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### ► To cite this version:

Adriane Mailhac, Jose Labarere, Florent Aptel, Sylvie Berthemy, Laurence Bouillet, et al.. Five-Year Trends in Multifocal Electroretinogram for Patients With Birdshot Chorioretinopathy. *American Journal of Ophthalmology*, 2019, 200, pp.138-149. 10.1016/j.ajo.2018.11.022 . hal-02272296

HAL Id: hal-02272296

<https://hal.science/hal-02272296>

Submitted on 22 Oct 2021

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## **Five-year trends in multifocal electroretinogram for patients with birdshot chorioretinopathy.**

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Financial support: Association for Research and Teaching in Ophthalmology (ARFO, Grenoble, France). The sponsor of the funding organization had no role in the design or conduct of this research.

No conflicting relationship exists for any author.

Running head: mfERG follow-up in patients with birdshot chorioretinopathy.

## INTRODUCTION

Birdshot chorioretinopathy (BSCR) is a posterior autoimmune uveitis, usually symmetric, and strongly associated with human leukocyte antigen A 29. BSCR accounts for 0.5 to 1.5% of uveitis, with a higher prevalence in female and a mean age of symptom onset of 53 years.<sup>1</sup> BSCR has an insidious progression and can cause a significant visual loss due to various complications, including macular edema, diffuse retinal atrophy, epiretinal membrane, and/or choroidal neovascularization.

Because visual acuity (VA) may remain stable despite steadily progressive deterioration of retinal function,<sup>2</sup> it lacks sensitivity for detecting or monitoring patients with BSCR. Several functional and imaging technologies have been proposed for monitoring BSCR,<sup>3</sup> including visual field,<sup>4</sup> color vision,<sup>5</sup> standard electroretinography (ERG),<sup>3,6–8</sup> fluorescein (FA) and indocyanine green (ICGA) angiography, and optical coherence tomography (OCT).<sup>9,10</sup> Yet these tests yield limited accuracy or reliability for assessing disease activity. This explains why monitoring BSCR patient remains challenging in routine practice.

Because electrophysiological testing may detect early functional changes, its use has been advocated for monitoring disease progression in uveitis.<sup>11</sup> Three types of electroretinogramm are currently used in the clinical setting: full field, pattern, and multifocal ERGs. Multifocal ERG (mfERG) is a non-invasive method for objectively measuring retinal function within localized patches, especially the central retina, that is, up to 45° of eccentricity around the central foveal area. Multifocal ERG waveform

can be understood as a combination of overlapping ON- and OFF-bipolar cell contributions combined with smaller contributions from inner retina and photoreceptors.<sup>12</sup> Many studies have reported on the diagnostic and prognostic values of full field ERG parameters for BSCR, including the light adapted 30-HZ flicker response.<sup>6-8</sup> In contrast, only two cross-sectional studies investigated the value of mfERG in BSCR.<sup>13,14</sup> Birch et al.<sup>13</sup> reported 1) lower mfERG responses for 6 eyes with macular atrophy compared to 8 eyes without macular thinning and 2) abnormal mfERG responses for patients with BSCR evolving for 10 years or more. Using a cross sectional study design, Chiquet et al.<sup>14</sup> showed that amplitudes (AMP) and implicit times (IT) of the mfERG parameters were impaired in BSCR patients and were associated with other anatomical and functional test findings. In contrast to full-field ERG, mfERG explores cone-driven light-adapted retinal function and provides objective assessment of central retinal function in different retinal areas within a short time frame. Furthermore, the multifocal technique may provide useful 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. Yet the value of mfERG for monitoring BSCR patients remains to be established and prospective longitudinal studies are warranted for this purpose.

This prospective cohort study of BSCR patients with a 5-year follow-up (FU) period aimed to investigate temporal trends in mfERG parameter values and elucidate their relationships with anatomical and functional tests.

## **METHODS**

### **Study design**

As part of a prospective observational case series of BSCR, the present analysis focused on consecutive adult patients who were monitored at baseline, 3 and 5 years of FU, using mfERG in Grenoble Alpes University Hospital. This study complied with the declaration of Helsinki guidelines for research involving human subjects and was approved by the local Institutional Review board (IRB 00008855). All study participants provided written informed consent for conducting all ophthalmologic examinations.

### **Patients**

All patients met the 2006 International consensus conference research criteria for diagnosis of BSCR,<sup>15</sup> were older than 18 years, had no medical contraindications for performing FA and ICGA. They were recruited between January 2008 and December 2010.

### **Data collection**

Baseline characteristics and FU data were prospectively collected, including measurement of VA (ETDRS chart), 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.<sup>16,17</sup> 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 assessed using the cross-cultural adaptation of the NEI Visual Function Questionnaire (VFQ-25) in French.<sup>18</sup>

Anatomical testing was based on FA, ICGA (Heidelberg, Germany) and optical coherence tomography (OCT) (Spectral domain Carl Zeiss Meditec Inc., or Spectral domain Heidelberg, Germany). Angiographic data were evaluated, in a blinded fashion by two independent investigators,<sup>19, 20</sup> and included optic disk hyperfluorescence, macular edema, retinal vascular staining and/or leakage (with an extension varying between 0 and 4 related quadrants), peripheral capillary leakage (extension: 0–4 quadrants), and posterior capillary leakage. Retinal vasculitis was defined as fluorescein staining of any retinal vessels proximal to the third bifurcation.<sup>21</sup> ICGA criteria were presence of hypopycnescence areas at the intermediate frame (10 min after the ICG injection).<sup>20</sup>

OCT data collected were central macular thickness (CMT), alteration of outer retina, and macular edema (ME). We defined ME in TD-OCT as CMT over 260 µm and in SD-OCT as CMT over 295 µm.<sup>22,23</sup> Other ME features included cystoid macular edema (CME), consisting of low-reflective intra-retinal spaces, clearly defined and separated by thin, high-reflective retinal tissue; diffuse ME consisting of increased macular thickness; small low-reflective areas with spongy appearance of the retinal layers. We defined alterations of the outer retina by the presence of a defects of at least one of four hyper-reflective outer retinal bands: the external limiting membrane (ELM); the ellipsoid portion of the inner segments (ellipsoid band); the cone outer segment/contact cylinder region (cone OS) and the RPE.<sup>24, 25</sup> CMT was defined as the mean retinal thickness within the 1-mm central subfield.

