Perifoveal Function in Patients with North Carolina Macular Dystrophy: The Importance of Accounting for Fixation Locus

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Purpose. To quantify the extent of visual function losses in patients with North Carolina Macular Dystrophy (NCMD) and to demonstrate the importance of accounting for eccentric fixation when making comparisons with normal data.

Methods. Five patients with NCMD who were from a single family were examined. Multifocal electroretinograms (mfERGs) and psychophysical assessments of acuity and luminance visual field sensitivities were measured throughout the central retina. Comparisons of responses from equivalent retinal areas were accomplished by shifting normal templates to be centered at the locus of fixation for each patient.

Results. Losses of psychophysically measured visual function in patients with NCMD extend to areas adjacent to the locations of visible lesions. The multifocal ERG amplitude was reduced only within the area of visible lesion. Multifocal ERG implicit times were delayed throughout the entire central retinal area assessed.

Conclusions. ERG timing is a sensitive assay of retinal function, and our results indicate that NCMD has a widespread effect at the level of the mid and outer retina. The findings also demonstrated that it is necessary to account for fixation locus and to ensure that equivalent retinal areas are compared when testing patients with macular disease who have eccentric fixation. (*Invest Ophthalmol Vis Sci.* 2006;47:1703–1709) DOI: 10.1167/iovs.05-0659

North Carolina Macular Dystrophy (NCMD) is an autosomal dominant retinal disease that affects the central retina.[1–4] Macular fundus changes range from drusen concentrated in the fovea to staphylomatous or colobomatous lesions associated with local atrophy of the retinal pigment epithelium (RPE) and/or choroid.[5] A defect has been identified on the long arm of chromosome 6 in patients with NCMD.[2,6–12] Although NCMD was initially thought to be a progressive macular dystrophy,[1,4] recent evidence suggests that the clinical course of the disease is stable, except in those patients who have choroidal neovascularization or other ocular disease (Kiel R, et al. IOVS 2000;41:ARVO Abstract 4699).[5,9,12–14]

There have been reports of normal full-field electrophysiological findings suggesting a relatively localized disease.[1,8,9,13] In addition, Small et al.[3] reported histologic evidence that the disease is confined to the macular area. Localized dysfunction has also been demonstrated by Rohrschneider et al.,[13] who reported absolute scotomas corresponding to areas of fundus changes in patients with NCMD. However, abnormalities outside of the area of the central lesion, including intercapillary pillar thickening of the choriocapillaris adjacent to the lesion[3] and drusen in the peripheral retina, have been observed.[3,5,12,15,16] Pattern electroretinograms, recorded from an area subtending an area larger than the macula (15° × 22°), have been reported to be reduced in patients with grade-3 lesions who had normal full-field electroretinograms (ERG).[9] In the present study, we examined the relationships among fundus findings, local psychophysical function (letter acuity perimetry and Humphrey visual field findings), and electrophysiological function (multifocal electroretinogram, mfERG), to document the extent of retinal involvement in patients with NCMD. In doing this, we demonstrated that it is critical to account for fixation locus when assessing local measures in patients who have macular disease and eccentric fixation.

Materials and Methods

We examined five patients from a single family with an autosomal dominant macular dystrophy mapped to the MCDR1 locus.[8] Informed consent, as approved by the University of Illinois at Chicago Institutional Review Board, were obtained. The clinical grades of severity were determined by one of the authors (MFR). The fundi were graded according to the scale proposed by Small et al.[5,10]: 1a, lesions consisting of drusen concentrated in the fovea; 1b, drusen with minimal pigment involvement; 2a, confluent drusen or pigment epithelial atrophy; 2b, a doughnut-shaped subretinal disciform scar surrounding the macula; 3a, discrete staphyloma with minimal involvement of the RPE; and 3b, a colobomatous lesion centered in the macula with atrophy of the RPE and/or choroid. Table 1 presents the clinical grade of each patient. The disease stage was equivalent bilaterally for each patient. Visual acuity was assessed using EDTRS charts, and the eye with better acuity was selected for testing. Visual acuities of the tested eyes ranged from −0.10 logMAR (logarithm of the minimum angle of resolution; ~20/16) to 0.50 logMAR (~20/63).

