	56	SS	1	R	20/20	1
				2	L	20/20	2
2	M	20	SS	3	R	20/25	1
				4	L	20/25	1
3	F	35	SS	5	R	20/20	2
				6	L	20/20	1
4	M	34	SS	7	R	20/20	1
				8	L	20/20	1
5	M	23	SS	9	R	20/20	1
				10	L	20/20	1
6	F	33	SS	11	R	20/20	1
				12	L	20/20	1
7	M	26	SC	13	R	20/20	2
				14	L	20/20	2
8	F	25	SC	15	R	20/25	1
				16	L	20/25	1
9	F	31	SC	17	R	20/20	1
				18	L	20/20	1
10	F	22	SC	19	R	20/20	2
				20	L	20/20	2
11	M	61	SC	21	R	20/20	2
				22	L	20/20	2
12	M	18	SC	23	R	20/20	2
				24	L	20/20	2

Hb, hemoglobinopathy; SS, double homozygous mutation; SC, double heterozygous mutation; VA, visual acuity; F, female; M, male; R, right; L, left.

ERG Data Analysis

The dark-adapted and light-adapted ffERG response amplitudes and implicit times were measured according to ISCEV standards.[26]

The ffERG responses were compared in the following groups: HbSS patients, HbSC patients, and an aged-matched control group without sickle cell disease.

The primary study endpoint was defined as b/a ratio for DA 3.0 at 10.0 comparison between HbSS and HbSC patients.

Statistical Analysis

Qualitative variables were described in percentages, and quantitative variables were described using medians and first and third quartiles. Chi square or Fisher exact tests were used to compare qualitative variables.

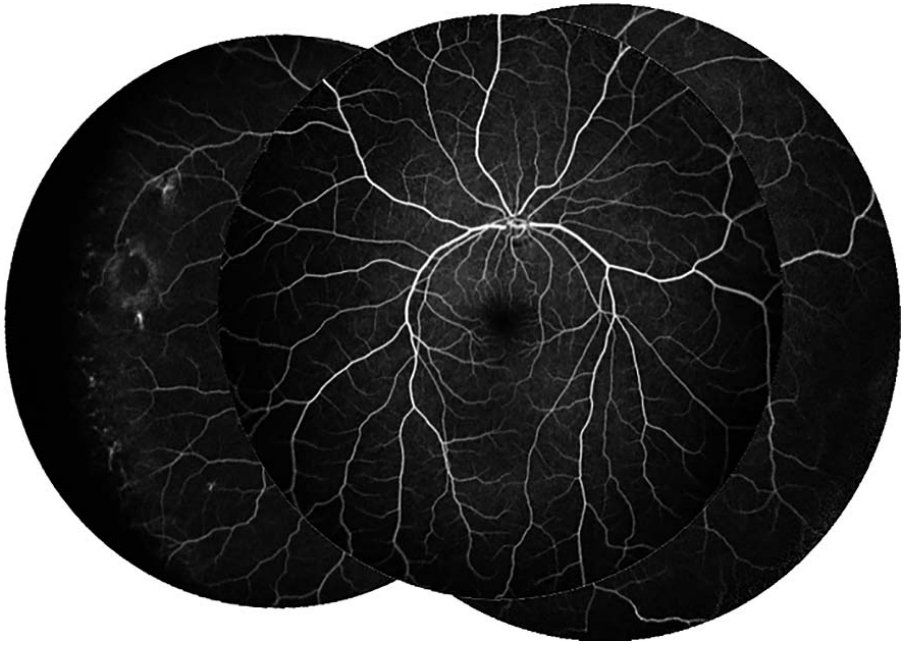

Figure 1. Peripheral retina fluorescein angiography imaging of one HbSC sickle cell patient included in the study (patient 7). Sickle cell retinopathy stage 2 with arteriolar peripheral occlusion and arteriovenous anastomosis on 105° magnification. Note the black sunburst with pigmentary changes evident as hypofluorescent areas (amount of pigment clumping) and hyperfluorescent areas (atrophy).

Variations of ffERG responses between groups (HbSS, HbSC, and control) were analyzed using mixed linear regression models with an individual eye as the unit of analysis. This model allowed us to take into account data from both eyes and their intraindividual correlation. Differences in each ffERG response between groups were assessed independently using a univariate model. For all analyses, associations were considered significant at $P < 0.05$. All statistical analyses were performed using SAS software (SAS, version 9.4; SAS Institute Inc., Cary, NC, USA).

