MULTIFOCAL ELECTRORETINOGRAM IN BIRDSHOT CHORIORETINOPATHY

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Purpose: To characterize multifocal electroretinogram parameters in patients with birdshot chorioretinopathy.

Methods: Twenty-eight patients with birdshot chorioretinopathy consecutively included from 2006 to 2011 were matched to 27 healthy subjects for age, axial length, and lens status. Multifocal electroretinogram was prospectively evaluated using the Vision Monitor system.

Results: Birdshot chorioretinopathy eyes differed significantly from healthy eyes by a decrease in mean root mean square values (–24.7%), P1 (–17.3%) and N2 (–27.5%) amplitude, and the P1/N1 ratio (–26.3%) as well as an increase in N1 (8.7%) and P1 (5.4%) implicit time (IT). An effect of the degree of eccentricity (5 zones) was found for root mean square ($P < 0.001$), P1 ($P < 0.001$) and N2 ($P < 0.001$) amplitude, and P1 IT ($P < 0.001$). Root mean square, the P1/N1 ratio, P1 and N2 amplitudes, P1 and N1 ITs were significantly correlated with visual acuity, mean defect of visual field, foveal threshold, and color vision score. The fluorescein angiographic score was significantly correlated to N1 and N2 amplitudes and N1 IT.

Conclusion: Amplitudes and ITs of the multifocal electroretinogram parameters are impaired in patients with birdshot chorioretinopathy and are well correlated with other anatomical and functional tests. Periodic testing could guide the immunosuppressive treatment.

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

The measurement of visual acuity alone is insufficient to monitor the disease,[6,7] and functional monitoring of patients can be facilitated through color vision[8] and/or visual field exploration.[9,10] Recent studies showed that the full-field electroretinogram (ERG) could also be of value in evaluating disease progression.[7,11–14]

The multifocal electroretinogram (mfERG) is a noninvasive method for objectively measuring retinal function within localized patches, especially the central retina, that is, up to 20° to 25° of eccentricity around the central foveal area.[15] Although it reflects the activity of cones under light-adapted conditions and provides an evaluation of the retinal function for 61 areas to the posterior pole, this functional test could be useful for the diagnosis of retinal dysfunction and then the repercussion of the disease, especially outside the macula. The mfERG is primarily used in the clinic to localize spatial alterations, with variations in the

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topographic array of signals more important than the absolute signal size.[15] The second advantage is that the mfERG helps differentiate 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 has addressed the contribution of mfERG in seven patients with BSCR, focusing on 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 and to correlate them with functional (visual acuity, color vision, visual field) and anatomical (fluorescein angiography [FA], indocyanine green angiography [ICGA], and optical coherence tomography [OCT]) data.

Material and Methods

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 patients' first examination 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 (IRB 00008855). All patients met the criteria for diagnosis of BSCR,[2] were older than 18 years, had no medical contraindications for performing angiography, and gave oral and written consent for conducting all ophthalmologic examinations. Each patient had a standardized prospectively defined examination including demographic information, medical history, and ophthalmologic examination. Functional testing included measurement of visual acuity (Monoyer chart, converted to logMAR), a 30-2 Swedish interactive threshold algorithm (SITA) standard program on the Humphrey Field Analyzer (Carl Zeiss Meditec Inc, Dublin, CA) and a Lanthony desaturated Panel D-15 test for color vision under standardized conditions of ambient illumination, with calculation of the total error score.[20,21] All patients had a reliable visual field test, defined as a false-positive error $<15\%$, a false-negative error $<15\%$, and a fixation loss $<20\%$. Quality of life (QoL) was estimated from the French translation of the NEI Visual Function Questionnaire (VFQ-25).[22]

Anatomical testing was based on FA and ICGA (Heidelberg, Germany) and OCT (Stratus; 2005 Carl Zeiss Meditec Inc, Oberkochen, Heidelberg, Germany) assessing macular thickness at the fovea, the foveal volume, and the presence or absence of epimacular membrane. Macular edema was defined as a central subfield thickness of >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 ≤ 130 μm using the Stratus OCT.[23] Angiographic data were quantitatively evaluated, in a masked fashion by one investigator, using a score established by the Angiography for Uveitis Scoring Working Group (ASUWOG).[24] This is a semiquantitative dual fluorescein and indocyanine angiography scoring system that is not specific to birdshot disease. A total maximum score of 40 is assigned to the FA signs, including optic disk hyperfluorescence, macular edema, retinal vascular staining and/or leakage, capillary leakage, retinal capillary nonperfusion, neovascularization of the optic disk, neovascularization elsewhere, pinpoint leaks, and retinal staining and/or subretinal pooling. A total maximum score of 20 is assigned to the ICGA signs, including early stromal vessel hyperfluorescence, choroidal vasculitis, dark dots or areas (excluding atrophy), and optic disk hyperfluorescence.[24] Retinal vasculitis was defined as fluorescein staining of any retinal vessels proximal to the third bifurcation.[6] Vitreous inflammatory reactions were quantified as previously described.[25] Cataract was quantified using the LOCSIII graduation.[26]

An mfERG (Vision Monitor; Métrovision, Pérenchies, France) was performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) protocol[27] 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 <4 cd/m^2. Dark frames were inserted after the white frames to achieve an 18-Hz stimulus frequency. The surrounding luminance was set at 30 cd/m^2. The stimulus was calibrated following the ISCEV guidelines.[28]