Electrophysiology

A camera/refracter system (VERIS; EDI, San Mateo, CA) stimulus array consisted of 103 hexagons that were scaled according to eccentricity.[17] The array subtended 46° horizontally and 39° vertically at the viewing distance of 32 cm. The m-sequence was set so that each hexagon had a 50% probability of being white or of being black on each frame (0F). The luminance of the white hexagons was 280 cd/m^2, that of the black hexagons was 0.5 cd/m^2, and the surround luminance was 100 cd/m^2. The subject's pupil was dilated (1% tropicamide, 2.5%

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TABLE 1. Patient Information

Patient	Gender	Grade	Age	Acuity	
				OD	OS
1	M	1b	55	20/16	20/25
2	M	2b	28	20/63	20/40
3	M	2b	6	20/63	20/125
4	F	2b	10	20/200	20/50
5	F	3b	30	20/80	20/63

phenylephrine hydrochloride), and the cornea was anesthetized (0.5% proparacaine) before insertion of a bipolar Burian-Allen contact lens electrode (Hansen Ophthalmic Development Laboratory, Iowa City, IA). The nontested eye was patched. The ERG signal was amplified (100,000 times), band-pass filtered between 10 and 300 Hz and digitized at 1200 Hz. The camera/refractor was used to provide each subject with his/her best optical correction for the viewing distance and to monitor eye movements. The first-order kernel mfERG responses (Fig. 1) were exported and then analyzed by using a program (written in MatLab; the MathWorks, Natick, MA) that calculated amplitude and implicit time of the first positive response.[18] The mfERG was not performed on patient 3 due to his young age.

Visual Acuity Field Mapping

Letter-acuity field maps were measured for each patient, by a fundus imaging system (FIS).[19] The system is an adaptation of the Marco G2 Ultra Slit Lamp (based on Zeimer et al.[20]). One accessory arm of the slit lamp was used to project the image of an external 5-in. CRT (80 Hz noninterlaced frame rate and resolution of 1600 × 1200 pixels; Moraine Displays, Inc., Big Bend, WI) through a 60-mm lens (AF Micronikkor; Nikon, Tokyo, Japan). The 25× magnification setting of the slit lamp, coupled with a 60-D lens, projected the CRT image to a 30° field of view. Illumination for fundus viewing was provided by filtering the light source of the slit lamp using an infrared pass filter (Wratten 89B; Eastman Kodak, Rochester, NY). An infrared sensitive charge-coupled device [CCD] camera (IR-1000; Dage MTI, Michigan City, IN) was mounted on the other arm of the slit lamp. The images collected by the camera were processed further with an enhancement board (Dage MTI) that allowed contrast and luminance control. The fundus image was then displayed on a 9-in. black-and-white monitor in real time. The experimenter viewed the patient's fundus image and a letter target overlaid on the fundus at the location of stimulation (BOB II Video OSD; On Screen Display Module; Decade Engineering, Turner, OR; Fig. 2A). The experimenter ensured that the letters were imaged on the intended retina area by presenting stimuli only when the eye was stable (determined by viewing the location of fundus landmarks).

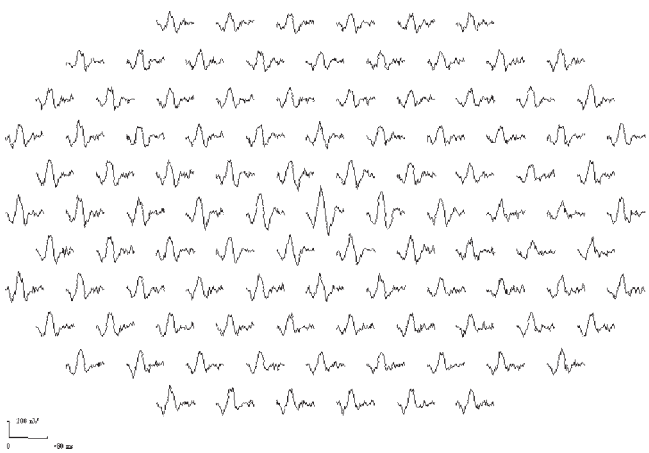

FIGURE 1. Normally sighted subject. First-order kernel mfERG responses recorded from a normally sighted subject.

