Electrorétinogramme multifocal et atteinte anatomofonctionelle dans la maladie de Birdshot

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Multifocal electroretinogram in birdshot chorioretinopathy

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Running title: mfERG and Birdshot chorioretinopathy

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ABSTRACT

Purpose: to characterize multifocal ERG parameters in patients with birdshot disease (BSCR)

Methods: The mfERG was prospectively evaluated in 28 patients using Vision Monitor, Métrovision™, France (2006-2011). One eye was randomized for the statistical analysis. The correlations between mfERG parameters and visual acuity, visual field, color vision, fluorescein and indocyanine green angiography, and optical coherence tomography were studied.
Twenty seven healthy subjects were matched to BSCR patients for age, axial length and lens status.

Results: The mean age of the patients was 56.7 ±9.7 years, and 46.4% of the patients were male. BSCR eyes differed significantly from healthy eyes by a decrease in mean RMS (- 24.7%), amplitude of P1 (-17.3%), N2 (-27.5%), and P1/N1 ratio (-26.3%) and an increase in implicit time of N1 (8.7%), P1 (5.4%). An effect of the degree of eccentricity (5 zones, figure 1) was found for RMS ($p<0.001$), amplitude of P1 ($p<0.001$) and N2 ($p<0.001$), and implicit times of P1 ($p<0.001$). RMS, P1N1 ratio, amplitudes of P1 and N2; implicit times of P1 and N1 were significantly correlated with VA, mean defect, foveal threshold, and colour vision score.

When the central zone (5°: ring 1+2) was considered , RMS, amplitudes of P1, N1 and N2, and not implicit time, were significantly associated with VA, and foveal threshold ; RMS, amplitudes of N1 and P1 were significantly correlated with the FA and ICG score.

Conclusion: Amplitudes and implicit times of mfERG parameters are impaired in BSCR patients and are well correlated with other anatomical and functional tests. The contribution of mfERG for the therapeutic management of patients remains to be determined.

INTRODUCTION:

Birdshot chorioretinopathy (BSCR) is a rare form of posterior uveitis, representing 0.6%-1.5% of patients consulting in reference centers for uveitis, and 6%-7% of cases of posterior uveitis,[1] more commonly in the third to the sixth decades.[2] Whereas diagnostic criteria may help the clinician to recognize this disease,[3] its clinical evolution is still poorly understood and variable among patients.[1] Long term complications which may explain the visual deterioration include macular edema, choroidal neovascularization and progressive chorioretinal atrophy. The care of patients with BSCR is challenging because of its relentless chronic nature.[2,4,5]

The measurement of visual acuity (VA) alone is insufficient to monitor the disease [6,7] and functional monitoring of patients can be facilitated through the exploration of colour vision[8] and/or visual field.[9] Recent studies showed that full field electroretinogramm (ERG) can also be of value to evaluate the disease progression. [7,10-13]

The multifocal electroretinogram (mfERG) is a non invasive method for objectively measuring retinal function within localized patches especially the central retina, i.e. 40 to 50° around the central foveal area.[14] Whereas it reflects the activity of cones under light-adapted conditions, and provides a track for each small area of the retina divided (61 areas in general to the posterior pole), this functional test could be useful for the diagnosis of retinal dysfunction and then the downward course of the disease, especially outside the macula. The mfERG is primarily used in the clinic to localize damage spatially, so that variations in the topographic array of signals are more important than absolute signal size.[15] The second advantage is that the mfERG provides spatial information not readily available in the full-field ERG in diseases of

the outer retina and help diferentiate diseases that affect the outer retina from those that affect the ganglion cell or optic nerve.[15] Finally, the mfERG is useful to follow the effects of clinical intervention, such as in uveitis,[16,17] retinal detachment, macular diabetic edema, and macular hole surgery.[18] Only one study addressed the contribution of mfERG in 7 patients with BSCR with a special attention to eyes with macula atrophy.[19]

The aim of this prospective study was to describe the baseline parameters of mfERG in a longitudinal cohort of 28 patients with BSCR, as compared to a population of age-matched healthy subjects and to correlate them with the functional (VA, colour vision, visual field) and anatomical (fluorescein and indocyanine green angiography, optical coherence tomography) data.

