Pattern-Reversal Electroretinographic Acuity in Untreated Eyes With Subfoveal Neovascular Membranes

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To define further the natural history of visual loss in eyes with age-related macular degeneration (ARMD) complicated by a subfoveal neovascular membrane, pattern-reversal electroretinograms (ERGs) were obtained from patients randomized to no treatment at the Dallas center of the Macular Photocoagulation Study (Texas Retina Associates). Study eyes (n = 20) were tested during the initial visit and at 3-, 6-, and 12-month follow-up visits. Responses were obtained to phase-alternating checkerboards of varying check size. Extrapolation of the best-fit regression line relating the logarithm of the check size to amplitude was used to determine “retinal” acuity (log MAR). The pattern-reversal ERG acuity rating (100 - [50 X log MAR]) was derived for each visit. Pattern-reversal ERG acuity ratings for all patients across visits were correlated significantly with visual acuity ratings derived from the Bailey-Lovie chart (r = 0.61, P < 0.001) and inversely related to neovascular membrane area (r = -0.55, P < 0.001). During 1 yr of follow-up, pattern-reversal acuity ratings dropped from 53 to 12, corresponding to an average decrease of approximately 0.2 octaves/month. These results suggest that the pattern-reversal ERG, which samples the resolving power of the central 20°, is a sensitive index of visual loss in age-related macular degeneration. Invest Ophthalmol Vis Sci 33:2097–2104, 1992

The prognosis for useful vision in age-related macular degeneration (ARMD) is particularly poor when a choroidal neovascular membrane extends under the fovea.1–5 The Macular Photocoagulation Study (MPS) is evaluating the possible efficacy of photocoagulation treatment of subfoveal neovascular membranes in a multicenter randomized trial, the Foveal Photocoagulation Study (FPS). The FPS also is addressing the possible treatment benefit in eyes with recurrent membranes after laser treatment. The recurrence rate of neovascular membranes within 5 yr of extrafoveal treatment may be as high as 50%, and frequently these membranes extend into the foveal avascular zone.6

As part of the FPS, patients are randomized to treatment or no-treatment conditions and are followed for up to 4 yr. The primary outcome variable is visual acuity. The group also measures contrast sensitivity and reading speed for large print text to supplement visual acuity. As an ancillary component of the FPS, we obtained pattern-reversal electroretinograms (ERGs) from patients enrolled at Texas Retina Associates, the Dallas MPS group. The pattern-reversal ERG is elicited from the macula by phase-reversing patterned stimuli (gratings or checks). Because the mean luminance of the pattern remains constant over time, contamination of the ERG by stray light is minimized. The response is generated entirely by the retinal area under stimulation.7,8 The pattern-reversal ERG shows a progressive decrease in amplitude with increasing artificial central scotoma size.9 When high-contrast patterns are used, responses to large check sizes (low spatial frequencies) contain luminance-specific components that mask the low-frequency roll-off of the contrast-specific response.10 Nevertheless, pattern-reversal ERG amplitude is proportional to the logarithm of the check size under these conditions, and estimates of macular integrity can be obtained from the linear regression of amplitude in relation to the log check size or log spatial frequency.10–12 We used this pattern-reversal ERG “acuity” as an objective quantitative measurement of the natural course.
of progression in untreated eyes with subfoveal neovascular membranes associated with ARMD.

Materials and Methods

Subjects

Pattern-reversal ERGs were obtained from 24 patients randomized to no treatment in the FPS. All patients were 50 yr of age or older at the time of their initial visit (range, 59–88 yr; mean, 72 ± 7 yr), had funduscopic evidence of ARMD, and angiographic evidence of a neovascular complex under the center of the foveal avascular zone. To be eligible for the study, best-corrected visual acuity had to be better than 20/320 and worse than 20/40. The size of the subfoveal membrane had to be less than four disc areas (< 80°2). Other inclusion criteria included media of sufficient clarity for detailed examination of the fundus and a willingness to return for follow-up. Exclusion criteria included other serious eye diseases that could compromise visual acuity and the use of systemic corticosteroids or other medications that could affect the macula.