After pupil dilation using phenylephrine 5% (Europhta, Monaco, Monaco) and tropicamide (Thea, Clermont-Ferrand, France), patient positioning, good fixation, best optical correction for near vision, and constant moderate room light for at least 15 minutes 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 5 concentric rings centered on the fovea for analysis (<2, 2–5, 5–10, 10–15, and >15 degrees of visual angle). Mathematically, the first-order kernel is obtained by adding all the records that follow the presentation of a white hexagon (luminance, 400 cd/m^2) and subtracting all the records that follow a black

hexagon. We refer to response density (nV/deg^2) as amplitude (AMP). The following data were collected: the root mean square values (RMS), implicit time (IT) and 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 AMP 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 to define normal values of our mfERG. For the purposes of this study, 27 healthy subjects were matched to BSCR patients for age, axial length, and lens status.

Statistical Analysis

One eye was randomly selected for each patient. Parameter normality was determined using the Shapiro–Wilks test. When the normal distribution was demonstrated, the quantitative parameters were described by their mean and standard deviation. Otherwise, the median and 25th and 75th percentiles described them. The qualitative parameters are expressed in numbers and percentages. The comparison of quantitative parameters between groups was performed using a Student's *t*-test or a nonparametric test (Mann–Whitney or Kruskal–Wallis test), according to the normality and homogeneity of variance. Two-way analysis of variance with an interaction term group (BSCR, healthy eyes) × eccentricity (Rings 1–5) was used to compare mfERG parameters by concentric rings (5 zones). To avoid alpha risk inflation, because of multiple comparisons, and to have an acceptable Type 1 error rate, the Bonferroni method for adjusting values of P was used. The correlation between quality parameters was studied using a Pearson or Spearman test if necessary. Statistical analysis was performed using the SPSS program (Statistical Package for the Social Sciences 17.0 program for Windows; Chicago, IL). 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 56.6 ± 9.6 years, and 42.9% of the patients were male. The mean duration of the disease (based on the date of the diagnosis) was 3.4 ± 3.6 years. Sixty-eight percent of the patients had a duration <4 years at the time of the examination. At baseline, 53.6% the patients were under systemic steroid treatment, 7% cyclosporine, 7% intravenous immunoglobulin, and 10.7% had subtenon injection of triamcinolone, some with >1 treatment. Absence of treatment was noted in 42.8% of the cases.

Birdshot Eye Selection for Data Analysis

To analyze only one eye per patient, randomization of eyes in the birdshot population was performed and allowed to define one eye in Group 1 (selected for further analysis) and the other eye in Group 2. No significant difference for anatomical and functional parameters was found between the randomly selected groups of eyes (Groups 1 and 2, Table 1).

Baseline Characteristics of Birdshot Chorioretinopathy Patients' Eyes

The ocular data of eyes with BSCR (Group 1) are shown in Table 1. Visual acuity was ≥20/40 in 78% of the eyes, and color vision was abnormal in 44% of the cases. Angiographic data showed posterior vasculitis in 50% of the eyes. The macula was considered atrophic in 3% of the eyes and thickened in 43%.

Multifocal electroretinogram recordings (Table 2) showed that BSCR eyes differed significantly from healthy eyes by a decrease in mean RMS (–24.7%), P1 (–17.3%) and N2 AMP (–27.5%), and the P1/N1 ratio (–26.3%), and an increase in N1 (8.7%) and P1 (5.4%) IT. An effect of the degree of eccentricity (5 zones, Figure 1) was found for RMS ($P < 0.001$), P1 ($P < 0.001$) and N2 AMP ($P < 0.001$), and P1 ITs ($P < 0.001$). Multifocal electroretinogram parameters did not differ according to the duration of the disease (defined as <4 years or ≥4 years).

Correlations Between mfERG Parameters and Functional Data in Eyes With BSCR

Correlations between previously identified abnormal mfERG parameters and functional testing are summarized in Table 3. In brief, RMS, the P1/N1 ratio, P1, N1 and N2 AMPs, and P1 and N1 ITs were significantly correlated with visual acuity, mean defect, foveal threshold, and color vision score.

The composite score was not associated with mfERG parameters but significantly correlated to foveal threshold (r = 0.42, $P = 0.03$) and visual acuity (r = –0.46, $P = 0.02$).

When the central zone (5°: Ring 1 + 2) was considered, RMS, P1, N1 and N2 AMPs—and not IT—were significantly associated with visual acuity and foveal threshold (Table 3). Root mean square and P1 AMP were significantly associated with the color vision score.