MATERIALS AND METHODS:

The patients with BSCR disease were included consecutively from 2006 to 2011 as part of a longitudinal cohort in a tertiary center. The data analyzed in this report correspond to the first examination of the patient in our center. This study followed the Declaration of Helsinki guidelines for research involving human subjects and was approved by the local Institutional Review Board (#5891). All patients met criteria for diagnosis of BSCR,[3] were older than 18 years, had no medical contraindications for performing angiography, and gave oral and written consent for conducting all ophthalmological exams. Each patient had a standardized prospectively defined examination including demographic information, medical history, and ophthalmological examination. Functional testing included measurement of VA

(Monoyer chart, converted to LogMAR),[20] a 30-2 Swedish Interactive Threshold Algorithm standard program on the Humphrey Field Analyser (Carl Zeiss Meditec Inc.™, Dublin, CA), and a Lanthony desaturated Panel D-15 test for colour vision under standardized conditions of ambient illumination, with calculation of the total score of error.[21,22] All patients had a reliable visual field test, defined as a false positive error of less than 15%, a false negative error of less than 15% and a fixation loss less than 20%. Quality of life (QoL) was estimated from the French translation if the NEI Visual function Questionnaire (VFQ-25).[23]

Anatomical testing were based on a fluorescein and indocyanine green angiography (Heidelberg™, Germany) and an optical coherence tomography (OCT, Stratus®, 2005 Carl Zeiss Meditec Inc™) assessing macular thickness at the fovea, the foveal volume, the presence or absence of epi-macular membrane. Macular edema was defined as a central subfield thickness of more than 250 µm or a center point thickness if necessary (to correct errors in defining outer and inner retinal boundaries). Macular atrophy was defined by a macular thickness less than or equal to 130 µm using the Stratus OCT.[24] Angiographic data were quantitatively evaluated using a score established by the Angiography for Uveitis scoring Working Group (ASUWOG).[25] Vitreous inflammatory reactions were quantified as described by Nussemblatt and associates.[26] Cataract was quantified using the LOCSIII graduation.[27] Retinal vasculitis was defined as fluorescein staining of any retinal vessels proximal to the third bifurcation.[6]

A mfERG (Vision Monitor, Métrovision™, France) was performed according to the ISCEV protocol [15] using a 61-hexagon strategy and scaled hexagons. Stimulations were generated on a cathode ray tube monitor with a 120 Hz frame rate. The luminance of white hexagons was 400 cd/m^2 and that of black hexagons less

than 4 cd/m2. Dark frames were inserted after the white frames to achieve a stimulus frequency of 18 Hz. The surround luminance was set to 30 cd/m^2. The stimulus was calibrated following ISCEV guidelines.[28]

After pupil dilation using phenylephrine 5 % (Faure™, France) and tropicamide (Thea™, France), patient positioning, good fixation, best optical correction for near vision, and constant moderate room light for at least 15 min were ensured for each patient. Care was taken to eliminate any reflections from lens surfaces and to keep any bright light sources out of the patient's direct view. The first-order kernel mfERG responses were analyzed. Individual mfERG responses for the hexagons were grouped into five concentric rings centered on the fovea for analysis (< 2, 2-5, 5-10, 10-15 and >15°). Mathematically the first-order kernel is obtained by adding all the records that follow the presentation of a white hexagon (luminance of 400 cd/m^2) and substracting all the records that follow a black hexagon. We refer to response density (nV/deg^2) as amplitude. The following data were collected: the RMS (root-mean-square values), implicit time (IT) and amplitude (AMP) of N1, P1, and N2 waves, and the N1/P1 ratio. The N1 response was measured from the starting baseline to the base of the N1 trough; the P1 response amplitude was measured from the N1 trough to the P1 peak. Implicit time was measured from the start of the trace to the trough or peak.

A cohort of 100 healthy subjects was previously recorded in order to define normal values of our mfERG. For the purpose of this study, 27 healthy subjects were matched to BSCR patients for age, axial length and lens status.

Statistical analysis:

One eye was randomized for each patient. Normality of parameters was determined by the Shapiro-Wilks test. When the normal distribution was demonstrated, the quantitative parameters were described by their mean and standard deviation (SD). Otherwise, they were described by the median and 25th and 75th percentiles. The qualitative parameters are expressed in numbers and percentages. The comparison of quantitative parameters between groups was performed by Student's t test or a non-parametric test (Mann-Whitney or Kruskal-Wallis test) according the normality and homogeneity of variance. Two-way ANOVA with interaction term randomisation group * zone was used to compare mfERG parameters by concentric rings (5 zones). In order to avoid alpha risk inflation, due to multiple comparisons, and to have an acceptable type 1 error rate, the Bonferroni method for adjusting p-values was used. The correlation between quality parameters was studied using a test of Pearson or Spearman if necessary. Statistical analysis was performed using the SPSS program (Statistical Package for the Social Sciences 17.0 program for Windows. Chicago. IL. USA). The $p < 0.05$ level was considered to define the significance of the statistical tests.

