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PREFERRED RETINAL LOCUS IN MACULAR DISEASE:

Characteristics and Clinical Implications

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Abstract

Purpose—To investigate the location and fixation stability of preferred retinal locations (PRLs) in patients with macular disease, and the relationship among areas of abnormal fundus autofluorescence, the PRL and visual sensitivity.

Methods—Fifteen patients (15 eyes) were studied. Seven had Stargardt disease, 1 bull's eye maculopathy, 5 age-related macular degeneration, 1 Best disease, and 1 pattern dystrophy. All tested eyes had areas of abnormal fundus autofluorescence. The PRL was evaluated with fundus photography and the Nidek microperimeter. Visual field sensitivity was measured with the Nidek microperimeter.

Results—Of the 15 eyes, 4 had foveal and 11 had eccentric fixation. Eccentric PRLs were above the atrophic lesion and their stability did not depend on the degree of eccentricity from the fovea. Visual sensitivity was markedly decreased in locations corresponding to hypofluorescent areas. Sensitivity was not decreased in hyperfluorescent areas corresponding to flecks but was decreased if hyperfluorescence was in the form of dense annuli.

Conclusion—Eccentric PRLs were in the superior retina in regions of normal fundus autofluorescence. Fixation stability was not correlated with the degree of eccentricity from the fovea. To assess the outcomes of treatment trials it is important to use methods that relate retinal morphology to visual function.

Keywords

Preferred retinal location (PRL); microperimetry; fundus autofluorescence; Stargardt disease; age-related macular degeneration

Patients with macular disease and central visual loss affecting the fovea often adopt an eccentric preferred retinal location (PRL). The existence of eccentric PRLs has been known for many years¹; however, their characteristics are still not fully understood. Studies have shown that their location can change as a function of the type of macular disease, the luminance level, and the functional task.^{2–6} Information as to their location and stability is not only useful for the clinician in planning future treatment of patients with macular disease but also is essential for the correct interpretation of measures of local function such as visual field sensitivity and focal

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or multifocal electroretinography. The information may also prove to be an indicator of disease progression. Recently a microperimeter, the Nidek microperimeter (MP-1) (Nidek Technologies Inc., Padova, Italy) has been developed that may be a useful clinical tool for assessing the location and stability of fixation while simultaneously measuring visual field sensitivity. The MP-1 combines fundus tracking microperimetry with color fundus photography. The examiner selects a landmark with high reflectivity on the fundus and stimuli are projected onto the retina in relation to this landmark using an LCD. An automatic eye tracker compensates for eye movements. A color fundus photograph is taken at the end of the examination and a registration technique is used to overlay the perimetric and fixation results on the fundus photograph. This allows visual function to be compared to retinal morphology. The technique has the potential to improve our understanding of PRLs and of visual sensitivity of the surrounding areas of patients with macular disease.

In this study the MP-1 and conventional fundus photography were used to investigate the location and fixation stability of PRLs in a group of patients with retinal disease affecting the macula. The visual sensitivity of the surrounding retinal region was measured with static perimetry and the relationship of the PRL to fundus abnormalities examined by overlaying the perimetric and fixation results onto the fundus photograph and onto the fundus autofluorescence (FAF) images. Finally the effect of an eccentric PRL on the interpretation of the results of functional tests such as the multifocal electroretinogram is discussed.

Methods

Subjects

Fifteen patients with retinal disease affecting the macula were recruited from the practices of three of the authors (S.H.T., R.T.S. and G.R.B.). Their clinical characteristics are shown in Table 1. Seven patients had a diagnosis of Stargardt disease, 1 bull's eye maculopathy, 5 had atrophic age-related macular degeneration, 1 Best disease, and 1 pattern dystrophy. The median age of the 3 males and 12 females was 39 years and the range was 11 to 87 years. Exclusion criteria were the presence of significant media opacities and/or other ocular diseases that could affect visual function. Only one eye was chosen for the study, either the eye with "better" visual acuity or, if visual acuity was equal in both eyes, the right eye was chosen. Best corrected visual acuity (BCVA) was determined with Early Treatment Diabetic Retinopathy Study charts at 4 m. Informed consent was obtained from all subjects before their participation. Procedures adhered to the tenets of the Declaration of Helsinki and the protocol was approved by the Columbia University Medical Center Institutional Review Board for Human Research.