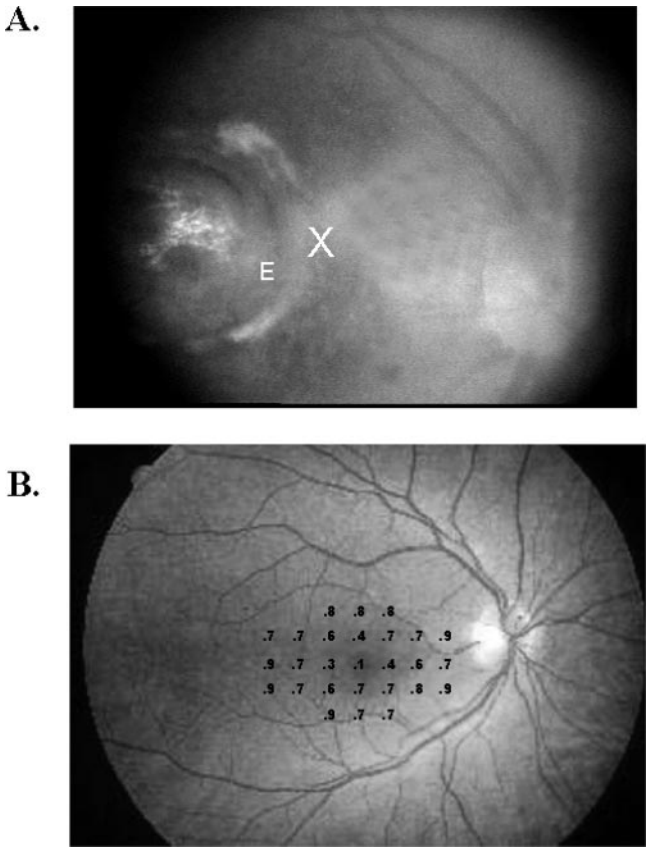

FIGURE 2. Acuity perimetry. (**A**) Infrared illuminated image of a patient's fundus with fixation target (X) and letter target (E) overlaid. (**B**) The mean acuities of the control group are plotted at the locations of stimulation overlaid on a normal fundus image.

The acuity field area extended 18° horizontally and 12° vertically. During each trial, a letter (randomly chosen from a set of eight letters) was presented at one of the testing locations (randomly chosen from 27 possible testing locations) (Fig. 2B). Letter-stroke widths ranged between 0.8 (−0.09 logMAR) and 16.4 minarc (1.21 logMAR; Snellen equivalent of ~20/16–20/328), and the minimum step size was 0.8 minarc. Twenty-seven threshold algorithms were run simultaneously to obtain a letter-acuity threshold value for each of the locations.

Humphrey Visual Field

Cone-system threshold visual fields were measured using perimeter (Humphrey Field Analyzer Model 750; Carl Zeiss Meditec, Dublin, CA). Forty-five retinal locations were tested, corresponding to the middle of the 45 mfERG hexagons in the central 20°. Each test spot subtended 26 minarc, and the background luminance was 10 cd/m^2. The nontested eye was patched.

RESULTS

The Importance of Accounting for Eccentric Fixation

For many patients with diseases that affect the central retina, an eccentric locus (a preferred retinal locus, PRL) is used for fixation because it provides better visual acuity than the diseased fovea. However, commonly, this shift in fixation is not