RESULTS:

This cohort included 28 patients who had a baseline examination between 2006 and 2011. The mean age of the series was 56.7 ±9.7 years, and 46.4% of the patients were male. At baseline, patients were under systemic steroid treatment in 53.6% of the cases, cyclosporine in 7%, intravenous immunoglobulin in 7%, and/or had subtenon injection of triamcinolone in 10.7%. Absence of treatment was noted in 42.8% of the cases.

Eye Selection for data analysis.

After randomization of eyes, one eye (group 1) was selected for further analysis. No significant difference for anatomical and functional parameters was found between the random selected group of eyes (group 1) and the group 2 (table 1).

Baseline characteristics of eyes of patients with Birdshot chorioretinopathy.

Ocular data of eyes with BSCR (group 1) are shown in **table 1.** Visual acuity was greater or equal to 20/40 in 78% of the eyes and vision colour was abnormal in 55% of the cases. Angiographic data showed posterior vasculitis in 50% of the eyes, epiretinal membranes in 35%. The macula was considered atrophic in 3% of the eyes and thickened in 43%.

mfERG recordings (table 2) showed that BSCR eyes differed significantly from healthy eyes by a decrease in mean RMS (- 24.7%), amplitude of P1 (-17.3%), N2 (-27.5%), and P1/N1 ratio (-26.3%) and an increase in implicit time of N1 (8.7%) and P1 (5.4%). An effect of the degree of eccentricity (5 zones, figure 1) was found for RMS ($p<0.001$), amplitude of P1 ($p<0.001$) and N2 ($p<0.001$), and implicit times of P1 ($p<0.001$).

Correlations between mfERG parameters and functional data in eyes with BSCR (table 3).

Correlations between previously abnormal identified mfERG parameters and functional testing are summarized in **table 3**. In brief, RMS, P1N1 ratio, amplitudes of P1, N1 and N2; implicit times of P1 and N1 were significantly correlated with VA, MD, foveal threshold, and colour vision score.

The composite score of QoL was 69.2±13.5. QoL subscale scores are reported in **table 5** and were considered abnormal for general health, general vision, near vision, limitation of activities, and depression.

The composite score was not associated with mfERG parameters but significantly correlated to foveal threshold (r=0.42, p=0.03) and VA (r=-0.46 p=0.02).

When the central zone (5°: ring 1 +2) was considere d, RMS, amplitudes of P1, N1 and N2, and not implicit time, were significantly associated with VA, and foveal threshold (Table 3B). Only RMS and amplitude of P1 were significantly associated with the colour vision score.

Correlations between mfERG parameters and anatomical data in eyes with BSCR (table 4).

Correlations between previously abnormal identified mfERG parameters and anatomical examinations are summarized in **table 4.** FA score was significantly correlated to amplitudes of N1 and N2, and implicit time of N1. There was a trend for the correlation with RMS, amplitude or implicit time of P1. ICG score was significantly associated with RMS, amplitude of N2, N1 and implicit time of P1. There was a trend for the correlation with amplitude of P1. In the central zone (5°, ring 1+2), RMS, amplitudes of N1 and P1 were significantly correlated with the FA and ICG score

(Table 4B). We found no relationship between mfERG parameters of these two central rings and macular thickness.

Implicit times of N1, P1 and N2 were positively correlated with foveal thickness. No significant difference was found for mfERG parameters according to the presence of absence of vasculitis.

Table 1: Comparisons of random eyes at the initial visit (supplementary material). Group 1 was considered for further analysis. Results are expressed as mean ± standard deviation or median [25th, 75th percentiles]. P values were obtained using Chi2 test, Student test, or Mann-Whitney test.