Each patient was followed using the same OCT machine. Patients initially included in 2008 had TD-OCT at baseline and were followed by TD-OCT over 5 years and SD-OCT from 2010. Cirrus measurement was defined as the reference measurement, and we used the conversion table to convert stratus (Cirrus = Stratus  $\times 1 + 55.6$ ) and Heidelberg measurements (Cirrus = Spectralis  $\times 0.8 + 36.4$ ) into cirrus CMT.<sup>26</sup>

Severity of the disease and progression of inflammation were based on anatomical (fluorescein and ICG angiography, OCT) and functional (VA, visual field parameters) examinations.

Multifocal ERG (Vision Monitor; Métrovision, Pérenchies, France) was performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) protocol,<sup>27</sup> 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<sup>2</sup> and that of black hexagons 4 cd/m<sup>2</sup>. The electrode used was the ERG-jet corneal electrode™. Dark frames were inserted after the white frames to achieve an 18-Hz stimulus frequency. The surrounding luminance was set at 30 cd/m<sup>2</sup>. The stimulus was calibrated following the ISCEV guidelines.<sup>27</sup> After pupil dilation using phenylephrine 5% (Europhta, 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 five concentric

rings centered on the fovea for analysis (2, 2–5, 5–10, 10–15, and beyond 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<sup>2</sup>) and subtracting all the records that follow a black hexagon. The following data were collected: the root mean square values (RMS), implicit time (IT) and AMP of N1, P1, and N2 waves. 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. IT was measured from the onset of the stimulation to the trough or peak. Only averaged data including five rings were presented in the Results section.

Normative values (obtained from the manufacturer Métrovision) are (mean  $\pm$ SD): -915  $\pm$ 260 nV for N1 AMP, 1633  $\pm$ 395 NV for P1 AMP, 23.2  $\pm$ 1.3 msec for N1 IT and 42.2  $\pm$ 1.6 msec for P1 IT. The reliability using the Metrovision device has been previously reported. in this study.<sup>28</sup> For N1 and P1 waves, the percentage change for the intraindividual reproducibility study was 9.1% and 6.7%, respectively, with the ERG-jet electrode and 18.2% and 13.5%, respectively, using the same electrode. These published data have been used in the present study to categorize evolution of mfERG parameters into unchanged/ improved / deteriorated evolution from baseline.

### **Statistical analysis**

Gender, treatments at baseline, evidence of photoreceptor alteration, ME and ERM on OCT, fluorescein and indocyanine green angiography findings were reported as numbers and percentages. Age, disease duration, VA, QoL score, foveal

threshold, VF parameters, color vision score, CMT and ERG data (i.e. N1 and P1 implicit times and amplitudes) were summarized with means and standard deviation. Because of skewed distribution, disease duration and total error score were summarized with the median and 25th–75th percentiles.

Time trends in continuous mfERG parameters were modeled using linear regression for longitudinal data with time to FU visit entered as an independent variable. The linear time trend reflected the long-run tendency of mfERG parameter values to increase or decrease over time.

Temporal trends in continuous mfERG parameters were modelled using linear regression for longitudinal data with time to FU visit entered as an independent variable. To investigate univariate associations of mfERG parameters, we performed longitudinal regression modeling for continuous dependent variables, with characteristics and time to FU entered as independent covariates. We assessed the linearity assumption for continuous independent variables by using fractional polynomial functions. First-order interactions involving time to FU and each independent covariate were systematically tested for statistical significance. If a significant interaction was found, coefficient estimates were stratified by time to FU. To account for the hierarchical data structure, we used generalized estimated equations with the eye and FU observations nested within participants.<sup>28,29</sup>

Regression coefficient point estimates were reported along with 95% confidence intervals. Regression coefficients represent the variation in predicted mfERG parameter value for a one-unit increase in the covariate value. In longitudinal analysis, changes in mfERG parameter values were reported as “per year of FU”. Two-sided p-values of <0.05 were considered statistically significant. All

analyses were performed using Stata Special Edition version 14.0 (Stata Corporation, College Station, TX, USA).

## RESULTS

Overall, 16 patients with a mean age of 60.2 (standard deviation, 7.8) were enrolled between 2008 and 2010 and underwent FU visits at 3.2 years (standard deviation 0.3) and 5.1 years (standard deviation, 0.2) of enrolment. Baseline characteristics are reported in Table 1. The mean time from diagnosis to enrolment was  $4.8 \pm 4$  years. Eight eyes (25%) had a cataract and none was pseudophakic at baseline while four eyes (12.5%) underwent cataract surgery during the FU period.

No significant temporal trend was found for VA (increase of 0.46 letter per year of FU, 95% confidence interval [CI], -0.51 to 1.44,  $P=.35$ ), color vision score (decrease of -9 per year of FU, 95% CI, -20 to 2,  $P=.12$ ), foveal threshold (increase of 0.19 dB per year of FU, 95% CI, -0.14 to 0.52,  $P=.26$ ) and mean deviation of visual field (increase of 0.07 dB per year of FU, 95% CI, -0.19 to 0.33,  $P=.60$ ), and quality of life score (increase of 0.71 per year of FU, 95% CI, -0.89 to 2.31,  $P=.39$ ) over the 5-year FU period.

The percentage of patients receiving corticosteroids alone or in combination with immunosuppressive treatment was 62% (10/16) and 56% (9/16) at baseline and 5 years of FU, respectively ( $P=.72$ ). The percentage of patients with corticosteroids alone decreased over time (from 50% at baseline to 25% at the 5-year FU) and the proportion of patients with corticosteroids and immunosuppressants increased (from 0% at baseline to 31%). Over the 5-year period, two out of 16 patients were newly

treated, 3 out 16 did not change their treatment, 3 out 16 stopped their previous treatment and 4 out 16 had no treatment.