Multifocal electroretinogram parameters were significantly correlated with visual field sensitivity (dB)

Table 1. Comparisons of Random Eyes at the Initial Visit

	Group 1 (n = 28)	Group 2 (n = 28)	*P*
Visual acuity (logMAR)	0.1 (0 to 0.3)	0.1 (0 to 0.25)	0.84
20/15–20/40	22/28 (78.6%)	22/28 (78.6%)	0.99
20/50–20/160	4/28 (14.3%)	4/28 (14.3%)	
20/200–LP	2/28 (7.1%)	2/28 (7.1%)	
Foveal threshold (dB)	32.5 (3 to 35)	33 (30.5 to 35)	0.59
Mean deviation (dB) of the sensitivity of the visual field	–5.03 (–9.6 to –3.2)	–5.2 (–8.9 to –3.3)	0.98
Color vision			
Total score error	230 (108 to 356)	222 (80 to 338)	0.61
Normal	15/27 (55.6%)	9/27 (33.3%)	0.40
Abnormal	12/27 (44.4%)	18/27 (66.7%)	—
FA score*	3 (1.5 to 5.5)	3 (1 to 5.5)	0.95
Retinal vascular staining and/or leakage at 5–10 minutes	14/28 (50%)	13/28 (46.4%)	0.79
ICGA score*	5.1 ± 2.5	5.2 ± 2.2	0.89
Foveal thickness (μm)	243.5 (198 to 282.5)	204 (177 to 262)	0.17
Macular thickness			
Atrophy ($<$130 μm)	1 (3.6%)	1 (3.6%)	0.889
Normal (130–250 μm)	15 (53.6%)	17 (60.7%)	
Edema ($>$250 μm)	12 (42.9%)	10 (35.7%)	
Macular volume	6.89 (6.32 to 7.74)	6.79 (6.07 to 8.37)	0.63
Epiretinal membrane	10 (35.7%)	8 (28.6%)	0.57

Group 1 was considered for further analysis. Results are expressed as mean ± standard deviation or median (25th, 75th percentiles). Values of *P* were obtained using the chi-square test, Student's *t*-test, or Mann–Whitney test.

*The total maximum FA score was 40, and the total ICGA was 20. Absence of inflammation gives a score of 0.

LP, light perception.

in the different regions of the posterior pole: Ring 1, Ring 1 + 2, Ring 3, Ring 4, and Ring 5 (Table 4).

The composite QoL score was 69.2 ± 13.5. The QoL subscale scores are reported in Table 5 and were considered abnormal for general health, general vision, near vision, difficulty with activities, and depression.

Table 2. Electrophysiologic Data of 28 Eyes With Birdshot Disease and Comparison With 27 Healthy Eyes

	Healthy Group	BSCR Group	*P*
Age (years)	57.4 ± 10.3	56.6 ± 9.6	0.9
Gender, n (%)			0.9
Male	12 (44.4)	12 (42.9)	
Female	15 (55.6)	16 (56.4)	
Laterality, n (%)			0.7
Right	15 (55.6)	14 (50)	
Left	12 (44.4)	14 (50)	
Mean RMS	1661 ± 413	1249 ± 486	0.003
Mean N1 AMP (nV/deg^2)	–769 ± 267	–636 ± 267	0.1
Mean N1 IT (milliseconds)	24.0 ± 1.6	26.3 ± 2.4	0.001
Mean P1 AMP (nV/deg^2)	1366 ± 434	1028 ± 494	0.01
Mean P1 IT (milliseconds)	43.7 ± 1.6	46.2 ± 3.4	0.002
Mean N2 AMP (nV/deg^2)	–1144 ± 359	–829 ± 371	0.004
Mean N2 IT (milliseconds)	63.5 ± 2.6	63.5 ± 5.1	0.4
Mean P1/N1 ratio	–1.9 ± 0.3	–1.4 ± 0.9	0.001

Correlations Between mfERG Parameters and Anatomical Data in Eyes With BSCR

Correlations between previously identified abnormal mfERG parameters and anatomical examinations are summarized in Table 6. The FA score was significantly correlated to N1 and N2 AMP and N1 IT. There was a trend for the correlation with RMS and P1 AMP and IT. The ICGA score was significantly associated with RMS, N2 AMP, and N1 and P1 ITs. There was a trend for the correlation with P1 AMP. In the central zone, RMS as well as N1 and P1 AMP were significantly correlated with the FA and ICGA scores (Table 6). We found no relationship between the mfERG parameters of these central rings and macular thickness.

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

Discussion

This prospective study allowed us to characterize abnormal parameters of mfERG in a cohort of patients with BSCR. We found that BSCR is associated with