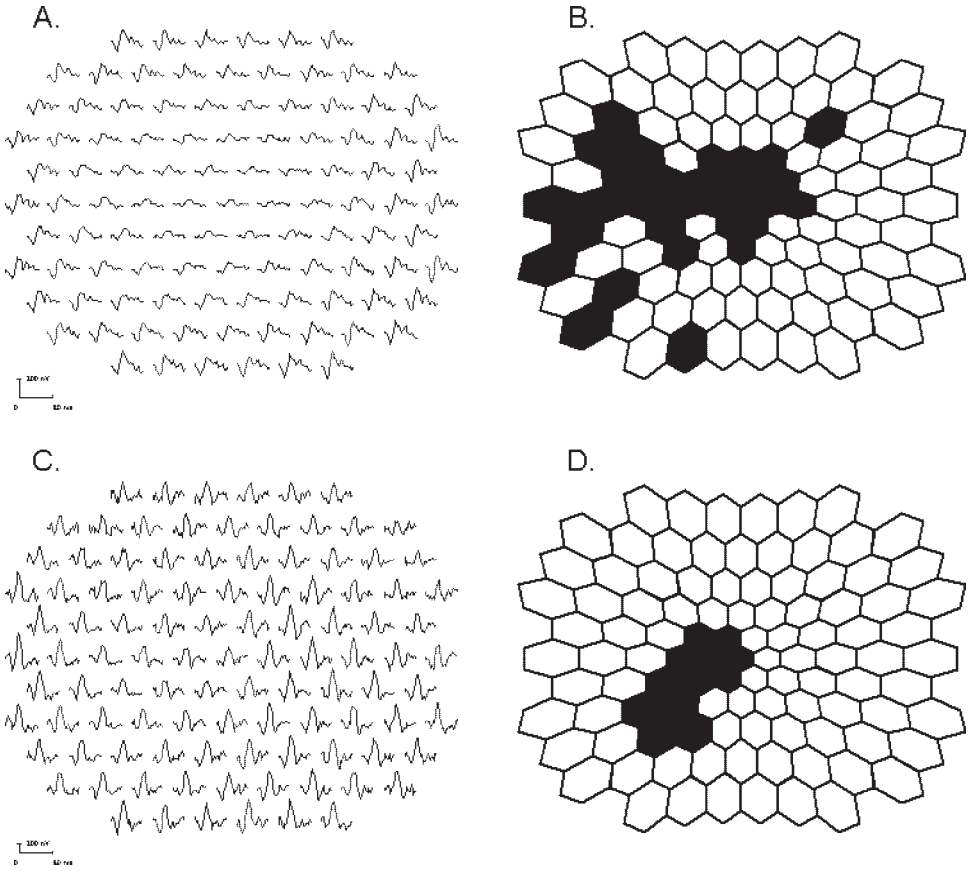

FIGURE 3. (**A**) First-order kernel mfERG responses recorded from a patient with NCMD. (**B**) Shaded hexagons indicate areas with significantly reduced amplitudes for this patient ($P \leq 0.001$). (**C**) First-order kernel mfERG responses recorded from a normally sighted subject who fixated 6° temporally (field view). (**D**) Shaded hexagons indicate areas with significantly reduced amplitudes ($P \leq 0.001$) for the responses shown in (**C**).

considered when local visual function is assessed in patients with macular disease. This failure may result in false abnormal findings, regardless of the underlying function. To illustrate this, the mfERG of patient 5 is shown in Figure 3A. There is an mfERG amplitude reduction of the patient's response to the central hexagons, which is consistent with macular disease. However, a reduction in amplitude can also be seen for hexagons adjacent to the central hexagons. When the amplitudes of this patient's mfERGs were compared to the average amplitudes for the equivalent hexagons of the control group, significant reductions ($P < 0.001$) were observed for the central and adjacent hexagons (Fig. 3B). The pattern of these findings match that expected for patients with macular disease; however, in some cases, such findings may be an artifact of the comparison method.

To mimic this patient's data, we asked a normally sighted subject to fixate on an X placed approximately 6° temporally on the stimulus array while we recorded the mfERG. We found that mfERG responses for the central and adjacent hexagons were reduced when the subject fixated eccentrically (Fig. 3C). Similar to the patient's findings, statistical analysis of equivalent hexagons for the eccentrically fixating subject showed significant amplitude reduction in the central and adjacent retina (Fig. 3D), even though the subject's retina was completely normal. This was simply because responses from equivalent areas of retina were not compared. For example, when the normally sighted subject fixated eccentrically, the central hexagon of the mfERG array elicited responses from the region of retina centered 6° nasal to the fovea. When the amplitude elicited from this eccentric retina was compared to the "normal" response of the central hexagon (i.e., when fixating centrally), significant reductions were found.

Correction Procedure for Eccentric Fixation

PRL location was estimated for each patient based on three fundus-fixation photographs. Because the disease may obscure the fovea, the approximate retinal location of the fovea was estimated for each patient, by using his or her optic nerve head as a landmark. This technique has been used in several studies.[21–24] The location of each patient's PRL was calculated as the average position relative to the estimated location of his or her fovea on each of the photographs.