A significant decreasing temporal trend was observed over the 5-year FU period for N1 (37 nV, 95% CI, 24 to 51, p<.001), P1 (61 nV, 95% CI, 38 to 84, p<.001), and N2 (35 nV, 95% CI, 11 to 58, p=.003) amplitudes. Over the same period, P1 implicit time increased (0.68 ms, 95% CI, 0.41 to 0.94, p<.001) while N1 (0.24 ms, 95% CI, -0.04 to 0.51, p=.08) and N2 (0.89 ms, 95% CI, -5.20 to 6.98, p=.78) implicit times did not vary significantly. Taken into account the intraindividual reproducibility of the mfERG, we reported that N1 AMP and P1 AMP deteriorated in 25/32 eyes (78%) between baseline and FU3 (last visit, Supplementary material, Table 4).

Increasing N1 and P1 IT were both associated with increasing values of EDTRS score (in letters), foveal threshold, and quality of life and with increasing color vision score, mean deviation of visual field over the 5-year FU period (Table 2). A significant relationship was observed between decreasing P1 AMP values and increasing MD of visual field. Increased N2 AMP and longer N2 IT were associated with decreasing values of mean deviation of visual field over the 5-year FU period (Table 2) whereas longer N2 IT was also associated with increasing values of VA (EDTRS letters).

Over the 5-year FU period, longer N1 and P1 IT were both associated with macular edema (Table 3). Additionally P1 IT was also associated with optic disk hyperfluorescence and peripapillary hypocyanescence. Univariate associations were found between reduced N1 AMP values and the presence of venous vasculitis and peripheral capillary leakage. Reduced P1 AMP values were associated with the

presence of photoreceptor layer alteration. No significant association was found between mfERG variables with posterior capillary leakage. Reduced N2 AMP and lower IT were significantly associated with photoreceptor alteration in OCT.

Figure 3 illustrates one case with a typical reduction of N1 and P1 AMP over time whereas visual field parameters and VA were stable, and no recurrence of vasculitis or CME occurred.

## DISCUSSION

This prospective observational case series study showed that mfERG parameters worsen in BSCR patients during a 5-year FU period, with decreasing N1 and P1 AMP values and increasing P1 IT. Importantly, these temporal trends in mfERG parameter values were not paralleled by changes in classical functional parameters such as VA and visual field. However, substantial associations were found between N1 AMP and venous vasculitis and peripheral capillary leakage, whereas P1 AMP reflected alterations of the outer retina in OCT, after adjusting for time to FU. Waves amplitudes were well correlated to the visual field parameters whereas IT was well correlated to quality of life, VA and visual field parameters.

We confirmed that BSCR patients exhibit reduced AMP of P1 and N1 waves and increased IT of P1 over time. These data are consistent with our previous findings in a cross-sectional study, showing that BSCR eyes differed significantly from healthy eyes by a decrease in P1 (-17%) and N2 AMP (-27%) and an increase in N1 (9%) and P1 (5%) IT.<sup>14</sup> In presence of macular atrophy in long-standing (> 10 years) BSCR patients, foveal mfERG amplitudes<sup>13</sup> are reduced by 2.3 when compared to BSCR eyes without anatomic thinning.

To our knowledge, the present study is the first to investigate trends in mfERG in patients with BSCR over a 5 year-period. The reduction in N1 and P1 AMP and increase in P1 IT suggest a worsening of retinal function across time whereas classical functional parameters such as VA, color vision and visual field parameters did not vary significantly. A previous study reporting standard ERG<sup>30</sup> showed that 70% of the patients had a loss of inner and/or outer retinal functions over prolonged FU. Previous studies reporting the full-field cone system 30-Hz flicker ERG peak time,<sup>6</sup> the scotopic bright flash amplitudes (combined rods and cones), reduction in the a-wave and b-wave amplitudes,<sup>31,32</sup> reduction in cone–b-wave implicit times and reduction in scotopic rod b-wave amplitudes<sup>7</sup> illustrated that both the rod and cone systems are involved in BSCR.

Previous studies showed that VA did not reflect accurately disease severity,<sup>33</sup> was stable<sup>2</sup> or yielded a slow decline over time.<sup>30</sup> Color vision is impaired in BSCR,<sup>5,14</sup> with 55-61% of patients abnormal color confusion scores. However the color vision score remained stable over 5 years in our study. There is more information in the literature concerning the abnormalities of the visual field, including peripheral constriction, generalized diminished sensitivity, enlarged blind spot, and central or paracentral scotoma.<sup>34,35</sup> Recent studies showed that MD might be stable<sup>2</sup> whereas PSD possibly reflecting sectorial changes increases, especially in patients who received short-term treatment. Pointwise linear regression analysis of luminance sensitivity can identify visual field loss despite a stable MD.<sup>35</sup> These data highlight the need of complementary functional tests, which can reliably estimate the evolution of the retinal function.

Our data show a positive correlation between mfERG and other functional tests despite the absence of temporal changes of VA, color vision, and visual field parameters over a 5-year period. Waves AMP were well correlated to the visual field sensitivity whereas ITs were well correlated to quality of life, VA and visual field parameters. An original finding of this study is the worsening of mfERG responses while VA and MD of visual field remains stable over time. There are several potential explanations for this discrepancy. First, changes in N1 and P1 AMP and/or IT may be early markers of worsening clinical outcomes that may not be captured over a 5-year FU period. Second, we cannot exclude that this study was underpowered to detect any significant time trends in visual acuity, quality of life, visual field or color vision. A perspective of this work will consist to investigate the prognostic value of mfERG responses at baseline for the prediction of visual function in the long-term.