This study followed the Declaration of Helsinki that is the current French legislation and was approved by the ethic committee of the Fédération France Macula.

Results

In this study, 24 eyes from 12 patients aged 18 to 61 years were included (mean 32 years ± 13.6 SD) with stages 1 or 2 sickle cell retinopathy (Table 1). The absence of retinal proliferative lesion was confirmed using FA (Fig. 1). Of interest, for 6 of 12 patients, the ultra-wild field angle was used to assess the absence of proliferative lesions. Retinopathy stages (1 or 2) repartition did not differ between groups ($P = 0.6$).

Table 2. Amplitudes in μV of the Dark-Adapted and Light-Adapted ffERG Responses*

Group†	DA 0.01 bw	DA 3.0 aw	DA 3.0 bw	DA 3.0 b/a	SOPs 3.0	DA 10.0 aw	DA 10.0 bw	DA 10.0 b/a	LA 3.0 aw	LA 3.0 bw	Fl30 Hz
HbSS and HbSC											
Total median	184	214	334.5	1.6	120	253.5	368.5	1.42	37.1	119.5	86.6
Q1-Q3	118-211.5	172.5-241.5	276-391.5	1.3-2	92-163.4	228.5-303	301.9-437	1.15-1.55	33.2-40.3	109-132	76.3-107
SS median	178.5	217.5	287.5	1.3	92	267	321.5	1.2	38	119.5	86.6
Q1-Q3	137-213.5	202.5-239	263.2-365.5	1.1-1.6	76.2-134.3	238.5-313.5	285.4-377.5	0.97-1.4	35-39.9	91.4-131	75-106.4
SC median	188.5	194.5	355.5	2.0	141.5	241.5	400.5	1.55	35.1	119	85.6
Q1-Q3	114-211	162.5-241.5	328.5-462.5	1.67-2.25	119.3-212.7	214.5-282	363.5-467.5	1.45-1.75	29.4-45.5	112.5-133	76.3-126.5
P (SS vs. SC)‡	0.92	0.21	0.07	0.002*	0.07	0.15	0.07	0.02*	0.92	0.52	0.15
Control											
Median	220	282	418	1.5	135.9	345	455	1.3	45.4	139.2	116
Q1-Q3	199-266	219-306	391-444	1.4-2	115-199.2	282-402	411-505	1.1-1.5	39.3-53.7	119-162.4	101.3-164
P (vs. SS)‡	0.02§	0.14	0.003§	0.09	0.09	0.12	0.005§	0.56	0.03§	0.09	0.01§
P (vs. SC)‡	0.18	0.03§	0.35	0.08	0.73	0.01§	0.26	0.10	0.03§	0.29	0.14
P (vs. SS+SC)‡	0.04§	0.04§	0.06	0.91	0.15	0.02§	0.04§	0.74	0.01§	0.11	0.02§

a-wave component (aw), b-wave component (bw), b/a-ratio in dark-adapted (DA), light-adapted (LA) ffERGs, and the sum of DA 3.0 oscillatory potentials (SOPs) in μV.

* Intensities in cd.s.m^{-2}.

† Medians and first and third (Q1-Q3) quartiles from the HbSS, HbSC, and control groups.

‡ *P* was assessed using mixed linear regression models adjusted for age.

§ $P < 0.05$.

Table 3. Implicit Times in ms of the Dark-Adapted and Light-Adapted ffERG Responses*

Group†	DA 0.01 bw	DA 3.0 aw	DA 3.0 bw	DA 10.0 aw	DA 10.0 bw	LA 10.0 aw	LA 10.0 bw	Fl30 Hz
HbSS and HbSC								
Total median	73.5	17.7	41.2	15.1	36.8	16.8	32.4	33.7
Total Q1–Q3	71.3–75.7	16.8–18.2	36.8–42	14.2–16	34.5–45.6	15.9–17.7	31.9–34.1	33.6–33.7
SS median	76.6	17.7	39.4	15.1	35.9	16.8	31.9	33.7
SS Q1–Q3	72.6–80.6	16.8–22.6	36.8–41.6	14.7–15.9	34.5–39.4	16.4–17.7	31.9–33.2	31.7–33.7
SC median	73.1	17.7	41.6	15.1	39.8	16.8	33.2	33.7
SC Q1–Q3	69.5–75.7	16.8–18.2	37.2–42.1	14.2–15.9	34.5–45.6	15.9–17.7	31.9–34.1	33.6–33.8
P (SS vs. SC)‡	0.85	0.37	0.38	0.74	0.20	0.59	0.78	0.19
Control								
Median	77.9	23.0	46.0	15.1	38.1	16.8	32.8	33.7
Q1–Q3	72.6–87.7	22.1–23.9	39–48.7	14.2–23	37.2–39.8	15.9–16.8	31.9–33.6	33.7–34.6
P (vs. SS+SC)‡	0.42	0.02§	0.045§	0.26	0.84	0.63	0.50	0.70

a-wave component (aw) and b-wave component (bw) in dark-adapted (DA) and light-adapted (LA) ffERGs.