Each patient's data array was then centered at his or her fixation locus (see the mfERG example for patient 5; Fig. 4). Equivalent normal comparison data were then derived by comparing the array of the normal group ($n = 20$, mean, 41.5 years; age range, 20–84 years) to each patient's shifted array. For example, patient 5's fixation locus was approximately 6° temporal (field view). At this fixation locus, the equivalent comparison data for the patient's central hexagon comprised an average of the responses from hexagons 44, 54, and 55 of the normal subjects (Fig. 5). This calculation was performed for every hexagon for each patient. Similar derivations of comparable normal data were also determined for the psychophysical results.

The difference in log values were then calculated for each position relative to the derived equivalent retinal responses of the control group as log(patient's value) − log(spatially averaged control groups' value). For the perimetry data, the differences in decibels were calculated and reported as log (i.e., dB/10). To check our logic, we compared the mfERG data for the eccentrically fixating normally sighted subject (Fig. 3C) to the derived normal responses of equivalent retinal areas for the control group and found no hexagon with significantly reduced amplitude.

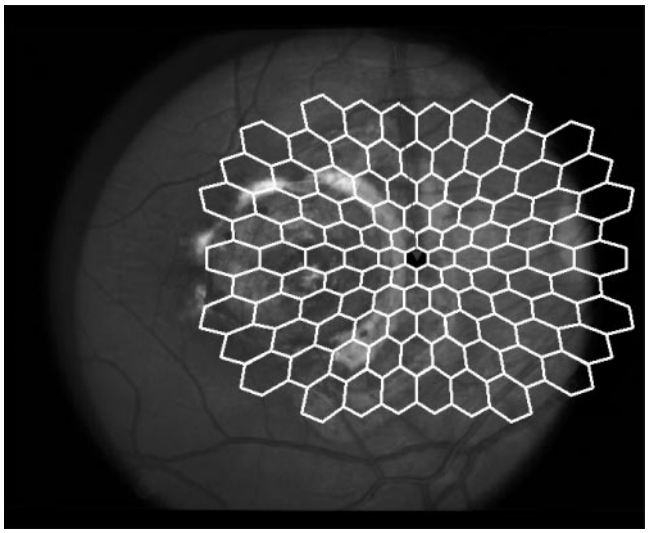

FIGURE 4. Fixation photograph of patient 5. The mfERG stimulus array is drawn on the photograph and centered at the locus of fixation.

Data Presentation

Each patient's fundus photograph was imported into a spreadsheet-based (Excel; Microsoft, Redmond, WA) digitizing software program (Grab It! XP; Datatrend Software, Raleigh, NC). Using this software, we outlined the disc and the extent of the visible lesion for each patient. The electrophysiological and psychophysical test results were then superimposed onto the digitized images by aligning the 0,0 coordinate of each test with the point of fixation for each patient.

Comparisons with Equivalent Retinal Areas

The log losses of mfERG amplitudes of patient 5 are plotted to the digitized map in Figure 6. The map is shown in fundus view. There is good agreement between the loci of the most severe mfERG abnormalities and the area of the visible lesion.

Local Analysis

We wanted to determine the extent of functional losses and their relationship to visible fundus changes in patients with NCMD. Therefore, we grouped the log loss data into three

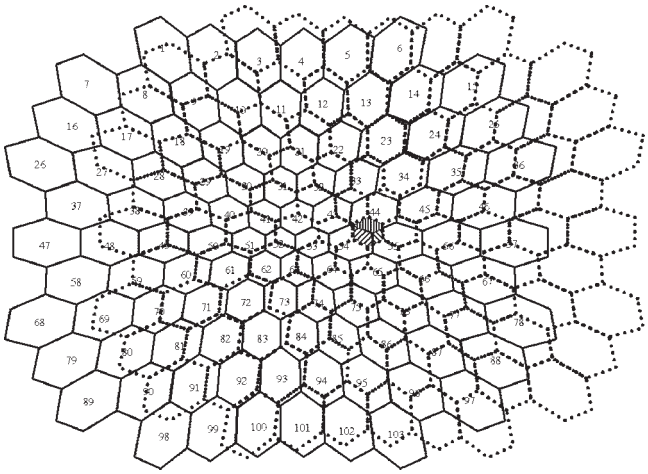

FIGURE 5. The eccentrically centered mfERG stimulus array for patient 5 (outlined in *dashed lines*) has been shifted relative to a foveally fixated array to allow calculation of norms for equivalent retina areas.