BSCR has a high impact on vision-related quality of life, especially for general health and near vision, difficulties with activities and depression,<sup>14</sup> with a mean global VFQ-25 score around 70 consistent with previous study.<sup>36</sup> In this study taking into account both eyes of each patient, we showed for the first time that (1) the reduced QoL score was not modified significantly during a 5-year period and (2) QoL score was significantly associated with N1 and P1 IT. This finding is interesting since previous report showed only a weak correlation between composite scores and VA.<sup>36</sup>

P1 wave abnormalities suggest a lesion at the cone receptor site and ON-bipolar cells, with a delayed response from both neurons.<sup>37</sup> The P1 IT is also known to be a very sensitive measure of outer retinal function.<sup>37</sup> In BSCR patients, the outer retina damages, such as photoreceptor layer alteration and presence of macular

edema were respectively correlated with decreased AMP and longer IT of P1. This finding confirms the pilot study of Birch who showed that BSCR patients with OCT macular thinning exhibit a significantly altered mfERG.<sup>13</sup> These data highlights the importance of analyzing the outer retina. Loss of OFF-bipolar cells is known to decrease the amplitude of N1.<sup>37</sup> We found that venous vasculitis and capillary leakage were specifically associated with a reduction in N1 AMP, probably by a deleterious effect on the inner retina, especially on bipolar cells. The origin of N2 wave remains uncertain.<sup>12</sup> A recent study indicated that the activity of retinal ganglion cells contributed to the amplitude of the N2 of the mfERG.<sup>39</sup> The univariate analysis done in our study shows that N2 AMP was associated with photoreceptor alterations but it was not possible to identify confounding factors and contributions of other retinal layers, such as the retinal ganglion cell layer. Contribution of N2 for the FU of uveitis patients should be confirmed by further studies, while association with VF and VA were found in this study.

The implicit times of the N1 and P1 response are also known to be a very sensitive measure of outer retinal function,<sup>37</sup> and were correlated to the presence of macular edema. This finding is consistent with the correlation between CMT or macular edema and longer IT found previously in BSCR<sup>14</sup> and diabetic patients.<sup>38,39</sup>

We did not find any correlations between mfERG parameters and ICGA data, such as the number of quadrants with hypopyanescence dots at the intermediate phase. This finding could be due to the relative independence between choroidal and retinal involvement.<sup>40,41</sup> P1 IT was correlated with peripapillary hypopyanescence, which is a frequent finding in BSCR.<sup>42,43</sup> Future studies are needed to correlate choroidal thinning with changes of mfERG.<sup>44</sup>

The limitations of our study deserve mention. First, our study might be underpowered in detecting clinically significant temporal trends, due to the relatively limited sample size. Second, we investigated univariate associations only. Indeed, too few observations were available relative to the number of predictors included in multivariate analysis of mfERG. Hence, the multivariable model would fit the data set too closely and be likely to perform less well in new patients - a statistical phenomenon called overfitting. Furthermore the limited series of patients did not allow statistical comparisons for each ring separately. Third, five patients of the cohort were followed using TD-OCT since they were examined at baseline using TD-OCT in 2008. For this reason, analysis of the outer retina was done according the IS/OS disruption and not systematically considering the four bands well described in SD-OCT (ELM, EZ, CIZ, RPE). We used a published formula in order to reduce the effect of using different OCT machines. We estimate that the range of error is slight and that CME detection was not affected by these calculations. Fourth, four eyes (12.5%) were operated on for cataract during the study and the surgery was done between baseline and the first visit. The change in lens status may have changed the mfERG parameters. Cataract may reduce N1 and P1 amplitudes<sup>45</sup> and cataract surgery may increase mfERG responses.<sup>46</sup> Finally, mfERG is limited to the central 30 degrees, much less than standard ERG. Our previous study<sup>14</sup> showed that the degree of eccentricity (five rings) modulated the values for RMS, P1 and N2 amplitude, and P1 implicit time. 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. This topographic information was not used statistically in the present study due to statistical limitations. We can therefore

hypothesize that full field RDG and mfERG are complementary. One should note that these exams are time consuming and necessitates cooperation of the patient.

In conclusion, this longitudinal study of BSCR patients provides for the first time the evidence of worsening of mfERG responses in patients who were stable for other standard visual tests. MfERG, which is considered a reliable and accurate functional test,<sup>47</sup> was able to detect variations in N1 and P1 AMP and P1 IT over the 5-year FU period. Longer N1 and P1 IT at each visit were associated with functional worsening and macular edema. On the other hand, waves AMP were associated with presence of venous vasculitis and peripheral capillary leakage for N1 and photoreceptor layer alteration for P1. Although our findings deserve replication, our study supports the use of mfERG for initial assessment and subsequent monitoring of BSCR activity.

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## TABLES LEGENDS

**Table 1:** Baseline patient and eye characteristics. Data are expressed as mean (standard deviation) or numbers (%). CMT was defined as the mean retinal thickness within the 1-mm central subfield.

**Table 2:** Longitudinal analysis of univariate associations between mfERG variables and functional parameters

Regression coefficients represent the variation in predicted mfERG parameter value for a one-unit increase in the covariate value.  $\beta$  regression coefficients represent change in multifocal electroretinogram parameters for a 1-unit variation in functional parameters. For instance, a one decibel increase in MD values (i.e. worsening of MD) is associated with a - 0.4 ms variation in predicted N1 IT. In addition, a one-decibel decrease in MD values (i.e. improvement of MD) is associated with a +23 nV variation in predicted N1 IT.

Abbreviations: CI = confidence interval; ms = millisecond; deg= degree; VA = visual acuity

**Table 3:** Longitudinal analysis of univariate associations between mf ERG parameters and anatomical parameters

Abbreviations: CI = confidence interval; ms = millisecond; OCT = optical coherence tomography, CMT= central macular thickness, PR = photoreceptor, CME = cystoid macular edema, FA = fluorescein angiography, ICGA = indocyanin green angiography

- $\beta$  regression coefficients represent change in multifocal electroretinogram parameters for 1-unit variation in functional parameters.

**Table 4 (supplementary material):** Eye status according to intra-individual relative variation from baseline to the last follow-up (5-year FU) in N1 and P1 amplitude.

Intra-individual relative change was computed as (baseline value – FU3 value) / baseline value. For example, P1 AMP was defined as stable if the change between baseline visit and follow-up 3 (FU3) was comprised between -6.7% and +6.7%, improved (increased AMP) if increased by 6.7% or more, and deteriorated (decreased AMP) if decreased by 6.7% or more.