Procedures

After pupil dilation (1% tropicamide and 2.5% phenylephrine hydrochloride) and a standard fundus examination, $30^\circ \times 30^\circ$ FAF images were obtained using a confocal scanning laser ophthalmoscope (Heidelberg Retinal Angiograph, HRA 2, Heidelberg Engineering, Heidelberg, Germany). The images were obtained by illuminating the fundus with an argon laser light (488 nm) and then viewing the resulting fluorescence through a band pass filter with a short wavelength cut off at 495 nm. (For a detailed description of the HRA and FAF see Ref. 7.)

The PRL for the study eye was then evaluated with color fundus fixation photography. A series of three 50° fundus photographs were obtained with a Zeiss 450 plus IR fundus camera. After a period of 30 minutes of adaptation to dim room illumination the MP-1 Microperimeter (Nidek Technologies Inc., Padova, Italy) was used to study the location, sensitivity, and fixation stability of the PRL. (For details of the MP-1 see Ref. 8.) To study the site(s) of the PRL, the patient's task was to fixate on a red cross (2° in diameter) and to maintain fixation on the center

of this target for 30 seconds. The non-tested eye was occluded throughout the procedure. This fixation test was followed by static perimetry on the MP-1. The sensitivity of the central visual field was tested with a 10-2 and a macular program. For both programs “white” test lights (stimulus size Goldmann III, duration 200 msec) were presented on a dim “white” background (1.27 cd/m^2) using a 4-2 threshold strategy. For the macular program, 28 locations centered on the fovea covering a circular area 12° in diameter were tested. For the 10-2 program, 68 locations covering an area 20° in diameter were tested. The results of the fixation and microperimetry tests were displayed on color digital photographs acquired by the MP-1 color camera.

The location of each subject’s PRL was referenced to the fovea and the distance and direction in millimeters was converted into degrees. The location of the fovea was determined by using visible landmarks such as perifoveal capillaries or xanthophyll. If there was difficulty localizing the fovea it was approximated based on measurements relative to the optic disk in normal subjects using a method similar to that described by Rohrschneider⁹ and Timberlake et al.¹⁰ For the MP-1 results, the fixation stability of the PRL was also evaluated. Stability was defined in terms of the percentage of fixation points that fell within a 2° and 4° diameter circle during the visual field test. Fixation was classified as “stable” if more than 75% of the recorded fixation points fell within a 2° diameter circle, “relatively unstable” if less than 75% fell within a 2° diameter circle but more than 75% fell within a 4° diameter circle, and “unstable” if less than 75% fell within a 4° diameter circle. This classification provided by the MP-1 is similar to one described in a recent study of patients with age-related macular degeneration using a scanning laser ophthalmoscope.¹¹

To compare the location of the PRL with FAF, the fixation images from the MP-1 and from conventional fundus photography were overlaid onto the 30° FAF images. This overlay was achieved using software available on the MP-1 after the images had been appropriately scaled using an image registration program in MatLab. The results of static perimetry obtained on the MP-1 were also overlaid on the 30° FAF images to evaluate the sensitivity of retinal areas showing altered autofluorescence.

Statistical Analysis

Pearson’s correlation test (r) was used to investigate the relationship between fixation stability of the PRL and its eccentricity relative to the fovea. It was also used to investigate the relationship between the eccentric fixation locus (omitting eyes with foveal fixation) and BCVA. Values of P less than 0.05 were considered statistically significant.