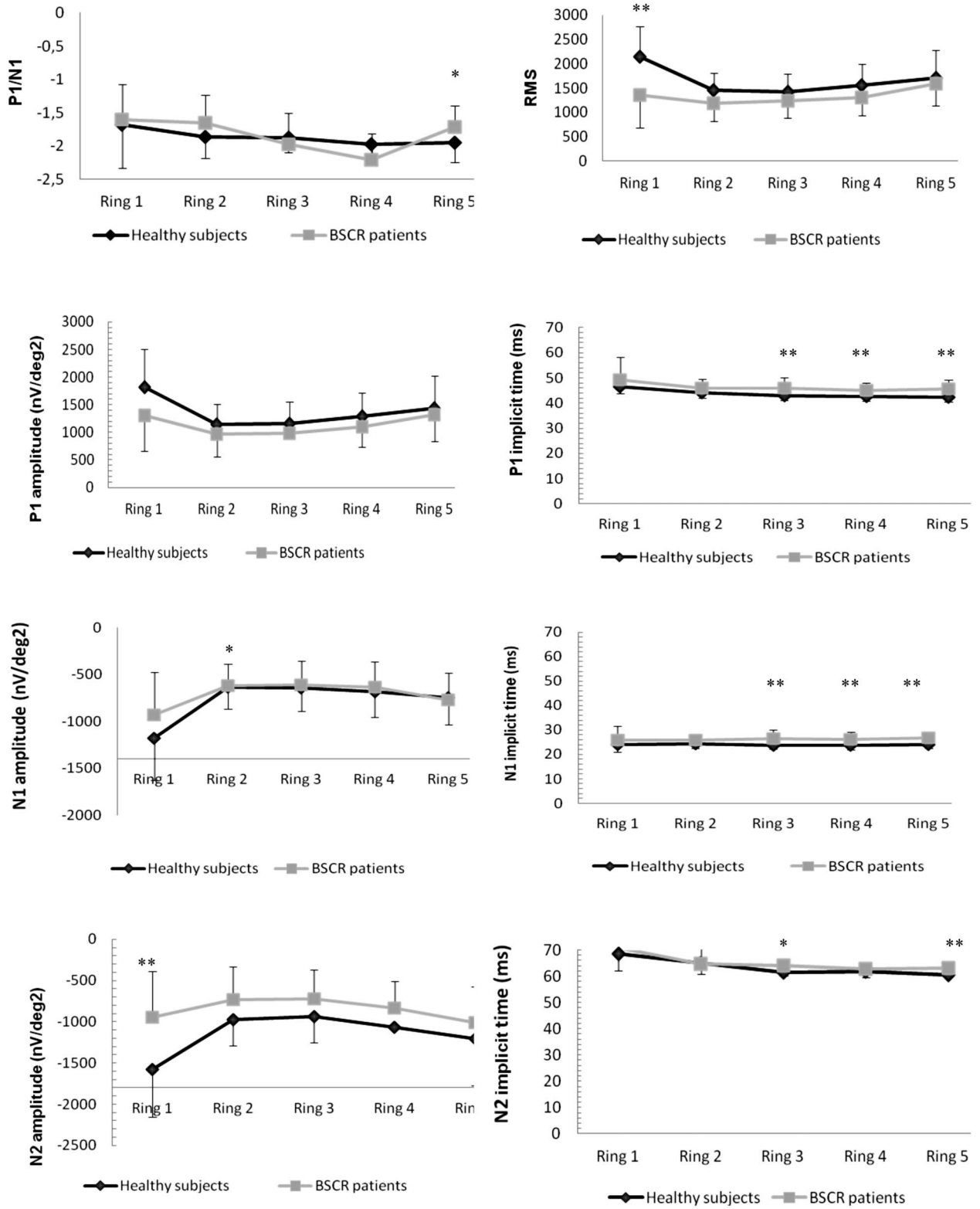

Fig. 1. Electrophysiologic data according to the degree of eccentricity of 28 eyes with birdshot disease and 27 healthy eyes. **P*-adjust < 0.05; ***P*-adjust < 0.01.

Table 3. Correlations Between Functional Ocular Data at Baseline and mfERG Parameters

For All Rings						
Global Zone	VA	*P*	Foveal Threshold	*P*	Color Vision Score	*P*
RMS	−0.45	**0.02**	0.39	**0.04**	−0.48	**0.02**
N1 AMP (nV/deg^2)	−0.44	**0.02**	0.48	**0.01**	−0.50	**0.02**
N1 IT (milliseconds)	0.55	**<0.01**	−0.81	**<0.01**	0.56	**0.01**
P1 AMP (nV/deg^2)	−0.48	**0.01**	0.47	**0.01**	−0.56	**<0.01**
P1 IT (milliseconds)	0.42	**0.02**	−0.60	**<0.01**	0.56	**<0.01**
N2 AMP (nV/deg^2)	−0.59	**<0.01**	0.57	**<0.01**	0.64	**<0.01**
N2 IT (milliseconds)	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**
For the Central Zone (Rings 1 and 2)						
Mean Ring 1 + Ring 2	VA	*P*	Foveal Threshold	*P*	Color Vision Score	*P*
RMS	−0.60	**<0.01**	0.56	**<0.01**	−0.44	**0.02**
N1 AMP (nV/deg^2)	−0.44	**0.02**	0.44	**0.02**	−0.21	0.28
N1 IT (milliseconds)	0.33	0.09	−0.41	**0.03**	0.28	0.16
P1 AMP (nV/deg^2)	−0.57	**<0.01**	0.60	**<0.01**	−0.38	**0.05**
P1 IT (milliseconds)	0.10	0.60	−0.23	0.24	0.15	0.46
N2 AMP (nV/deg^2)	−0.52	**0.01**	0.48	**0.01**	−0.25	0.22
N2 IT (milliseconds)	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

VA, visual acuity, LogMAR. P values in bold are statistically significant (< 0.05).

reduced AMPs and increased ITs of the mfERG main waves (N1, P1). These abnormalities were well correlated with functional (visual field, visual acuity, and color vision) and anatomical (angiography and OCT) tests.

The demographics of our series are similar to what has been reported in the literature, with a slight female predominance and a mean age of 50 years.[1,29] Because asymmetry exists between the 2 eyes in 24% of the cases (a difference of >2 Snellen lines between the eyes),[1,6] it may be difficult to define the better or the worse eye, anatomically and functionally, and both eyes may not be independent (for axial length, inflammation, genetic background, and response to treatment), we randomly selected the study eye. In this series, we showed that both eyes were similar according to the inflammation status and disease severity. The second important methodological point was that the control population was matched to the BSCR series according to factors affecting mfERG responses, such as age, lens status, and axial length.[18,30]

The study's limitations were the inclusion of patients with different histories (time to diagnosis and treatment) and clinical severity. These patients' characteristics may have represented a bias in the severity of mfERG findings according to the status of inflammation, treatment, and chronicity of the disease. However, these data may have less impact on the correlation between mfERG parameters and functional or anatomical factors.