\* Eye status at follow-up was determined using an intra-individual relative variation threshold of 9.1% for N1 amplitude and 6.7% for P1 amplitude, respectively.<sup>28</sup>

## FIGURES LEGENDS

**Figure 1:** Trends in average values of mfERG parameter values at baseline (BL), follow-up 2 (FU2) at approximately 3 years and follow-up 3 (FU3) at approximately 5 years. The filled square is the average value of 16 patients and the vertical line is the standard deviation.

A: N1 amplitude (increase of 37 nV per year of FU, 95% CI, 24 to 51,  $P<.001$ ).

B: N1 implicit time (increase of 0.24 ms per year of FU, 95% CI, -0.04 to 0.51,  $P=.09$ ).

C: P1 amplitude (decrease in 61 nV per year of FU, 95% CI, -84 to -38,  $P<.001$ ).

D: P1 implicit time (increase of 0.68 ms per year of FU, 95% CI, 0.41 to 0.94,  $P<.001$ ).

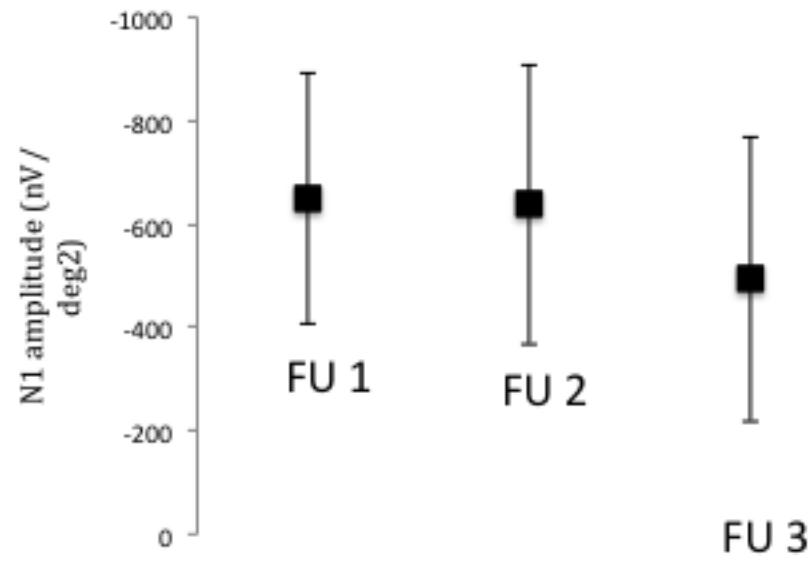
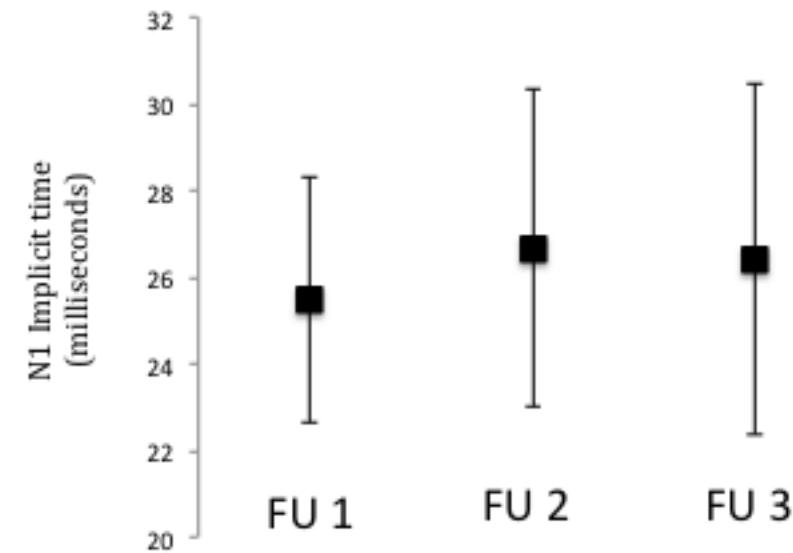
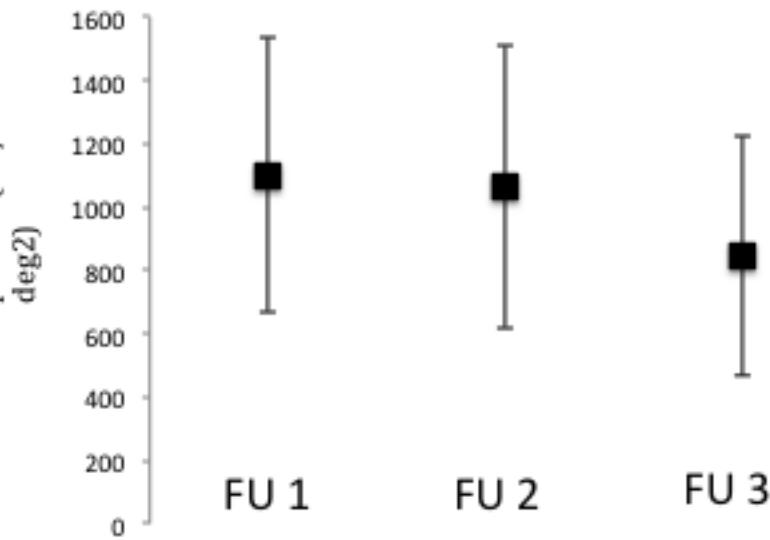
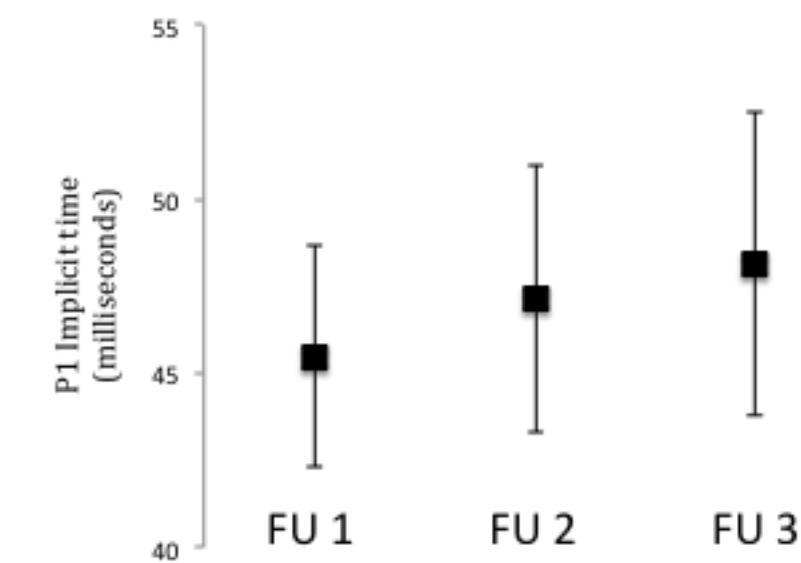
Data are means and bars represent standard deviation.