Results

Preferred Retinal Loci and Stability

The location and fixation stability of the PRLs for the 15 eyes of the 15 patients obtained with fundus photography and with the MP-1 are shown in Table 2. Of the 15 eyes, 4 had foveal fixation and 11 had eccentric fixation. The retinal location of the eccentric PRL was above the fovea for all 11 eyes and was in a similar area for all methods (i.e., the locus of fixation was similar for the three fundus photographs, the MP-1 fixation test, and the visual field test despite differences in duration of the procedures). The degree of eccentricity from the fovea ranged from 2° to 11° . Figure 1 shows the position of the PRL for P4 obtained with fundus photography (Figure 1A) and with the MP-1 (Figure 1B) during visual field testing using the 10-2 program. For both methods, the PRL is superior to the fovea and the distance from the fovea is similar. The results of the MP-1 shown in Figure 1B not only provide information about the location of the PRL but also information about scotomas, the sensitivity of the region of the PRL, and its fixation stability during visual field testing. For P4 there is a dense central scotoma, defined

by the failure to detect the stimulus presented at 0 dB (400 apostilbs), and the PRL was classified as being relatively unstable as only 43% of the recorded fixation points fell within a 2° diameter circle and 79% fell within a 4° diameter circle.

All 11 eyes with an eccentric PRL had a dense central scotoma that included the fovea. Fixation was “stable” for 3 of these eyes, “relatively unstable” for 4, and “unstable” for the remaining 4 eyes (see Table 2). The fixation stability of the PRL did not depend on its eccentricity relative to the fovea ($r = -0.10$, $P = 0.76$). This is illustrated in Figure 2 which shows the percentage of recorded fixation points falling within a 2° diameter circle compared to the distance of the PRL in degrees from the fovea. For example, P8 (indicated by *) had “stable” fixation using an eccentric PRL located 7° superior to the fovea, and P2 and P14 (indicated by #) also had “stable” fixation using eccentric PRLs located 5° superior to the fovea.

Preferred Retinal Loci and Visual Acuity

The relationship between the eccentric fixation locus (omitting eyes with foveal fixation), as determined by fundus fixation photography, and BCVA was $r = -0.61$ ($P = 0.038$); however when eccentric fixation locus as determined by the MP-1 was compared to BCVA the correlation was $r = -0.53$ ($P = 0.10$). The difference may be due to the fact that the locus of fixation for the MP-1 was based upon a number of fixation points recorded over a 30 seconds period.

Preferred Retinal Loci and Altered Fundus Autofluorescence

To determine the relationship between the location of the PRL and areas of altered FAF, the combined PRL, MP-1, and FAF images were examined. For all 11 eyes with an eccentric PRL, the underlying retinal areas appeared to have normal FAF. In addition, the visual field sensitivities associated with the PRLs were within ± 2 dB of the mean sensitivity values for each of the 11 patients. Figure 3 provides an example. It shows the location of fixation points used by P4 during a 10–2 visual field test with the MP-1. The fixation points and the visual field sensitivities in dB are superimposed on the patient’s FAF image. This patient had “relatively unstable” fixation and the fixation points are scattered over an area of approximately 3°. The underlying retina appears to have normal FAF; however, there are two small areas of hyperfluorescence bordering the temporal side of the fixation points. There is also a relatively large area of hypofluorescence (approximately $7^\circ \times 6^\circ$) that encompasses the foveal area. The visual field sensitivities in this central area are markedly decreased or nonrecordable.

Examination of the combined FAF and MP-1 images showed that visual field sensitivities were either nonrecordable (failure to detect 0 dB) or markedly decreased (detected at full intensity 0 dB) over areas of hypofluorescence. For the patients with Stargardt disease, flecks that presented on FAF as areas of hyperfluorescence were not associated with decreased sensitivity. However, dense rings of hyperfluorescence surrounding hypofluorescent regions showed decreased visual field sensitivities. The dense rings of hyperfluorescence were seen in two patients, P9 (Best disease) and P10 (pattern dystrophy). An example is provided in Figure 4 which shows the combined FAF and MP-1 10-2 visual field image obtained from the right eye of P9.