	Group 1 (n=28)	Group 2 (n=28)	P value
Visual acuity (Logmar)	0.1 [0 ; 0.3]	0.1 [0 ; 0.25]	0.84
20/15 – 20/40 20/50 – 20-160 20/200 - LP	22/28 (78.6%) 4/28 (14.3%) 2/28 (7.1%)	22/28 (78.6%) 4/28 (14.3%) 2/28 (7.1%)	0.99
Foveal threshold (dB)	32.5 [30 ; 35]	33 [30.5 ; 35]	0.59
Mean defect (dB)	-5.03 [-9.6 ; -3.2]	-5.2 [-8.9 ; -3.3]	0.98
Colour vision • total score error • normal • abnormal	230 [108 ; 356] 15/27 (55.6%) 12/27 (44.4%)	222 [80 ; 338] 9/27 (33.3%) 18/27 (66.7%)	0.61 0.40
Score of fluorescein angiography*	3 [1.5 ; 5.5]	3 [1 ; 5.5]	0.95
Retinal vascular staining and/or leakage at 5-10 mins	14/28 (50%)	13/28 (46.4%)	0.79
Score of indocyanine green angiography*	5.1 ± 2.5	5.2 ± 2.2	0.89
Foveal thickness (µm)	243.5 [198 ; 282.5]	204 [177 ; 262]	0.17
Macular thickness • atrophy (< 130 µm) • normal (130-250 µm) • edema (> 250 µm)	 1 (3.6%) 15 (53.6%) 12 (42.9%)	 1 (3.6%) 17 (60.7%) 10 (35.7%)	0.889
Macular Volume	6.89 [6.32 ; 7.74]	6.79 [6.07 ; 8.37]	0.63
Epiretinal membrane	10 (35.7%)	8 (28.6%)	0.57

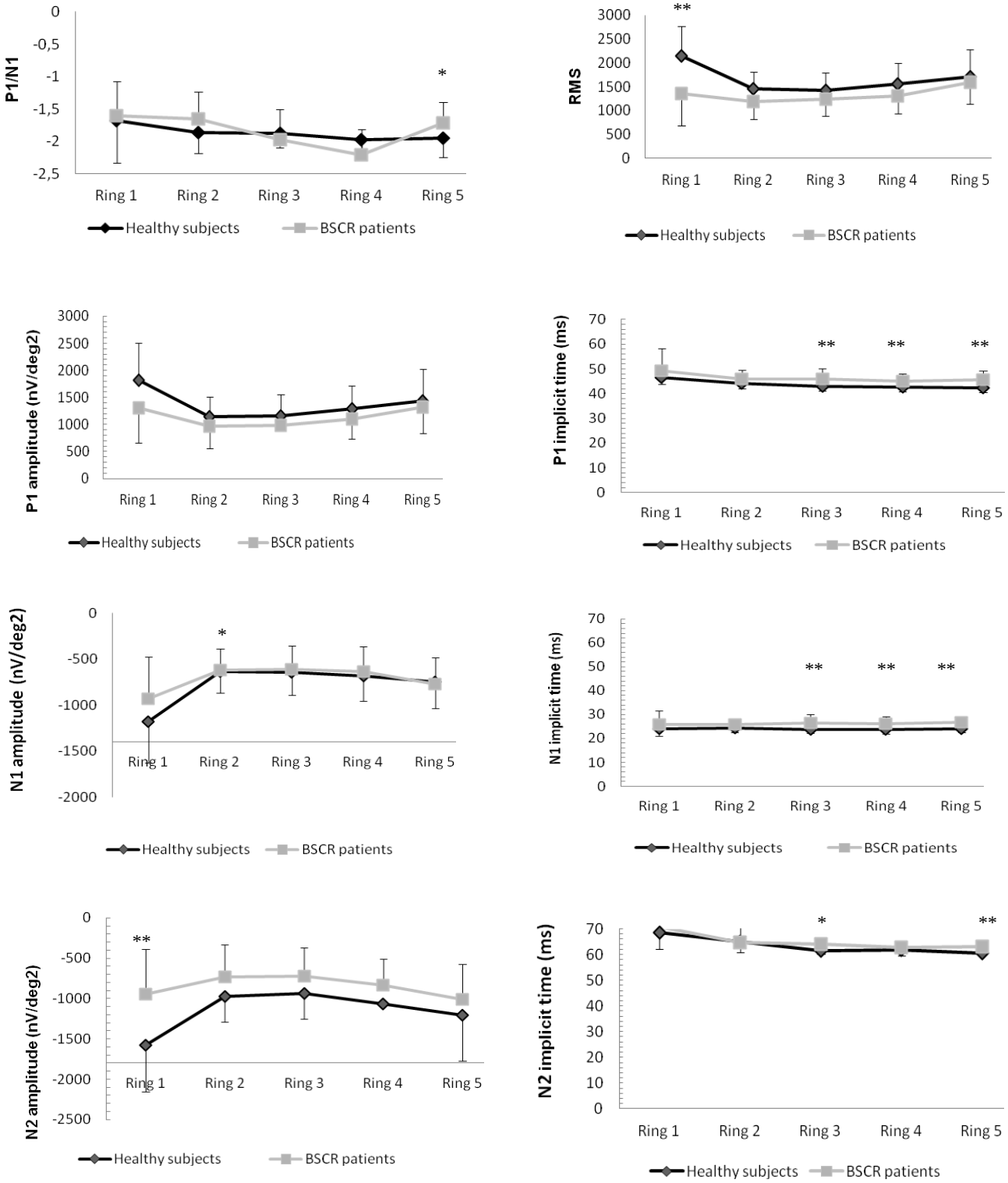
*The total maximum score of fluorescein angiography is 40 and that of ICGA is 20. Absence of inflammation gives a score of 0.[25] LP: light perception