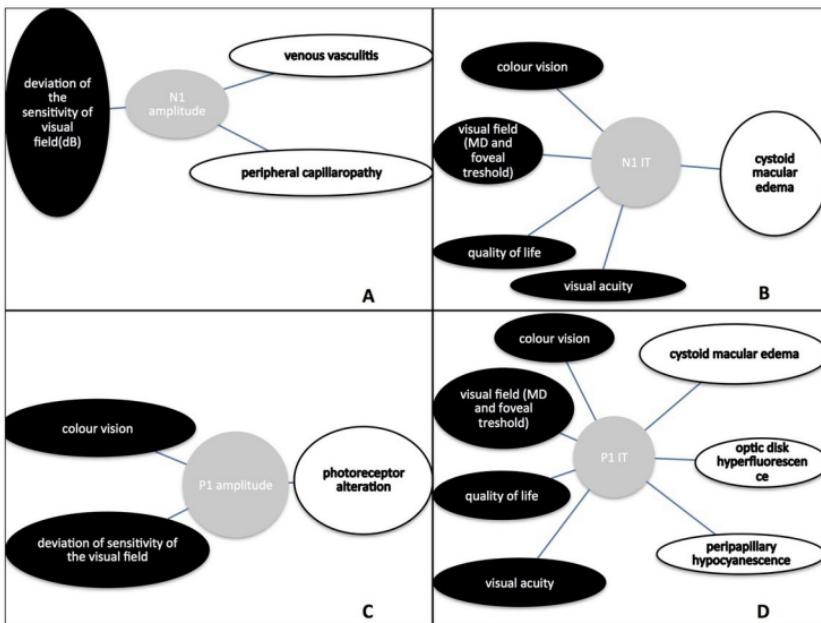
FU: follow-up

**Figure 2:** Univariate associations between mf ERG parameters and anatomical and functional parameters

**Figure 3: Time trend of mfERG parameters over a 5 year follow-up, with visual field and mfERG N1 and P1 amplitude 3D representation.** This female patient, 50 years old, diagnosed for Birdshot disease in 2008. Visual acuity was 20/30, had a venous vasculitis and a macular edema, and was initially treated by steroids and mycophenolate mofetil. In 2010, the patient was free of macular edema and vasculitis, under treatment with mycophenolate mofetil. Visual field was stable within the 5-year period with MD varying between -1.94 dB and -0.92 dB. Foveal sensitivity and visual acuity were stable (37 dB and 20/20, respectively). This case illustrates

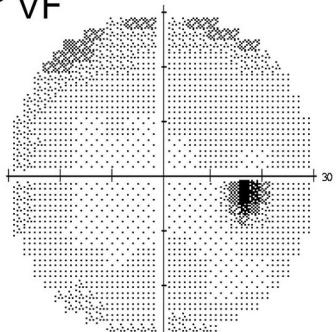
the worsening of mfERG parameters within the 5-year period: decrease in N1 amplitudes (from -865 nV to -738 nV) and P1 amplitudes (from 1398 nV to 1197 nV). Note that N1 amplitudes are illustrated in positive absolute values in the 3D graph.

**A****B****C****D**

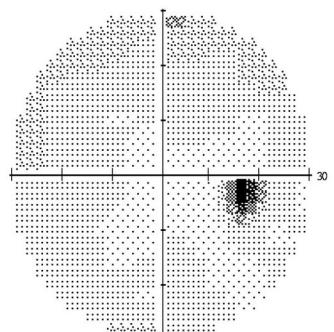


30° VF

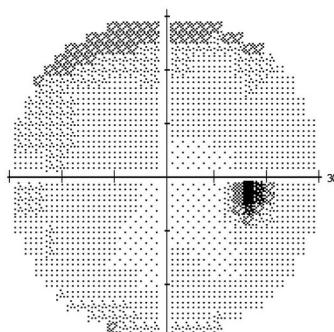
2010



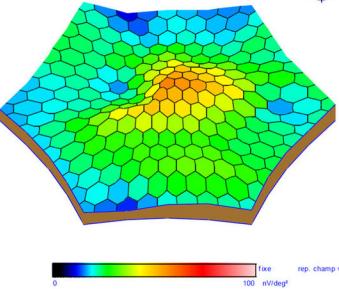
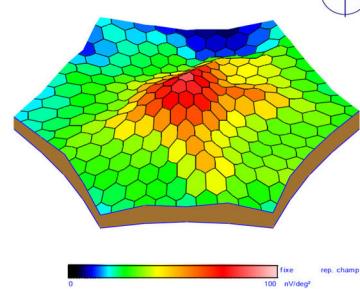
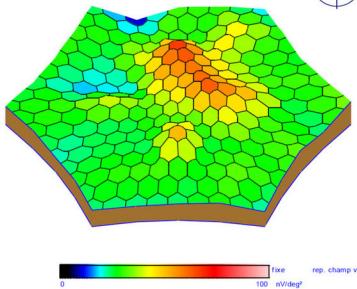
2012