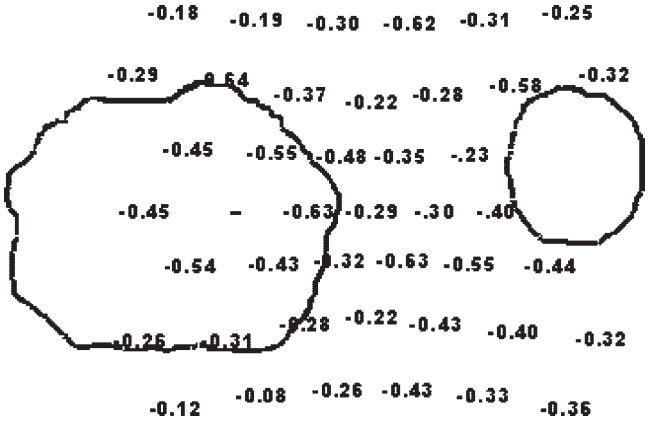

FIGURE 6. Log mfERG amplitude losses. Log losses in patient 5 are plotted as a function of location. The lesion and optic disc have been outlined based on digitization of the fundus photograph.

regions: *Inside*: points falling within the lesion and area of subretinal fibrosis. *Adjacent*: points immediately eccentric to the edge of the *inside* region. The average distance between the lesion edge and *adjacent* points on the FIS was 1.3 ± 0.65° (384 ± 188 μm), and on the mfERG and perimeter, it was 1.6 ± 0.7° (470 ± 312 μm). *Outside*: the remaining points.

Median mfERG log amplitude losses were calculated across all patients for each region. The magnitude of the mfERG amplitude loss decreased as a function of distance from the lesion (Fig. 7A). The median log difference for a group of 10 normally sighted control subjects is also shown. This was calculated as $\log(\text{amplitude hexagon}_{i,j}) - \log(\text{average amplitude hexagon}_j)$ for all subjects i and all hexagons j. A Kruskal-Wallace one-way ANOVA yielded a significant main effect ($P < 0.001$), with post hoc analyses (rank sum tests) yielding significant amplitude differences among all three regions. However, only the *inside* region had significantly reduced mfERG amplitudes relative to those of the control subjects (Table 2).

In Figure 7B, the median log losses of mfERG implicit time data are plotted as a function of the region. The magnitude of the implicit time delays decreased as the distance from the lesion increased, but the losses were large in all regions. There was a significant main effect ($P < 0.001$). Post hoc analyses showed significant differences between *inside* and *adjacent* regions and between *inside* and *outside* regions. The delays for all regions were significantly greater than control group (Table 2).

The FIS acuity data are plotted in the same manner in Figure 7C. Acuity deficits were largest for the *inside* region and decreased with eccentricity. A Kruskal-Wallace one-way ANOVA yielded a significant main effect ($P < 0.001$). Post hoc analyses showed significant differences between all three regions. The patients' acuities in the *inside* and *adjacent* regions were significantly poorer ($P \leq 0.001$) than those of the control group (Table 2).

We also examined the acuity at fixation (the central FIS location) for each patient. Each patient's acuity at fixation was compared to the average acuity of the normally sighted control group at an equivalent retinal location (Fig. 8). For patient 1, acuity at fixation was better than the average acuity for the control subjects. For the other patients, acuities at their PRLs were significantly poorer ($P \leq 0.001$) than those of control subjects at equivalent retinal locations.

The median Humphrey log losses were significantly decreased as a function of distance from the lesion ($P < 0.001$; Fig. 7D). There were significant differences between *inside* and *outside* and between *adjacent* and *outside* regions. The patients' Humphrey sensitivities in the *inside* and *adjacent*