The mfERG offers an objective electrophysiologic evaluation of visual function and provides spatial

Table 4. Correlations Between Humphrey 30.2 Visual Field Sensitivity and Multifocal Electroretinogram Parameters

	Ring 1 (Foveal Threshold)		Ring 1 + 2		Ring 3		Ring 4		Ring 5	
mfERG and VF	r_2	*P*	r_2	*P*	r_2	*P*	r_2	*P*	r_2	*P*
RMS	0.64	<0.01	0.68	<0.01	0.51	0.01	0.44	0.02	0.52	0.01
N1 AMP (nV/deg^2)	−0.45	0.04	−0.56	<0.01	−0.56	<0.01	−0.53	0.01	−0.60	<0.01
N1 IT (milliseconds)	−0.37	0.07	−0.50	0.01	−0.82	<0.01	−0.60	0.01	−0.77	<0.01
P1 AMP (nV/deg^2)	0.59	<0.01	0.73	<0.01	0.75	<0.01	0.62	<0.01	0.67	<0.01
P1 IT (milliseconds)	−0.11	0.60	−0.20	0.31	−0.74	<0.01	−0.55	<0.01	−0.66	<0.01
N2 AMP (nV/deg^2)	−0.45	0.04	−0.50	0.01	−0.55	<0.01	−0.38	0.06	−0.50	0.01
N2 IT (milliseconds)	−0.26	0.24	−0.35	0.08	−0.66	<0.01	−0.47	0.02	−0.54	<0.01

Ring 1 equals the first 2 degrees in the mfERG and the foveal threshold of the VF; Ring 2 equals the first 5 degrees in the mfERG and VF; Ring 3 equals 5 degrees to 10 degrees in the mfERG and VF; Ring 4 equals 10 degrees to 15 degrees in the mfERG and VF; Ring 5 equals >15 degrees in the mfERG and VF.

VF, visual field.

Table 5. Quality of Life of 28 Patients With BSCR

VFQ-25 Subscale	Mean ± SD	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 bills	75.2 ± 26.5	77.5 (50–100)
Shaving, styling hair, putting on make-up	74.3 ± 29.8	75 (50–100)
Recognizing people, distance vision	69.8 ± 31.9	75 (50–100)
Taking part in sports, outdoor activities	78.9 ± 24.7	80 (50–100)
Watching TV	78 ± 18.8	75 (75–100)
Social function	96.5 ± 11.1	100 (100–100)
Need help from other people	70.4 ± 24.6	62.5 (50–100)
Difficulty with activities	64.6 ± 22.7	50 (50–75)
Depression	61.7 ± 29.5	75 (25–75)
Dependency	85.6 ± 19.3	100 (75–100)

Normal scores have values of 100.

information not readily available in the full-field ERG in diseases of the outer retina. Furthermore, the multifocal technique may provide interesting insights into the mechanisms of BSCR because 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 P1 wave abnormalities, with reduced AMP and increased IT. Our results suggest a lesion at the cone receptor site and ON-bipolar cells.[15] However, increased P1 IT suggests a delayed ON-bipolar response (from the cone receptor to ON-bipolar cells). The IT of the N1 and the P1 response is known to be a very sensitive measure of outer retinal function,[15] and the BSCR patient data showed a significant but moderate increase in N1 and P1 IT. Damage to bipolar cells, and of inner nuclear layer, can also have a profound effect on the mfERG.[15] These electrophysiologic data strongly suggest considerable damage of the outer retina in BSCR patients. Histologic analyses of eyes with BSCR are rare and have shown a foci of lymphocytes in the choroid[31,32] and around some retinal vessels.[29] Further analysis should be undertaken using spectral domain OCT and enhanced depth imaging OCT in regions with decreased AMP and increased IT.

The spatial resolution of mfERG allowed us to note that the degree of eccentricity (5 rings) modulated the values for RMS, P1 and N2 AMP, and P1 IT. These differences were found essentially between Ring 1 + 2 and the other rings, suggesting that the macula is more sensitive to inflammation than the extrafoveal retina. As previously reported in other conditions,[15] we also showed a high correlation between reduction in visual field sensitivity and changes in mfERG parameters in different locations of the posterior retina. The P1 and N1 AMPs were positively correlated with the visual field defect, whereas the implicit N1 and P1 times increased significantly in the regions of the visual field defect.