Ten subjects who were 50 yr of age or older with normal ophthalmologic examinations (range, 55–77 yr; mean, 69 ± 7 yr) provided normative data. All patients and normal subjects consented to the testing after the procedures, potential risks, and benefits were explained. The study protocol was reviewed and approved by the MPS Executive Committee and by the Institutional Review Board of Texas Retina Associates.

Procedure

Visual acuity after refraction was measured on Bailey-Lovie charts during each visit as part of the FPS protocol. Acuity measures were converted to visual acuity ratings13 where:

\[ \text{visual acuity rating} = 100 - (50 \times \log \text{MAR}) \] (1)

Pattern-reversal ERGs were obtained from patients and normal subjects after pupil dilation. Recording from FPS patients was conducted at least 1 hr after fundus photography, which allowed sufficient time for recovery from light exposure in normal subjects.14 Pattern-reversal ERGs were recorded in an electrically isolated chamber at a distance of 1 m from a video monitor measuring 26° diagonally. Responses were obtained with a Burian-Allen bipolar contact-lens electrode. Optical correction was determined through retinoscopy with the contact lens in place. The patient was fitted with a trial lens frame containing the appropriate correction over the contact-lens electrode and asked to read a Snellen eye chart projected onto a white screen placed immediately in front of the video monitor. The refraction then was refined until acuity was equal to or within one line of FPS protocol acuity.

During each visit, responses were obtained to seven check sizes (640' to 10') and two temporal frequencies (2 and 30 reversals per second). A single high-contrast level (98%) was used for all stimuli. The average luminance of the screen was 150 cd/m2. Raw signals for both reversal rates were amplified (gain, 10,000; band width, 1–50 Hz) and recorded on tape with frequency modulation electronics. Additional filtering at 30 reversals per second15 was provided by a band-pass amplifier (gain, 20; Q, 16). Signals were averaged on line (n = 100) with a general-purpose laboratory computer. The software contained an artifact-reject buffer to eliminate responses from blinks and eye movements. Amplitudes were measured from baseline to the peak of the primary positive component (P1). A full sequence of 14 stimulus conditions (seven check sizes, 2 reversal rates) was obtained in approximately 25 min.

For purposes of analysis, each check size was adjusted for the power in the diagonal.16 The best-fit line relating amplitude to the logarithm of the adjusted check size over the linear region then was used as a measurement of resolution (criterion, 0.0 μV). To facilitate comparisons to visual acuity ratings, pattern-reversal ERG resolution (log MAR) was converted to a pattern-reversal ERG acuity rating:

\[ \text{pattern-reversal ERG acuity rating} = 100 - (50 \times \log \text{MAR}) \] (2)

The size of the subfoveal neovascular membrane was measured by an ophthalmologist (GEF) on each visit by determining the perimeter of the membrane from fluorescein and fundus photographs. The outline of the membrane was computer digitized to determine the area. A significant intraclass correlation was found between areas measured in this manner and measurements provided by the FPS reading center in Baltimore for the initial visit (r = 0.93, P < 0.001).