Discussion

For all 11 patients with an eccentric PRL, fixation was above the atrophic lesion. This finding is consistent with previous studies of patients with Stargardt disease reporting that for the majority of patients the PRL is in the superior retina.^{2,12-15} However, there are conflicting reports regarding its location for patients with other maculopathies such as age-related macular

degeneration. For example, there are reports that the PRL can be to the right, to the left of the lesion, or in some cases it can be above the lesion i.e., in the superior retina.^{2,16}

The location of the PRL in the superior retina makes sense intuitively as it results in the scotoma being superior to fixation in visual field space, thus allowing the subject to read text and perform many everyday, lower visual field tasks without obstruction by the scotoma. However, the area chosen for fixation was not at the border of the atrophic area but was located some distance away from the border. This finding regarding the location of fixation in relation to the scotoma was reported by Sunness et al.² for a group of patients with Stargardt disease. The authors suggested that there might be “subclinical” pathology that affects visual performance. However, it seems unlikely that this can solely account for our findings, as one would expect that visual sensitivity would be decreased in the intervening retinal region. Perhaps, the increased distance affords a slightly larger visual field for the region of fixation to enhance visual function, but the precise reasons for this observation remain unknown.

The use of the MP-1 not only allowed us to determine the retinal location of fixation but also to determine fixation stability during the visual field task that on average took 15 minutes to complete. One might predict that fixation would become unstable with increasing eccentricity of the PRL. However, in agreement with a recent study quantifying fixation in Stargardt patients using a scanning laser ophthalmoscope, fixation stability of the PRL did not appear to depend on the degree of eccentricity from the fovea.¹² For example, there were three patients with eccentric PRLs 5° and 7° from the anatomical fovea who had stable fixation, and four patients with PRLs at similar eccentricities who had unstable fixation. One might also predict that there would be a relationship between the degree of eccentricity of the PRL and BCVA. We did find a significant correlation when we used the position of the PRL determined by fundus photography but not when determined by the MP-1.

To try to improve our understanding of the underlying mechanisms that may be involved in the selection of eccentric PRLs and in the visual field sensitivities we measured, the MP-1 results were overlaid on the 30° FAF images. FAF provides information on the physiologic and morphologic status of the retinal pigment epithelium (RPE) and has been suggested as a noninvasive tool for evaluating the photoreceptor and RPE fluorophore metabolism in ocular disease.¹⁷ The AF emission spectrum closely resembles that of A2E lipofuscin, a by-product of the shedding of the outer segments of the photoreceptors. The absence of autofluorescence, hypofluorescence, suggests absence of RPE cells or degenerated RPE cells and may also be indicative of loss of photoreceptors or at least their outer segments.¹⁸ Areas of high density or hyperfluorescence suggest accumulation of lipofuscin in RPE cells and disruption of the metabolism of the RPE. Hyperfluorescence may be a precursor of photoreceptor death and RPE atrophy.¹⁹ The use of AF in this study showed that patients with eccentric PRLs had central areas of hypofluorescence that corresponded to areas of macular atrophy. Visual sensitivity was either nonrecordable or markedly decreased in these areas. Unlike in geographic atrophy, areas of hyperfluorescence were not always associated with decreased visual sensitivity. For example, for the patients with Stargardt disease, areas of hyperfluorescence that corresponded to yellowish white flecks confined to the macular area were not associated with decreased visual sensitivity. In age-related macular degeneration, there is a diffuse reduction of retinal sensitivity particularly in the areas with soft drusen and RPE hypopigmentation.²⁰ However, hyperfluorescence in the form of a dense annulus surrounding a central hypofluorescent region was associated with decreased visual field sensitivity, and this annulus was seen in the patient with Best disease and the patient with pattern dystrophy.

The determination of the PRL, the stability of fixation, and assessment of the sensitivity of the central macular area have important clinical implications. Information as to the location(s) and fixation stability of the eccentric PRL is essential for the interpretation and measurement of

local visual and retinal function. Being unaware of the adoption of an eccentric PRL can for example lead to misinterpretation of conventional visual field results and multifocal electroretinography results.²¹ Losses in visual field sensitivity and decreases in multifocal electroretinography amplitudes may not appear to correspond to retinal areas showing visible lesions. It is necessary to account for the adoption of an eccentric PRL in these cases by shifting the corresponding templates. The ideal approach is to assess the locus of fixation in each patient before functional testing. In the case of the multifocal electroretinography the examiner can then displace the fixation target so that it coincides with the patient's eccentric PRL. For visual field testing a fundus-related perimetry technique should be used.