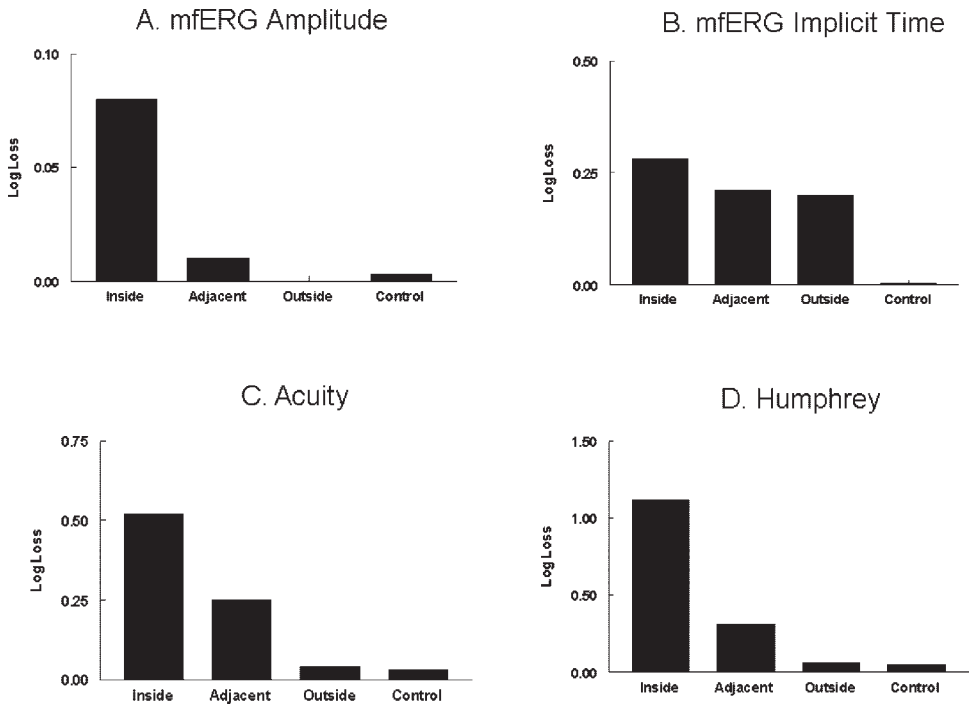

FIGURE 7. (**A**) mfERG amplitude. Averaged log losses of mfERG amplitude relative to retinally equivalent data from the control subjects are plotted as a function of distance from the funduscopically visible lesion. (**B**) mfERG timing. Averaged log mfERG implicit time losses relative to retinally equivalent data from control subjects are plotted as a function of distance from the funduscopically visible lesion. (**C**) Acuity. Averaged log acuity losses relative to retinally equivalent data from control subjects are plotted as a function of distance from the funduscopically visible lesion. (**D**) Humphrey visual field sensitivity. Averaged sensitivity losses (in log units) relative to retinally equivalent data from control subjects are plotted as a function of distance from the funduscopically visible lesion.

regions were statistically less ($P \leq 0.001$) than those of the control group (Table 2).

DISCUSSION

We examined the local distribution of electrophysiological and psychophysical losses in five patients with NCMD. After correcting for eccentric fixation locus, we found that patients with NCMD had significant mfERG amplitude losses within the areas of visible fundus lesions only. This finding is consistent with reports of normal full-field ERG amplitudes in patients with NCMD.[1,8,9,13] It is not uncommon to record normal electro-oculograms and/or full-field ERGs in patients with discrete macular problems.[25–36]

In contrast to the amplitude findings, we found mfERG implicit time abnormalities throughout the central 40° of retina. None of the previous reports of full-field ERG in patients with NCMD have commented on timing. Full-field ERG timing losses in the absence of amplitude losses have been reported in other diseases.[28,37–44] In addition, delays in mfERG implicit time outside of the diseased central areas and without accompanying amplitude losses also have been reported.[31,45–50] ERG timing is thought to be a sensitive indicator and/or predictor of retinal dysfunction.[45,50–54] The current findings indicate that the pericentral retina is not electrophysiologically normal in patients with NCMD.

Significant visual acuity losses were found within the lesions and in regions adjacent to the lesions. There have been reports in the literature that acuity in patients with NCMD is better than expected, given the loci of the lesions.[5,13] It been hypothesized that there may be a developmental change in the location of the fovea that would account for this better-than-expected acuity.[13] No study has compared acuities of patients with NCMD at their eccentric PRLs to the acuities of a healthy retina at an equivalent eccentricity. We found that four of the five patients with NCMD had significantly worse acuities than the acuities expected from a healthy retina at equivalent eccentricities.