Table 2: Electrophysiological data of 28 eyes with birdshot disease and comparison with 27 healthy eyes. IT = Implicit time, AMP = Amplitude

	Healthy group	BSCR group	p value
Age	57.4 ±10.3	56.6 ±9.6	0.9
Gender - male - female	 12 (44.4%) 15 (55.6%)	 12 (42.9%) 16 (56.4%)	0.9
Laterality - right - left	 15 (55.6%) 12 (44.4%)	 14 (50%) 14 (50%)	0.7
Mean RMS	1661.0 ± 413.2	1249.6 ± 486.3	0.003
Mean AMP N1 (nV/deg^2)	-769.2 ± 266.9	-636.0 ± 267.0	0.1
Mean IT N1 (msec)	24.0 ± 1.6	26.3 ± 2.4	0.001
Mean AMP P1 (nV/deg^2)	1366.7 ± 434.4	1028.6 ± 494.2	0.01
Mean IT P1 (msec)	43.7 ± 1.6	46.2 ± 3.4	0.002
Mean AMP N2 (nV/deg^2)	-1144.0 ± 359.0	-829.2 ± 371.3	0.004
Mean IT N2 (msec)	63.5± 2.6	63.5 ± 5.1	0.4
Mean P1/N1 ratio	-1.9 ± 0.3	-1.4 ± 0.9	0.001

<u>Figure 1</u>: Electrophysiological data according the degree of excentricity of 28 eyes with birdshot disease and 27 healthy eyes.

**p-adjust <0.05 **p-adjust < 0.01*



<u>Table 3</u>: Correlations between functional ocular data at baseline and mfERG parameters. IT = Implicit time, AMP = Amplitude

3A: for all rings

Global Zone	**VA**	p value	**Foveal threshold**	p value	**Colour Vision Score**	p value
RMS	-0.45	**0.02**	0,39	**0.04**	-0.48	**0.02**
N1 AMP (nV/deg2)	-0.44	**0.02**	0,48	**0.01**	-0.50	**0.02**
N1 TI (msec)	0.55	**<0.01**	-0,81	**<0.01**	0.56	**0.01**
P1 AMP (nV/deg2)	-0.48	**0.01**	0,47	**0.01**	-0.56	**<0.01**
P1 TI (msec)	0.42	**0.02**	-0,60	**<0.01**	0.56	**<0.01**
N2 AMP (nV/deg2)	-0.59	**<0.01**	0,57	**<0.01**	0.64	**<0.01**
N2 TI (msec)	0.33	0.09	-0,55	**<0.01**	0.55	**<0.01**
P1/N1	-0.39	**0.04**	0,36	0.06	-0.42	**0.05**

3B: for the central zone (ring 1 and 2)

Mean ring 1 + ring 2	**VA**	p value	**Foveal threshold**	p value	**Colour Vision Score**	p value
RMS	-0.60	**<0.01**	0.56	**<0.01**	-0.44	**0.02**
N1 AMP (nV/deg2)	-0.44	**0.02**	0.44	**0.02**	-0.21	0.28
N1 TI (msec)	0.33	0.09	-0.41	**0.03**	0.28	0.16
P1 AMP (nV/deg2)	-0.57	**<0.01**	0.60	**<0.01**	-0.38	**0.05**
P1 TI (msec)	0.10	0.60	-0.23	0.24	0.15	0.46
N2 AMP (nV/deg2)	-0.52	**0.01**	0.48	**0.01**	-0.25	0.22
N2 TI (msec)	0.26	0.21	-0.40	**0.04**	0.48	**0.01**
P1/N1	-0.08	0.69	0.10	0.60	-0.33	0.09

Table 4: Correlations between anatomical parameters and mfERG.
IT = Implicit time, AMP = Amplitude

4A: global mfERG (5 rings)