Information as to the location and stability of the eccentric PRL and the ability to compare function to structure are essential to the clinician for planning future treatment and for evaluating treatment effects in patients with macular disease. The MP-1 may prove to be an essential tool for the clinician. With the MP-1 we were able to obtain information about the location and stability of fixation in a group of patients with macular disease and to compare visual function to retinal morphology.

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Fig. 1.

A. Fundus photograph of Patient 4 showing the retinal location of the PRL. **B.** Fundus photograph with overlay of MP-1 10-2 visual field data. The numbers are the sensitivity values in dB. The blue data points represent the locations used for fixation during the visual field test.

Fig. 2.
The stability of fixation as a function of its distance from the fovea. * = stable fixation for P8;
= stable fixation for P2 and P14.

Fig. 3.
Combined FAF and MP-1 10-2 visual field images for Patient 4.

Fig. 4.
Combined FAF and MP-1 10-2 visual field images for Patient 9.

Table 1

Clinical Characteristics

Subject	Age	Sex	Eye	BCVA	Diagnosis
1	25	F	OD	0.2	Bulls eye maculopathy
2	27	F	OD	0.5	Stargardt disease
3	33	F	OD	0.5	Stargardt disease
4	55	M	OD	0.7	Stargardt disease
5	20	F	OD	0.7	Stargardt disease
6	22	F	OS	0.7	Stargardt disease
7	30	F	OS	0.8	Stargardt disease
8	11	M	OS	0.8	Stargardt disease
9	39	M	OD	0.6	Best disease
10	60	F	OS	0.5	Pattern dystrophy
11	72	F	OS	0.1	AMD
12	79	F	OS	0.3	AMD
13	77	F	OD	0.4	AMD GA
14	87	F	OD	0.9	AMD
15	70	F	OD	1.3	AMD

BCVA = best corrected visual acuity.

Table 2
Position and Stability of PRL and Mean Visual Field Sensitivity

Subject	Fundus Photo. #1	Fundus Photo. #2	Fundus Photo. #3	MP-1 PRL	MP-1 Stability of PRL % Within 2° and 4° During Visual Field Test	MP-1 VF MS dB	MP-1 MS 8 dB
1	Foveal	Foveal	Foveal	Foveal	Stable 90% 100%	17.3	17.1
2	Sup 5°	Sup 4.5°	Sup 5°	Sup 5°	Stable 77% 97%	16.3	16.3
3	Sup 7°	Sup 7°	Sup 7°	Sup 6°	Rel. unstable 68% 94%	12.3	13.3
4	Sup 10°	Sup 10°	Sup 10°	Sup 7°	Rel. unstable 43% 79%	12.3	14.9
5	Sup 6°	Sup 6°	Sup 6°	Sup 6°	Unstable 24% 58%	12.2	11.5
6	Sup 3°	Sup 3°	Sup 3°	Sup 3°	Rel. unstable 41% 77%	14.1	12.1
7	Sup 3°	Sup 3°	Sup 3°	Sup 4°	Unstable 25% 67%	13.2	14.0
8	Sup 8°	Sup 8°	Sup 9°	Sup 7°	Stable 83% 98%	17.9	17.6
9	Foveal	Foveal	Foveal	Foveal	Stable 75% 97%	12.4	4.0
10	Sup 10°	Sup 10°	Sup 7°	Sup 7°	Unstable 21% 47%	8.0	8.9
11	Foveal	Foveal	Foveal	Foveal	Stable 100% 100%	15.8	16.0
12	Foveal	Foveal	Foveal	Foveal	Stable 96% 99%	15.8	15.8
13	Sup 10°	Sup 10°	Sup 11°	Sup 8°	Unstable 23% 64%	9.0	8.9
14	Sup 5°	Sup 5°	Sup 5°	Sup 5°	Stable 79% 99%	2.2	1.3
15	Sup 2°	Sup 2°	Sup 4°	Sup 4°	Rel. unstable 49% 93%	3.2	2.1

Sup = superior; VF MS = mean visual field sensitivity; MS 8 = mean sensitivity of 8 locations surrounding the PRL.