Another interesting point is the correlation between mfERG and anatomical data. We found that ERG

Table 6. Correlations Between Anatomical Parameters and mfERG

Global mfERG (5 Rings)								
Global Zone	FA Score	*P*	ICG Score	*P*	Macular Thickness	*P*	Macular Volume	*P*
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 IT	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 IT	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 IT	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
mfERG for Ring 1 + 2								
Mean Ring 1 + Ring 2	Total FA	*P*	Total ICG	*P*	Macular Thickness	*P*	Macular Volume	*P*
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 IT	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 IT	–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 IT	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

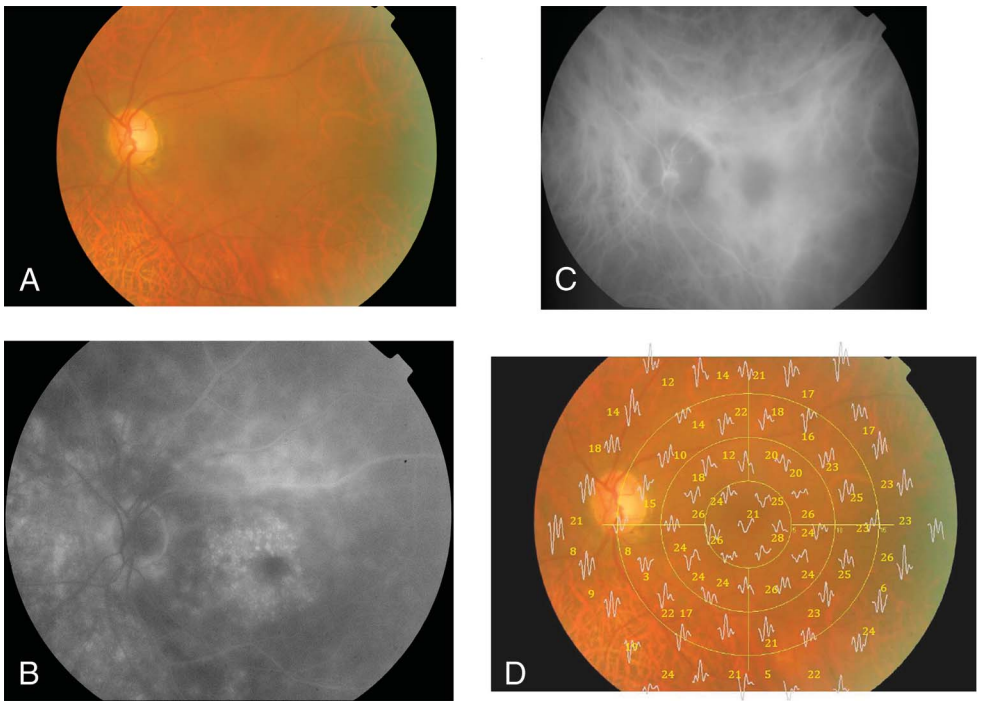

Fig. 2. Fundus photography (**A**), FA (**B**), and ICGA (**C**), mfERG, and visual field sensitivity (**D**) of a male patient, who was 58 years old. This patient had a venous vasculitis complicated by cystoid macular edema. The reduction in mfERG parameters was coupled with a reduction in visual field sensitivity (MD, −7.9 dB) and reduced visual acuity (20/50). Central macular thickness was 498 μm.

parameters were correlated with FA, the ICGA score, and retinal thickness (Figure 2). These results suggest that in the central 50° of the posterior pole, the inflammatory lesions of BSCR at the choroid and/or the retinal site have a negative impact on the visual function as evaluated using mfERG. Macular edema is probably the most common cause of decreased visual acuity and occurs in up to 50% of the patients reported.[1,6] Our data show a positive correlation between retinal thickness and IT, and not AMPs, which is consistent with the correlation found in patients with diabetic macular edema.[30] The absence of correlation with AMPs has also been reported in patients with neovascular age-related macular degeneration treated with photodynamic therapy.[31] Delays in IT have also been described in patients with retinal venous occlusion with macular ischemia,[33,34] in diabetic macular edema,[32] an enlarged foveal avascular zone in diabetic patients,[35] vitelliform macular dystrophy,[36] and Stargardt disease.[33] In diabetic retinopathy, the changes in IT were found to be more diffuse compared with AMP changes and extended to areas without clinically manifesting macular edema.[41,42] Multifocal electroretinogram also shows more widespread retinal dysfunction compared with subjective visual field testing in multiple evanescent white dot syndrome[18] or visual acuity in Vogt–Koyanagi–Harada disease.[17] The smaller variability in mfERG ITs in healthy eyes compared with the greater variability of AMPs[35,43] was also found in our BSCR population (Table 2). Therefore, the contribution of ITs in comparison with that of AMPs for the follow-up of these patients needs to be further studied.

The relationship between retinal morphology and ERG parameters may be complex because 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 spectral domain OCT and may be differently associated with ERG parameters. One mfERG study reported that macular atrophy in long-standing (>10 years) BSCR patients[19] was characterized by reduced foveal mfERG AMPs.

We found that mfERG parameters were well correlated with other functional tests such as visual field (measuring MD and foveal threshold), visual acuity, and color vision. Visual acuity is stable over several years when 20/60 or better, over time in 73% of the patients with BSCR[34] and has shown a slow decline as soon as 2 or more Snellen lines 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[37] and vitelliform macular dystrophy,[46] P1 IT was correlated with visual acuity. However, visual acuity only reflects the function of <1° of visual angle and is probably better associated with mfERG Ring 1 + 2. We also found that mfERG parameters were correlated with other central tests such as color vision and foveal threshold of the visual field. The latter tests

are part of the functional testing in BSCR patients, with 8.7% complaining of poor color 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] Our results show that both foveal threshold and MD of the 30-2 SITA standard visual field were correlated with reduced AMPs and increased mfERG ITs.