Global Zone	**TOTAL AF**	p value	**TOTAL ICG**	p value	**Macular Thickness**	p value	**Macular volume**	p value
RMS	-0.35	0.07	-0.43	**0.02**	-0.08	0.68	0.06	0.76
N1 AMP	-0.40	**0.04**	-0.30	0.12	-0.17	0.38	0.07	0.72
N1 TI	0.62	**<0.01**	0.52	**<0.01**	0.48	**0.01**	0.31	0.11
P1 AMP	-0.36	0.06	-0.35	0.07	-0.13	0.50	0.05	0.79
P1 TI	0.32	0.09	0.37	**0.05**	0.37	**0.05**	0.17	0.40
N2 AMP	-0.49	**<0.01**	-0.50	**0.01**	-0.23	0.24	-0.09	0.65
N2 TI	0.17	0.38	0.14	0.47	0.38	**0.05**	0.18	0.38
P1/N1	-0.24	0.22	-0.60	**<0.01**	-0.06	0.76	-0.23	0.25

4B: mfERG for ring 1+2

Mean ring 1 + ring 2	**TOTAL AF**	p value	**TOTAL ICG**	p value	**Macular Thickness**	p value	**Macular volume**	p value
RMS	-0,55	**<0.01**	-0.58	**<0.01**	-0.23	0.24	-0.17	0.39
N1 AMP	-0.50	**0.01**	-0.53	**<0.01**	-0.25	0.18	0.02	0.93
N1 TI	0.43	**0.02**	0.29	0.13	0.26	0.17	0.11	0.57
P1 AMP	-0.55	**<0.01**	-0.59	**<0.01**	-0.29	0.14	-0.17	0.37
P1 TI	-0.06	0.76	0.06	0.78	0.30	0.12	0.06	0.76
N2 AMP	-0.37	0.06	-0.32	0.11	-0.35	0.08	-0.25	0.22
N2 TI	0.07	0.73	0.08	0.70	0.28	0.17	0.07	0.75
P1/N1	-0.10	0.60	-0.10	0.62	0.07	0.73	-0.16	0.41

Table 5: Quality of Life of 28 patients with BSCR.
Normal scores have values of 100.

VFQ-25 Subscale	Mean	Median [IQ range]
General Health	69.6 ± 17.4	70 [50 - 80]
General Vision	60.9 ± 20	60 [50 - 80]
Near Vision	55.2 ± 32.4	50 [25 - 80]
Verifying invoices	75.2 ± 26.5	77.5 [50 - 100]
To make-up	74.3 ± 29.8	75 [50 - 100]
Recognize people, Distance vision	69.8 ± 31.9	75 [50 - 100]
Play sports	78.9 ± 24.7	80 [50 - 100]
Watching TV	78 ± 18.8	75 [75 - 100]
Social functioning	96.5 ± 11.1	100 [100 - 100]
Need help from other people	70.4 ± 24.6	62.5 [50 - 100]
Limitation of activities	64.6 ± 22.7	50 [50 - 75]
Depression	61.7 ± 29.5	75 [25 - 75]
Dependency	85.6 ± 19.3	100 [75 - 100]

DISCUSSION:

This prospective study allowed to characterize abnormal parameters of mfERG in a cohort of Birdshot chorioretinopathy. We found that BSCR is associated with reduced amplitudes and increased implicit times of the main waves of mfERG (N1, P1). These abnormalities were well correlated with functional (visual field, visual acuity and colour vision) and anatomical (angiography and OCT) tests.

Demographics of our series is similar to that described in the literature, with a slightly female predominance, and a mean age of 50 years.[1,29] Since there can exist an asymmetry between both eyes in 24% of the cases (difference of more than 2 Snellen lines between eyes),[1,6] it may be difficult to define the better or the worse eye, anatomically and functionally and that both eyes may not be independent (for axial length, inflammation, genetic background and response to treatment), we randomized the study eye. In our series we showed that both eyes were similar according to the inflammation status and disease severity. The second methodological important point was that the control population was matched to the BSCR series according factors affecting mfERG responses, such as age, lens status, and axial length.[18,30]

The mfERG offers an objective electrophysiological evaluation of visual function and provides spatial information not readily available in the full-field ERG in diseases of the outer retina.[15] Furthermore, the multifocal technique may provide interesting insights into the mechanisms of BSCR since the N1 wave represents the hyperpolarization of cones, and the P1 wave represents the depolarization of bipolar cells.[15] We found that BSCR was characterized by abnormalities of P1 waves, with reduced amplitude and increased IT. These results suggest a lesion at the site of cone receptor and ON-bipolar cells.[15] On the other hand, increased IT of P1 suggests a delayed ON-bipolar response (from cone receptor to ON-bipolar cells). The timing

of the mfERG is known to be a very sensitive measure of the health of the outer retina,[15] and data in BSCR patients showed a significant but moderate increase in implicit times of N1 and P1. Damages to bipolar cells, and of inner nuclear layer, can also have a profound effect on the mfERG.[14] These electrophysiological data strongly suggest an important damage of the outer retina in BSCR patients. Histological analysis of eyes with BSCR are rare and showed a foci of lymphocytes in the choroid [31,32] and around some retinal vessels.[31] Further analysis should be performed using SD-OCT in regions with decreased amplitude and increased IT.