* Intensities in cd.s.m^{-2}.

† Medians from the HbSS, HbSC, and control groups.

‡ *P* was assessed using mixed linear regression models adjusted for age.

§ $P < 0.05$.

Six aged-matched patients without hemoglobinopathy were also enrolled in the control group with a mean age of 35 years (± 11 SD).

The ffERG results are presented in Tables 2 (amplitudes) and 3 (implicit times). ERG illustrative examples are reported in Figure 2. The following significant modifications were found for amplitudes between the three groups:

- patients from the HbSS+HbSC groups exhibited reduced a-wave amplitudes for all dark-adapted and light-adapted ffERG responses, reduced Flicker 30 Hz amplitudes, and reduced b-wave amplitudes for DA 0.01 and DA 10.0 responses when compared with the control group.
- patients from the HbSC group showed reduced a-wave amplitudes for all dark-adapted and light-adapted ffERG responses when compared with the control group.
- patients from the HbSS group showed reduced a-wave amplitudes only for light-adapted ffERG responses, reduced Flicker 30 Hz amplitudes, and a dramatic

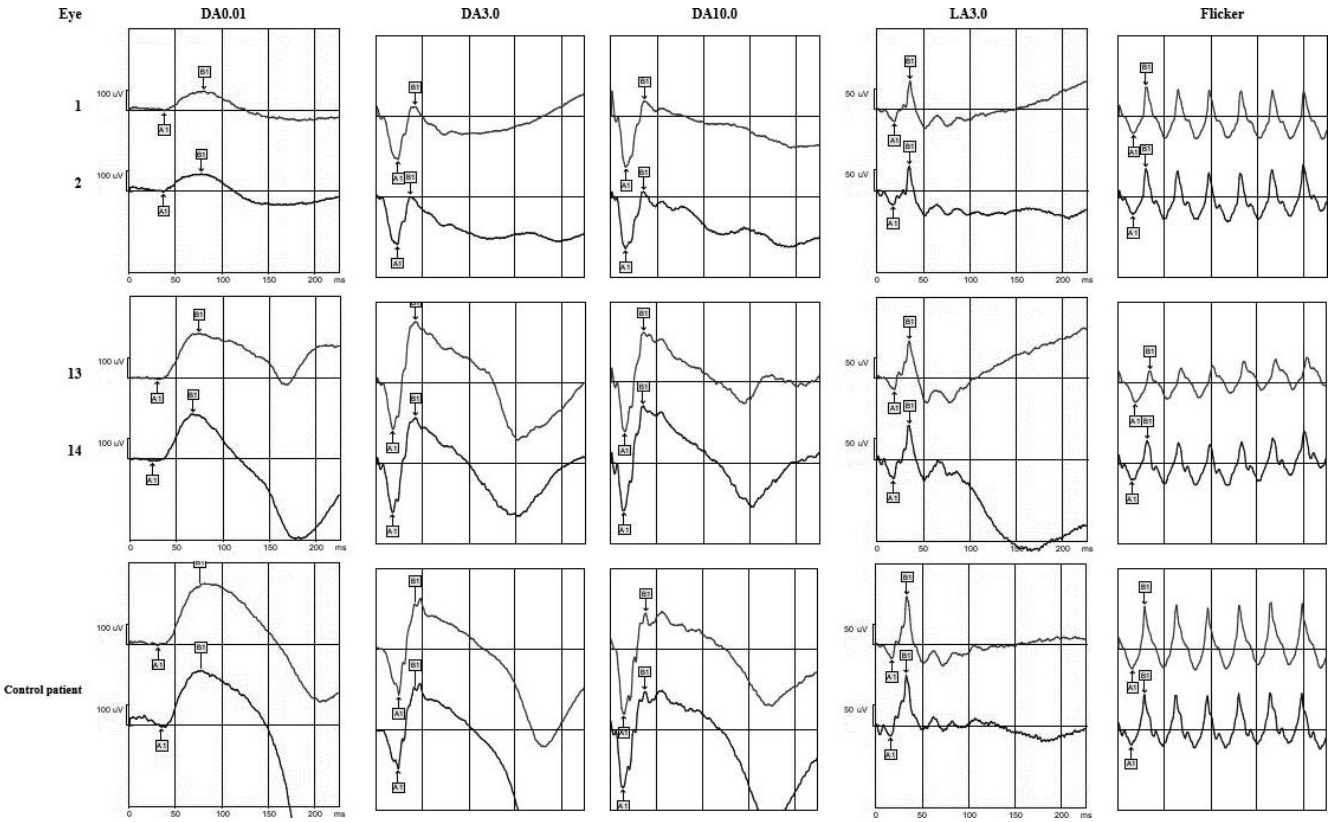

Figure 2. ffERG responses from one HbSS sickle cell patient (eyes 1 and 2), one HbSC sickle cell patient (eyes 13 and 14), and one control patient. Recordings conform to ISCEV standards. Note reduced amplitudes in the HbSS sickle cell patient (eyes 1 and 2) for the DA 3.0 and DA 10.0 cd.s.m^{-2} stimulations. DA, dark adapted; LA, light adapted.

decrease of b-wave amplitudes for all dark-adapted ffERG responses when compared with the control group.

Discussion

The present study reports dark-adapted and light-adapted ffERG changes in patients with early sickle cell retinopathy (stages 1 or 2). The HbSS group exhibited abnormal dark-adapted ffERG responses with a dramatic reduction of b-wave amplitudes for all scotopic responses, whereas the HbSC group exhibited abnormal dark-adapted and light-adapted ffERG responses with decreased a-wave amplitudes. To the best of our knowledge, there is no previous report on electrophysiologic modifications in HbSS and HbSC patients occurring so early in the evolution of sickle cell retinopathy, except in the case of deferoxamine treatment, as it can influence ffERG results.[27,28] The latter does not apply to our patient population, as none of the patients had ever received deferoxamine.