2014



N1 amplitude

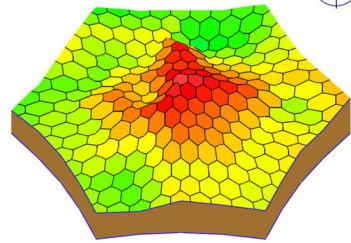
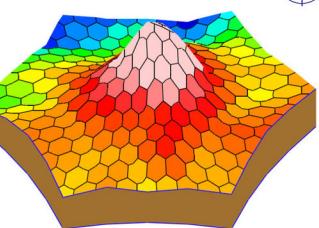
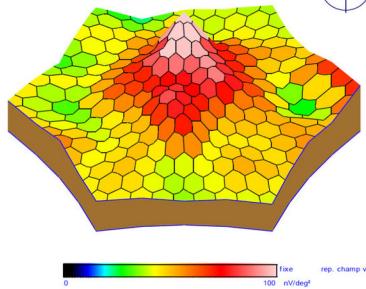


0 100 nV/deg<sup>2</sup> Fixe rep. champ visuel

0 100 nV/deg<sup>2</sup> Fixe rep. champ visuel

0 100 nV/deg<sup>2</sup> Fixe rep. champ visuel

P1 amplitude



0 100 nV/deg<sup>2</sup> Fixe rep. champ visuel

0 100 nV/deg<sup>2</sup> Fixe rep. champ visuel

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**Table 1.** Baseline characteristics.

<b>BASELINE PATIENT CHARACTERISTICS (n=16)*</b>			Abbreviations : ERG = electroretinography; IQR = interquartile range (i.e., 25–75 <sup>th</sup> percentiles); OCT = optical coherence tomography; SD = standard deviation.
Male gender, n (%)	6	(37.5)	
Disease duration, median (IQR), y	4.2	(1.6–7.3)	
Quality of life score, mean (SD)	70.3	(15.2)	
Treatment, n (%)			
None	6	(37.5)	
Corticosteroids	8	(50.0)	
Immunosuppressive therapy	2	(12.5)	
<b>BASELINE EYE CHARACTERISTICS (n=32)†</b>			range (i.e., 25–75 <sup>th</sup> percentiles); OCT = optical coherence tomography; SD = standard deviation.
Visual acuity (ETDRS letters), mean (SD)	76.6	(14.5)	
Visual field			
Foveal threshold, mean (SD), dB	33.3	(4.5)	
Mean deviation of the sensitivity of visual field, mean (SD), dB	-6.24	(6.04)	
Color vision			
Total error score, median (IQR)	140	(88–244)	
OCT data			
Central macular thickness, mean (SD), $\mu$ m	260	(90)	
Photoreceptor alteration, n (%)	5	(15.6)	
Cystoid macular edema, n (%)	4	(12.5)	
Epiretinal membrane, n (%)	12	(37.5)	
ERG data			Normative values (obtained from the manufacturer)
N1 amplitude, mean (SD), nV	-648	(243)	
N1 implicit time, mean (SD), ms	25.4	(2.8)	
P1 amplitude, mean (SD), nV	1099	(432)	
P1 implicit time, mean (SD), ms	45.4	(3.1)	
N2 amplitude, mean (SD), nV	-821	(380)	
N2 implicit time, mean (SD), ms	65.3	(4.8)	
Fluorescein angiography			Métrovision)
Posterior capillary leakage, n (%)	10	(31.2)	are (mean $\pm$ SD): -915
Optic disk hyperfluorescence, n (%)	6	(18.8)	nV for N1 AMP, 1633
Venous vasculitis, n (%)			$\pm$ 260 ms for P1 AMP, 23.2
Absence	19	(59.4)	
1 quadrant	3	(9.4)	$\pm$ 1.3 ms for N1 IT and
2 quadrants	4	(12.5)	42.2 $\pm$ 1.6 ms for P1 IT.
3 quadrants	4	(12.5)	
4 quadrants	2	(6.2)	
Peripheral capillary leakage, n (%)			
Absence	20	(62.5)	
1 quadrant	2	(6.2)	
2 quadrants	1	(3.1)	
3 quadrants	0	(0.0)	
4 quadrants	9	(28.1)	
Indocyanin green angiography			* Values were missing for quality of life (n=1) and
Peripapillary hypocyanescence, n (%)	17	(53.1)	
Dark dots, n (%)			
Absence	2	(6.2)	
1 quadrant	3	(9.4)	
2 quadrants	3	(9.4)	
3 quadrants	7	(21.9)	
4 quadrants	17	(53.1)	

\* Values were missing for quality of life (n=1) and

disease duration (n=1).

† N2 amplitude and N2 implicit times were missing at baseline for one eye in one patient.

**Table 2.** Longitudinal analysis of univariable associations between mfERG and functional parameters.

Parameters	N1 amplitude, nV			N1 implicit time, ms			P1 amplitude, nV			P1 implicit time, ms		
	$\beta^*$	(95%CI)	P	$\beta^*$	(95% CI)	P	$\beta^*$	(95% CI)	P	$\beta^*$	(95% CI)	P
Visual acuity (ETDRS letters)	-2.24	(-4.91 to 0.43)	.10	-0.09	(-0.13 to -0.04)	<.001	2.33	(-2.36 to 7.02)	.33	-0.05	(-0.10 to 0.00)	.05
Quality of life	-1	(-4 to 2)	.52	-0.08	(-0.13 to -0.02)	.004	0.7	(-4.8 to 6.3)	.80	-0.06	(-0.12 to -0.02)	.04
Visual field, dB												
Foveal threshold	2.3	(-5.8 to 10.4)	.56	-0.3	(-0.4 to -0.1)	<.001	4	(-11 to 18)	.61	-0.2	(-0.4 to -0.1)	.003
Mean deviation	-9.3	(-18.5 to -0.1)	.05	-0.4	(-0.5 to -0.3)	<.001	23	(8 to 38)	.002	-0.4	(-0.6 to 0.3)	<.001
Color vision	0.20	(-0.03 to 0.43)	.10	0.01	(0.007 to 0.01)	<.001	-0.5	(-0.9 to -0.1)	.01	0.008	(0.004 to 0.010)	<.001

(Continued)