The spatial resolution of mfERG allowed us to note that the degree of eccentricity (5 rings) was found different for RMS, amplitudes of P1 and N2, and implicit time of P1. These differences accounted essentially between ring 1 (fovea) and the other rings, suggesting that the macula is more sensitive to the extrafoveal retina to inflammation.

One other interesting point is the correlation between focal macular ERG and anatomical data. We found that ERG parameters were correlated with FA and ICG score, and retinal thickness. These results suggest that in the 50° of the posterior pole, inflammatory lesions of BSCR at the choroid and/or retinal site have a negative impact on the visual function as evaluated using mfERG. Macular edema is probably the most common cause of decreased VA and occurs in up to 50% of reported patients.[1,6] Our data shown a positive correlation between retinal thickness and implicit times, and not amplitudes, which is consistent with that found in patients with diabetic macular edema.[33] The absence of correlation with amplitudes have also been reported in patients with neovascular AMD treated by photodynamic therapy.[34] Delays in implicit times have been also described in patients with retinal venous occlusion with macular ischemia,[35,36] in diabetic macular edema,[37] enlarged foveal

avascular zone in diabetic patients,[38] vitelliform macular dystrophy [39] and Stargardt disease.[40] In diabetic retinopathy, the changes in implicit times were found to be more diffuse compared with amplitude changes and extended to areas without clinically manifesting macular edema.[41,42] mfERG shows also more widespread retinal dysfunction compared with subjective visual field testing in MEWDS [18] or VA in VKH disease.[17] The smaller variability in mfERG implicit times among healthy eyes compared to the greater variability of amplitudes[33,43] was also found in our BSCR population **(table 2)**. Therefore, the contribution of implicit times in comparison to those of amplitudes for the follow-up of these patients need to be further studied.

The relationship between retinal morphology and ERG parameters may be complex since anatomical examinations provide very different information, from inflammation within retinal vessels or choroid, papilledema, to macular edema or atrophy. Quantitative (thickness) and qualitative (structural change of the outer and inner retina) data are now accessible to SD-OCT and may be differently associated with ERG parameters. One recent mfERG study reported that macular atrophy in long-standing (> 10 years) BSCR patients[19] was characterized by a reduced foveal density.

We found that mfERG parameters were well correlated with other functional tests such as visual field (measuring MD, foveal threshold), VA and colour vision test. These results suggest that functional degradation. Visual acuity may be stable over years with VA 20/60 or better, over time in 73% of the patients with BSCR[44] and a slow decline in VA since 2 or more lines of Snellen are lost in 19.6% of eyes over a median follow-up period of 3.5 years.[1] In other diseases, such as epiretinal membrane,[45] vitelliform macular dystrophy,[46] P1 implicit time was correlated with VA. However, VA only reflects the function of less than 1° of visual angle, and is probably

better associated with ring 1 and 2 of mfERG. We also found that mfERG parameters were correlated with other central tests such as colour vision and foveal threshold of the visual field. These latter tests are part of the functional testing in BSCR patients, with 8.7% complaining of poor colour vision[1] and 61% having deficiencies.[8] Visual field abnormalities may be variable, including peripheral constriction, generalized diminished sensitivity, enlarged blind spot, and central or paracentral scotoma.[1,26] Ours results showed that both foveal threshold and MD of the 30-2 sita-standard visual field were correlated with reduced amplitudes and increased implicit times of mfERG.

In the literature, abnormal ERGs are reported in 89% of the patients [1] and may not be correlated to visual acuity.[7] Previous authors suggest that a negative ERG pattern (decrease in b-wave compared to a-wave amplitude) seen in the early stage of the disease may indicate an abnormal function of Muller and bipolar cells. Rod dysfunction (rod isolated b-wave) may also occur before cone dysfunction (photopic b-wave).[1] Retinal vasculitis has also been noted to correlate with electro-oculogram.[44] With time the rod and cone b-wave amplitudes and oscillatory potential decreased. The late stages are commonly associated with progressive decrease in a a-wave and b-wave amplitudes which suggested impairment of the inner retina.[4,44,47,48]

BSCR has a high impact on vision related QoL,[51] especially for general and near vision, limitation of activities, and depression. Our composite scores are similar to that previously described.[49,51] One previous study showed that a median composite score was 75.9 on 127 patients,[49] and related to VA but not age or duration of uveitis. We found no correlation between mfERG parameters and VFQ-25

score. One reason may be that our ocular data concerned only one eye and explained insufficiently the relationship between visual impairment and reduced QoL. Previously a weak correlation was found between composite scores and VA.[51] Further analysis is needed to study the relationship between mfERG parameters and subscale scores.