Results

The mean pattern-reversal ERG amplitudes (± standard error) from ten elderly normal subjects are shown for two reversal rates in Figure 1. At both reversal rates, amplitudes decreased monotonically with check size. Amplitudes at a reversal rate of 2 Hz were larger than amplitudes at 30 Hz (steady state) across all check sizes, with amplitude ratios varying
from 1.91 for the largest checks to 6.9 for the smallest.
The best-fit regression line (dashed line) for the 2-Hz
reversal rate extrapolated to 0.0 μV at approximately
log MAR = 0.2, corresponding to a pattern-reversal
ERG acuity rating of 90 and a Snellen equivalent of
20/30. The range of extrapolated pattern-reversal
ERG acuity values for elderly normal subjects was
109 (20/10) to 65 (20/80). The regression line for 30
Hz data led to an extrapolated log MAR value of 0.9,
corresponding to a pattern-reversal ERG acuity rating
of 55 and a Snellen equivalent of approximately
20/150.
Although the resolution of the macula (as measured
by the transient pattern-reversal ERG and Snellen vi-
sual acuity) typically showed good correspondence
in normal subjects, they did not necessarily correspond
in patients with ARMD. One of the rationales for the
use of the pattern-reversal ERG as an ancillary test in
the FPS study was that it might reflect differences in
macular function between treated and untreated eyes
with similar acuities. Figure 2 shows responses from
two patients with subfoveal neovascular membranes
and comparable FPS protocol visual acuity ratings of
50 (20/200); they had distinctly different transient
pattern-reversal ERGs. The extrapolated pattern-rever-
sal ERG acuity rating for patient 2517 was 74. Pa-
tient 3177 had a much larger neovascular membrane
and a pattern-reversal ERG acuity rating of 10.
Relationships between pattern-reversal ERG acuity
and subfoveal neovascular membrane area are shown
for all patients on all visits in Figure 3. Pattern-rever-
sal ERG acuity declined with increasing membrane
area until membranes reached about 200°2 or ten disc
areas. Responses were not recordable for eyes with
membranes larger than this, presumably because the
area of the membrane approached the area subtended
by the display monitor.
Of 24 patients enrolled in the study and ran-
domized to no treatment, 3 had nondetectable pattern-rever-
sal ERG responses to all check sizes on the first two
visits and were not followed further. One patient
moved out of the region and was lost to follow-up.
The remaining 20 patients had measurable pattern-reversal
ERGs over a sufficient range of check sizes at the
2-Hz reversal rate to determine pattern-reversal
ERG acuity ratings. Responses to 30-Hz reversal rates
were measurable for only the largest checks. Prospective
data for 1 yr of follow-up were, therefore, based
on the responses at 2 Hz for 20 patients.
Responses for one patient over a 1-yr follow-up are
shown in Figure 4. Fluorescein angiograms (Fig. 5)
show the extent of the membrane on the first three
visits. The visual acuity rating during the initial visit
(visits 0) was 72 (20/75). During the 3-month visit
(visits 1), the membrane was larger, but pattern-reversal
ERGs were still fairly robust for large checks. The vi-
sual acuity rating on the second visit was 54 (20/166).
Six months after the initial visit (visit 2), there was
additional growth of the membrane, a drop in the vi-
sual acuity rating to 43 (20/230), and another reduc-
tion in pattern-reversal ERG amplitude, especially to
intermediate-sized checks. One year after the initial
visit (visit 3), the membrane appeared to have stabi-
lized, but responses were present only to the largest
checks. The visual acuity rating dropped to 8 (20/
Pattern-reversal ERG acuity ratings on each visit are shown in Figure 6A. The decline in pattern-reversal ERG acuity paralleled the decline in visual acuity and was related inversely to the growth of the membrane (Fig. 6B).

Responses from a patient with a more rapid progression are shown in Figure 7. During the initial visit (visit 0), the visual acuity rating was 55 (20/159), but the pattern-reversal ERG was robust, presumably because the membrane was barely in the fovea and much of the macula was initially clear (Fig. 8). Three months later (visit 1), the visual acuity rating had dropped to 20 (20/796), and the membrane had increased dramatically in area. Over these 3 months, the pattern-reversal ERG even to the largest checks virtually had been abolished. During the 6-month (visit 2) and 1-yr (not shown) visits, the pattern-reversal ERG was not detectable although the membrane was stable and the visual acuity rating was constant at 10 (20/1262). The rapid decline in the pattern-reversal ERG acuity rating for this patient is summarized in Figure 9A. The pattern-reversal ERG acuity rating
Fig. 5. Fluorescein angiograms showing size of subfoveal neovascular membrane for patient 2357. (A) Visit 0; (B) visit 1; (C) visit 3.