The significantly decreased a-wave amplitude found in the ffERG responses of the HbSC patients (although b-wave amplitudes were not significantly decreased, there was also a tendency toward smaller b-waves) are likely related to outer retina damage, as seen in chronic retinal ischemia.[29,30] In the HbSS patients, the significant decrease of the dark-adapted b-wave amplitudes was not associated with a significant a-wave reduction, suggesting inner retina dysfunction.[31,32] The trend toward reduced oscillatory potentials is another strong argument for this latter hypothesis in HbSS patients.[33] Those results are puzzling compared to what is commonly described in sickle cell vascular retinopathy patients. Although patients affected with the HbSS form classically exhibit less severe retinopathies and less neovascular complications, when compared with the HbSC form, we found a surprising early electrophysiologic alteration in the HbSS subgroup.

Recent imaging studies demonstrated significant thinning of the inner retina and vascular abnormalities in the superficial and deep capillary plexus to be common and early features in sickle cell patients, even before severe peripheral sickle cell retinopathy.[22,34–36] This thinning seemed to be more frequent in the HbSS subtype.[22] This would be consistent with our finding of significant inner retinal dysfunction in HbSS patients. Unfortunately, none of these studies reported retinal electrophysiology results or extra-macular retinal architecture. However, in 1987, Peachey et al.[23] studied retinal function in sickle cell disease patients. The authors reported scotopic and photopic ffERG response abnormalities from sickle cell patients with peripheral retinal neovascularization. The amplitudes of a- and b-waves from the scotopic and photopic responses were reduced and the authors concluded that this was the result of a photoreceptor dysfunction, supposedly related to severe choroidal ischemia. It was hypothesized that the reduction of b-wave amplitudes could mirror the reduction of the a-wave amplitudes or could be related to affected neuroglial pathway. The latter differences reported compared with our results could be potentially be explained by differences in the ERG methods (pre-ISCEV standardization era) and possible differences in the study population (unknown proportion of HbSS and HbSC patients).

The main limitation of this study is the small number of patients included. Larger studies are needed to support our hypothesis. It would also be of interest to compare ffERG results to optical coherence tomography–angiography findings; however, current systems mostly cover the area of the central retina, whereas ffERG collects responses from the whole retina. Evaluating the ffERG responses of sickle cell patients would help to determine possible correlations between global retinal function and the severity of vascular systemic complications.

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