Abnormal ERGs are reported in 89% of the patients[1] and may not be correlated to visual acuity.[7] Standard ERG has the advantage of exploring the global activity of the retina, in contrast to mfERG being allotted to the central retina. Previous studies suggest that rod dysfunction (rod isolated b-wave) may occur before cone dysfunction (photopic b-wave).[1] The late stages are commonly associated with a progressive decrease in a-wave and b-wave AMPs, which suggests impairment of the inner retina.[4,44,47,48]

Birdshot chorioretinopathy has a high impact on vision-related QoL, especially for general health and near vision, difficulties with activities, and depression. Our composite scores are similar to those previously described.[38,39] A previous study showed that a median composite score was 75.9 in 127 patients[39] and related to visual acuity but not age or duration of uveitis. We found no correlation between mfERG parameters and the VFQ-25 score. One reason may be that our ocular data concerned with only one eye and explained the relationship between visual impairment and reduced QoL insufficiently. In an earlier study, a weak correlation was found between composite scores and visual acuity.[38] Further analysis is needed to study the relationship between mfERG parameters and subscale scores.

In conclusion, this is the first prospective study demonstrating that AMPs and ITs of mfERG parameters are impaired in BSCR patients and are well correlated with other anatomical and functional tests. Periodic testing is necessary to guide the immunosuppressive treatment given to these patients and to evaluate the efficacy of these treatments. The utility of mfERG for the follow-up of BSCR patients remains to be established in a longitudinal study of mfERG and other ancillary tests, such as standard ERG, visual field, FA, and ICGA.

Key words: birdshot chorioretinopathy, uveitis, multifocal electroretinogram.

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References

1. Shah KH, Levinson RD, Yu F, et al. Birdshot chorioretinopathy. Surv Ophthalmol 2005;50:519–541.
2. Levinson RD, Brezin A, Rothova A, et al. Research criteria for the diagnosis of birdshot chorioretinopathy: results of an international consensus conference. Am J Ophthalmol 2006;141: 185–187.
3. Ryan SJ, Maumenee AE. Birdshot retinochoroidopathy. Am J Ophthalmol 1980;89:31–45.
4. Kaplan HJ, Aaberg TM. Birdshot retinochoroidopathy. Am J Ophthalmol 1980;90:773–782.
5. de Courten C, Herbort CP. Potential role of computerized visual field testing for the appraisal and follow-up of birdshot chorioretinopathy. Arch Ophthalmol 1998;116:1389–1391.
6. Monnet D, Brezin AP, Holland GN, et al. Longitudinal cohort study of patients with birdshot chorioretinopathy. I. Baseline clinical characteristics. Am J Ophthalmol 2006;141: 135–142.
7. Oh KT, Christmas NJ, Folk JC. Birdshot retinochoroiditis: long term follow-up of a chronically progressive disease. Am J Ophthalmol 2002;133:622–629.
8. Holland GN, Shah KH, Monnet D, et al. Longitudinal cohort study of patients with birdshot chorioretinopathy II: color vision at baseline. Am J Ophthalmol 2006;142:1013–1018.
9. Thorne JE, Jabs DA, Kedhar SR, et al. Loss of visual field among patients with birdshot chorioretinopathy. Am J Ophthalmol 2008;145:23–28.
10. Tomkins-Netzer O, Taylor SR, Lightman S. Long-term clinical and anatomic outcome of birdshot chorioretinopathy. JAMA Ophthalmol 2014;132:57–62.
11. Zacks DN, Samson CM, Loewenstein J, Foster CS. Electroretinograms as an indicator of disease activity in birdshot retinochoroidopathy. Graefes Arch Clin Exp Ophthalmol 2002; 240:601–607.
12. Sobrin L, Lam BL, Liu M, et al. Electroretinographic monitoring in birdshot chorioretinopathy. Am J Ophthalmol 2005;140: 52–64.
13. Holder GE, Robson AG, Pavesio C, Graham EM. Electrophysiological characterisation and monitoring in the management of birdshot chorioretinopathy. Br J Ophthalmol 2005;89:709–718.
14. Comander J, Loewenstein J, Sobrin L. Diagnostic testing and disease monitoring in birdshot chorioretinopathy. Semin Ophthalmol 2011;26:329–336.
15. Hood DC. Assessing retinal function with the multifocal technique. Prog Retin Eye Res 2000;19:607–646.
16. Li D, Kishi S. Restored photoreceptor outer segment damage in multiple evanescent white dot syndrome. Ophthalmology 2009;116:762–770.
17. Yang P, Fang W, Wang L, et al. Study of macular function by multifocal electroretinography in patients with Vogt-Koyanagi-Harada syndrome. Am J Ophthalmol 2008;146:767–771.
18. Lai TY, Chan WM, Lai RY, et al. The clinical applications of multifocal electroretinography: a systematic review. Surv Ophthalmol 2007;52:61–96.
19. Birch DG, Williams PD, Callanan D, et al. Macular atrophy in birdshot retinochoroidopathy: an optical coherence tomography and multifocal electroretinography analysis. Retina 2010; 30:930–937.
20. Török B. 2006.
21. Lanthony P. Evaluation of the desaturated Panel D-15. I. Method of quantification and normal scores [in French]. J Fr Ophtalmol 1986;9:843–847.