Local Analysis

We have demonstrated the importance of using appropriate retinal areas for comparison when examining patients with macular disease who use eccentric fixation. If this is not done, abnormal function might be inferred based on a comparison of responses from retinal areas that are not equivalent, regardless of underlying disease.[55–57]

A second question with eccentric viewing is fixation stability. For example, patients with age-related macular degeneration (AMD) have been reported to have decreased fixation stability,[58–62] and such instability might contribute to overall lower visual function. Møller and Bek[63] reported a correlation

TABLE 2. Statistical Comparisons

	Main Effect H*	Inside vs. Adjacent	Inside vs. Outside	Adjacent vs. Outside	Inside vs. Control	Adjacent vs. Control	Outside vs. Control
mfERG Amp	<0.001	0.01	0.05	0.05	0.003	NS	NS
mfERG IT	<0.001	0.05	0.008	NS	<0.001	<0.001	<0.001
Acuity Field	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	NS
Humphrey	<0.001	NS	<0.001	0.002	<0.001	<0.001	NS

* Kruskal-Wallace one-way ANOVA. The remainder of the comparisons are by post hoc analyses (rank sum tests).

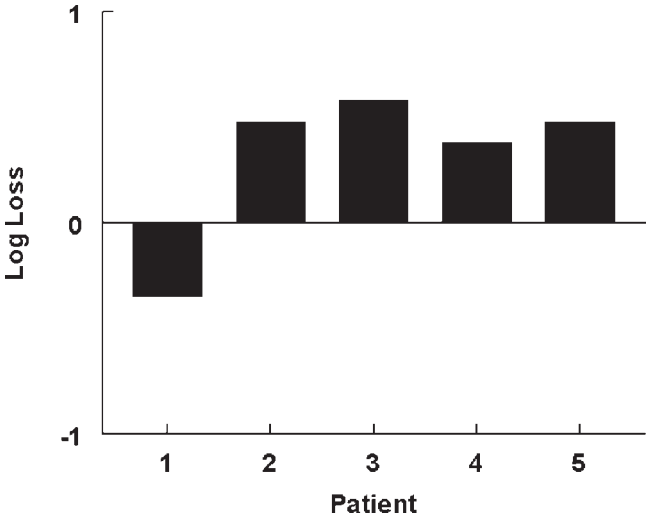

FIGURE 8. Acuity losses at fixation. The log differences between the patients' acuities and those of normally sighted subjects at equivalent eccentricities are shown.

between increase in the area of the locus of fixation and decrease in visual acuity in patients with diabetic and nondiabetic macular disease. However, this finding may have been due to the covariance of fixation eccentricity, fixation stability, and visual acuity, because these authors reported no relation between change in fixation stability and change in visual acuity in a second study.[64] Keesey[65] found that there was no change in visual acuity when comparing a condition with stabilized retinal images and one that allowed involuntary eye movements. Timberlake et al.[66] and Rohrschneider et al.[62] also reported low correlations between fixation stability and visual acuity in patients with macular scotomas.

Rohrschneider et al.[62] measured fixation stability during perimetry with a scanning laser ophthalmoscope and reported that normally sighted subjects had standard deviations (SDs) of fixation of $<0.7°$. For 38 patients with AMD, the mean SDs of fixation was 1.04°, with approximately 50% of the patients' eyes showing SDs of fixation of <1.0.[62] The extent of fixation deviations was not related to visual acuity or age in the patients. Using the same technique, Rohrschneider et al.[13] reported that fixation stability in a group of five patients with NCMD was near normal, ranging from 0.14 to 1.0°, with 80% of the eyes below the normal value of 0.7°. In these patients with NCMD, fixation stability was not related to fundus appearance, and the correlation between fixation stability and visual acuity was -0.21 ($P = 0.55$).

Fixation instability might reduce the spatial sensitivity of the amplitude measure of the mfERG, decreasing its ability to distinguish a localized region of dysfunction.[57] In the present study, we found good localization of macular dysfunction using mfERG amplitude. This supports the relatively good fixation stability in our patients with NCMD. In any case, fixation instability alone would not be expected to alter the timing characteristic of the mfERG significantly, and we found widespread mfERG timing delays in our patients.

Summary

We found that losses in visual function in patients with NCMD extend to areas immediately adjacent to the location of visible lesion for all measures, except for mfERG amplitude. We also found that mfERG implicit times were delayed throughout the entire retinal area assessed. Our results indicate that NCMD has widespread effects at the level of the mid and outer retina. We have also demonstrated that primary concerns when testing patients with macular disease are accounting for fixation locus and ensuring that the same retinal areas are compared.

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