Limitations of this study are the limited number of patients, the fact that mfERG data were not collected in absence of treatment, and the use of Time domain Stratus OCT during the baseline examination of patients.

In conclusion, this prospective study showed for the first time that amplitudes and implicit times of mfERG parameters are impaired in BSCR patients and are well correlated with other anatomical and functional tests. One perspective of this work is the longitudinal analysis of electrophysiological parameters in addition to other ancillary tests in order to identify disease progression, as suggested by standard ERG,[50] visual field and FA and ICG angiography. Periodic testings are necessary to guide the immunosuppressive treatment given to these patients and to evaluate the efficacy of these treatments. One other perspective will be the study of correlations between mfERG parameters and retinal ultrastructure defined in SD-OCT.

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THESE SOUTENUE PAR :

Joséphine Altayrac-Bethenod

TITRE :

Evaluation fonctionnelle par ERG multifocal dans la choriorétinopathie de Birdshot.

CONCLUSION

Cette étude prospective, comparative, montre que la choriorétinopathie de Birdshot (n = 28) est caractérisée par des anomalies de l'électrorétinogramme multifocal (ERGmf) comme une diminution globale du RMS, des amplitudes des ondes P1, N2 et du ratio P1/N1 ; ainsi qu'une augmentation des temps implicites des ondes N1, P1 comparativement à une population de sujets sains. Il existe une corrélation entre l'acuité visuelle, le seuil fovéolaire, le déficit moyen du champ visuel 24/2 sita-standard, le score de la vision des couleurs et les temps implicites N1 et P1 et à les amplitudes N1 et P1. L'épaisseur maculaire calculée en tomographie à cohérence optique est uniquement corrélée aux temps implicites de N1, P1 et N2. L'existence d'une vascularite rétinienne en angiographie à la fluorescéine et le score de qualité de vie ne sont pas corrélés aux paramètres de l'ERGmf. Ces résultats montrent que la choriorétinopathie de Birdshot est caractérisée par une atteinte fonctionnelle de la rétine externe et que l'atteinte

fonctionnelle caractérisée à l'ERGmf est bien corrélée aux autres marqueurs de la fonction visuelle.

Ce travail prospectif est la première étape d'une étude longitudinale sur 6 ans qui permettra d'évaluer les réponses électrophysiologiques de l'ERGmf en fonction de l'évolution anatomique et des traitements. L'ERGmf sera probablement un outil complémentaire qui guidera le traitement immunosuppresseur. Une deuxième perspective sera d'étudier les atteintes électrophysiologiques du pôle postérieur de l'oeil en fonction des atteintes ultrastructurales de la rétine, désormais analysables en tomographie à cohérence optique de très haute définition (SD-OCT).

VU ET PERMIS D'IMPRIMER

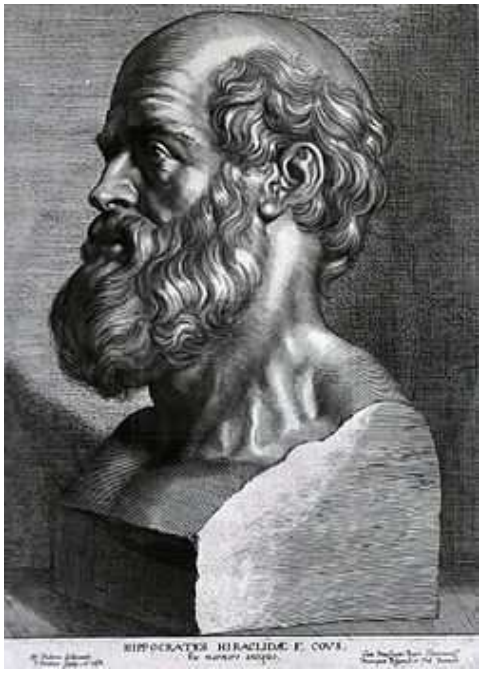
Grenoble, le 05/09/13

LE DOYEN

J.P. ROMANET

LE PRESIDENT DE LA THESE

PROFESSEUR J.P. ROMANET



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,
Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.
Je donnerais mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.
Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.
Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.
Je garderai le respect absolu de la vie humaine.
Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.
Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.
Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.
Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.