Extrapolated pattern-reversal ERG acuity ratings and visual acuity ratings over 1 yr of follow-up in all 20 patients are summarized in Figure 10. The pattern-reversal ERG acuity rating was correlated with the visual acuity rating on each visit ($r = 0.61, P < 0.001$) and inversely related to the mean area of the subfoveal neovascular membrane ($r = -0.55, P < 0.001$). The visual acuity rating was related inversely to the area of the membrane ($r = -0.45, P < 0.001$). Pattern-reversal ERG acuity ratings dropped, on average, from 54 (Snellen equivalent, 20/166) to 12 (Snellen equivalent, 20/1150). Over the entire year, the average decline was 2.5 octaves or roughly 0.2 octaves/month.

Discussion

The value of visual acuity as a predictive measure of functional status is well established. Acuity, however, samples only that region of the macula with the highest resolution and may not reflect the extent of macular disease. Full-thickness macular holes, for example, typically enlarge over time even though visual acuity decreased.
acuity remains stable.\textsuperscript{17} Furthermore, longitudinal measurements of acuity might not always be testing the same retinal location. Because our patients were free to fixate eccentrically during an acuity measurement, the retinal location being tested probably varied as the neovascular membranes changed.

The pattern-reversal ERG provides an objective measurement of macular function and appears to be a suitable test for elderly visually impaired patients. However, its value as a predictive measurement of functional status has not been addressed adequately. The pattern-reversal ERG is the summed response from the entire central retina. As a measurement of the integrity of the entire macula, it may index capabilities that are necessary for more complex visual tasks, such as face recognition, visual orientation, and mobility. Studies currently are underway to evaluate these relationships. Patients were encouraged to maintain gaze on the center of the large display screen and those with membranes larger than 200°\textsuperscript{2} had no detectable responses. Nevertheless, it is possible that a reduction in the pattern-reversal ERG amplitude could be attributable to eccentric fixation in some patients. Regardless, our results in untreated eyes with a subfoveal neovascular membrane suggested that the pattern-reversal ERG is correlated with visual acuity but does not always decline in parallel. It may, therefore, be a useful ancillary measurement in treatment trials designed to assess the efficacy of laser photocoagulation therapy for subfoveal neovascular membranes.

Linear regression techniques relating amplitude to the logarithm of the check size have been used previously with high-contrast checks to assess pattern-reversal ERG "acuity" in normal subjects.\textsuperscript{10-12} Extrapolated resolution at two reversals per second was comparable to that reported previously, and as in previous studies, resolution was lower with steady-state (30 reversals/sec) stimulation. Responses to large high-contrast checks included a luminance-specific component in addition to a contrast-specific component.\textsuperscript{10} However, the complex origin of the pattern-reversal ERG does not limit its value as a measurement of macular integrity in our study. Neovascular membranes affect cones directly, reducing both their luminance and pattern-contrast contributions. All eyes with a subfoveal neovascular membrane had a significantly lower-than-normal pattern-reversal ERG acuity rating during the initial visit, consistent with the reduced visual acuity required to be eligible for the FPS. Pattern-reversal ERG acuity ratings in patients dropped from an average of 54 (20/180) to 12 (20/1200) over a 1-yr period. The largest decrease occurred within 3 months of the initial visit. These findings are consistent with previous studies that document the rapid decline in visual acuity in untreated eyes with a subfoveal neovascular membrane.\textsuperscript{1-5}

Growth rates for choroidal neovascular membranes have not been reported previously to our knowledge over a fixed duration of follow-up. The average increase in diameter over the initial 3-month period was 12.4 μm/d (range, 4.8–31.4 μm/d). This is
consistent with average rates reported previously for serial angiograms taken at variable intervals. As might be expected, pattern-reversal ERG acuity ratings were correlated inversely with membrane area. Over 1 yr of follow-up, the rate of change in area was relatively constant at 26,210 μm²/d. These values should be considered preliminary because they are based on a subset of untreated eyes from the Texas
Retina Associates center. More accurate growth rates will become available when the growth rate for the entire FPS untreated group is reported.

Key words: ARMD, macular disease, subfoveal neovascular membrane, electroretinography, pattern-reversal ERG, retinal disease, retina

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References