22. Mangione CM, Lee PP, Gutierrez PR, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2001;119:1050–1058.
23. Forooghian F, Yeh S, Faia LJ, Nussenblatt RB. Uveitic foveal atrophy: clinical features and associations. Arch Ophthalmol 2009;127:179–186.
24. Tugal-Tutkun I, Herbort CP, Khairallah M. Scoring of dual fluorescein and ICG inflammatory angiographic signs for the grading of posterior segment inflammation (dual fluorescein and ICG angiographic scoring system for uveitis). Int Ophthalmol 2010;30:539–552.
25. Davis JL, Madow B, Cornett J, et al. Scale for photographic grading of vitreous haze in uveitis. Am J Ophthalmol 2010; 150:637–641.e1.
26. Chylack LT Jr, Wolfe JK, Singer DM, et al. The Lens Opacities Classification System III. The Longitudinal Study of Cataract Study Group. Arch Ophthalmol 1993;111:831–836.
27. Brigell M, Bach M, Barber C, et al. Guidelines for calibration of stimulus and recording parameters used in clinical electrophysiology of vision. Doc Ophthalmol 2003;107:185–193.
28. Gasch AT, Smith JA, Whitcup SM. Birdshot retinochoroidopathy. Br J Ophthalmol 1999;83:241–249.
29. Seiple W, Vajaranant TS, Szlyk JP, et al. Multifocal electroretinography as a function of age: the importance of normative values for older adults. Invest Ophthalmol Vis Sci 2003;44: 1783–1792.
30. Pulido JS, Canal I, Salomao D, et al. Histological findings of birdshot chorioretinopathy in an eye with ciliochoroidal melanoma. Eye (Lond) 2012;26:862–865.
31. Gaudio PA, Kaye DB, Crawford JB. Histopathology of birdshot retinochoroidopathy. Br J Ophthalmol 2002;86: 1439–1441.
32. Fortune B, Schneck ME, Adams AJ. Multifocal electroretinogram delays reveal local retinal dysfunction in early diabetic retinopathy. Invest Ophthalmol Vis Sci 1999;40:2638–2651.
33. Mackay AM, Brown MC, Grierson I, Harding SP. Multifocal electroretinography as a predictor of maintenance of vision after photodynamic therapy for neovascular age-related macular degeneration. Doc Ophthalmol 2008;116:13–18.
34. Hvarfner C, Andreasson S, Larsson J. Multifocal electroretinography and fluorescein angiography in retinal vein occlusion. Retina 2006;26:292–296.
35. Dolan FM, Parks S, Keating D, Dutton GN. Wide field multifocal and standard full field electroretinographic features of hemi retinal vein occlusion. Doc Ophthalmol 2006; 112:43–52.
36. Leozappa M, Micelli Ferrari T, Grossi T, et al. Prognostic prediction ability of postoperative multifocal ERG after vitrectomy for diabetic macular edema. Eur J Ophthalmol 2008;18: 609–613.
37. Tyrberg M, Ponjavic V, Lovestam-Adrian M. Multifocal electroretinogram (mfERG) in patients with diabetes mellitus and an enlarged foveal avascular zone (FAZ). Doc Ophthalmol 2008;117:185–189.
38. Wittstrom E, Ekvall S, Schatz P, et al. Morphological and functional changes in multifocal vitelliform retinopathy and biallelic mutations in BEST1. Ophthalmic Genet 2011;32: 83–96.
39. Eksandh L, Ekstrom U, Abrahamson M, et al. Different clinical expressions in two families with Stargardt's macular dystrophy (STGD1). Acta Ophthalmol Scand 2001;79:524–530.
40. Greenstein VC, Holopigian K, Hood DC, et al. The nature and extent of retinal dysfunction associated with diabetic macular edema. Invest Ophthalmol Vis Sci 2000;41:3643–3654.
41. Yamamoto S, Yamamoto T, Hayashi M, Takeuchi S. Morphological and functional analyses of diabetic macular edema by optical coherence tomography and multifocal electroretinograms. Graefes Arch Clin Exp Ophthalmol 2001;239:96–101.
42. Bearse MA Jr, Adams AJ, Han Y, et al. A multifocal electroretinogram model predicting the development of diabetic retinopathy. Prog Retin Eye Res 2006;25:425–448.
43. Priem HA, De Rouck A, De Laey JJ, Bird AC. Electrophysiologic studies in birdshot chorioretinopathy. Am J Ophthalmol 1988;106:430–436.
44. Kim KS, Lee SB, Lee WK. Vitrectomy and internal limiting membrane peeling with and without gas tamponade for myopic foveoschisis. Am J Ophthalmol 2012;153:320–326.e1.
45. Schatz P, Bitner H, Sander B, et al. Evaluation of macular structure and function by OCT and electrophysiology in patients with vitelliform macular dystrophy due to mutations in BEST1. Invest Ophthalmol Vis Sci 2010;51:4754–4765.
46. Hirose T, Katsumi O, Pruett RC, et al. Retinal function in birdshot retinochoroidopathy. Acta Ophthalmol (Copenh) 1991;69:327–337.
47. Rothova A, Van Schooneveld MJ. The end stage of birdshot retinochoroidopathy. Br J Ophthalmol 1995;79:1058–1059.
48. Levinson RD, Monnet D, Yu F, et al. Longitudinal cohort study of patients with birdshot chorioretinopathy. V. Quality of life at baseline. Am J Ophthalmol 2009;147:346–350.e2.
49. Kuiper JJ, Missotten T, Baarsma SG, Rothova A. Vision-related quality of life in patients with birdshot chorioretinopathy. Acta Ophthalmol 2013;91:e329–e331.