**Table 2.** (Continued)

Parameters	N2 amplitude, nV			N2 implicit time, ms		
	$\beta^*$	(95%CI)	P	$\beta^*$	(95% CI)	P
Visual acuity (ETDRS letters)	-2.45	(-7.07 to 2.17)	.30	1.18	(0.86 to 1.49)	<.001
Quality of life	-0.5	(-6.3 to 5.4)	.88	-0.43	(-0.28 to 1.13)	.24
Visual field, dB						
Foveal threshold	-3.0	(-17.3 to 11.3)	.68	1.3	(-0.9 to 3.4)	.26
Mean deviation	-22.3	(-36.5 to -8.2)	.002	1.9	(0.8 to 3.0)	.001
Color vision	0.55	(0.14 to 0.96)	.009	-0.02	(-0.08 to 0.05)	0.59

Abbreviations: CI = confidence interval; ms = millisecond; deg = degree

\*  $\beta$  regression coefficients represent change in multifocal electroretinogram parameters associated with a 1-unit variation in functional parameters. For instance, a 1-decibel decrease in mean deviation value from -5 dB to -6dB (reflecting a worsening in mean deviation value) was associated with a 0.4 ms increase in N1 implicit time. A 1-decibel increase in mean deviation value from -5 dB to -4dB (reflecting an improvement in mean deviation value) was associated with a 23 nV increase in P1 amplitude.

**Table 3.** Longitudinal analysis of univariate associations between multifocal electroretinogram parameters and anatomical parameters.

Parameters	N1 amplitude, nV				N1 implicit time, ms				P1 amplitude, nV				P1 implicit time, ms			
	β*	(95%CI)	P	β*	(95%CI)	P	β*	(95%CI)	P	β*	(95%CI)	P	β*	(95%CI)	P	
<b>OCT</b>																
CMT	0.06	(-0.35 to .49)	.75	0.001	(-0.006 .01)	to	.67	0.22	(-0.52 to 0.96)	.56	0.001	(-0.007 to .01)	.72			
PR alteration	2.37	(-70.51 to 75.25)	.95	0.90	(-0.62 2.43)	to	.25	-145.46	(-273.56 to -17.36)	.03	0.92	(-0.59 to 2.44)	.23			
CME	-9.4	(-72.93 to 54.1)	.77	1.38	(0.08 to 2.68)	.04	-75.63	(-186.48 to 35.21)	.18	1.48	(0.21 to 2.75)	.02				
Fluorescein angiography																
Posterior capillary leakage	-21.90	(-85.30 to 41.49)	.50	-0.34	(-1.64 to .95)	.60	31.95	(-79.55 to 143.46)	.57	-0.87	(-2.15 to .39)	.18				
Venous vasculitis	-24.10	(-42.51 to -5.70)	.01	0.26	(-0.12 to .65)	.18	30.21	(-2.77 to 63.20)	.07	-0.02	(-0.41 to .36)	.88				
Peripheral capillary leakage	-21.35	(-39.07 to -3.63)	.02	-0.24	(-0.61 to .12)	.19	59.82	(30.31 to 89.33)	<0.001	-0.35	(-0.72 to .004)	.05				
Optic disk hyperfluorescence	16.78	(-46.97 to 80.54)	.61	0.72	(-0.60 2.05)	to	.28	-75.73	(-186.94 to 35.47)	.18	1.62	(0.36 to 2.89)	.01			
Indocyanine green angiography																
Dark dots areas	-14.46	(-39.19 to 10.25)	.25	0.00	(-0.50 to .52)	.98	17.89	(-25.80 to 61.59)	.42	-0.17	(-0.68 to .33)	.50				
Peripapillary hypcyanescence	79.48	(-3.54 to 162.50)	.06	0.50	-(1.13 2.14)	to	.55	-16.39	(-163.47 to 130.68)	.83	2.23	(0.64 to 3.83)	.006			

**Table 3.** (Continued)

Parameters	N2 amplitude, nV			N2 implicit time, ms		
	$\beta^*$	(95%CI)	P	$\beta^*$	(95%CI)	P
<b>OCT</b>						
CMT	-0.32	(-1.05 to .42)	.40	0.08	(-0.04 to .21)	.19
PR alteration	182.9	(57.5 to 308.4)	.004	-21.9	(-42.6 to -1.1)	.04
CME	104.9	(-10.9 to 220.6)	.07	7.1	(-18.7 to 32.9)	.59
Fluorescein angiography						
Posterior capillary leakage	38.9	(-74.3 to 152.2)	.50	13.1	(-6.7 to 32.8)	.19
Venous vasculitis	-2.1	(-38.4 to 34.2)	.91	2.3	(-4.5 to 9.0)	.51
Peripheral capillary leakage	-32.5	(-64.9 to -0.1)	.05	3.6	(-1.9 to 9.0)	.21
Optic disk hyperfluorescence	81.5	(-35.4 to 198.5)	.17	2.6	(-23.0 to 28.1)	.84
Indocyanin green angiography						
Dark dots areas	10.7	(-33.9 to 55.2)	.64	-2.4	(-10.7 to 5.9)	.57
Peripapillary hypcyanescence	3.5	(-144.9 to 152.0)	.96	-7.9	(-27.4 to 11.7)	.43

Abbreviations: CI = confidence interval; CME = cystoid macular edema; CMT = central macular thickness; FA = fluorescein angiography; ICGA = indocyanin green angiography; ms = millisecond; OCT = optical coherence tomography; PR = photoreceptor.

\*  $\beta$  regression coefficients represent change in multifocal electroretinogram parameters for a 1-unit variation in functional parameters.

**Table 4.** Eye status according to intra-individual relative variation from baseline to the last follow-up (5-year FU) in N1 and P1 amplitude.

Status at follow-up*	No. eyes	Intra-individual relative variation, %	
		Median	(range)
<b>N1 amplitude</b>			
Unchanged	5	-2.9	(-6.8 to 3.0)
Improved	2	-27.3	(-40.6 to -14.0)
Deteriorated	25	32.1	(12.0 to 66.8)
<b>P1 amplitude</b>			
Unchanged	7	2.9	(-2.0 to 5.2)
Improved	0	...	(...)
Deteriorated	25	23.9	(7.0 to 66.4)