Microperimetric Assessment of Patients with Type 2 Idiopathic Macular Telangiectasia

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PURPOSE. To assess changes of the light increment sensitivity (LIS) of the macular area in patients with type 2 idiopathic macular telangiectasia (IMT).

METHODS. Fifty-eight eyes of 30 patients were examined in a cross-sectional study. All eyes were assigned to group A (early disease stages) or group B (late disease stages with retinal pigment clumping or vascular membranes). Investigation of visual function included visual acuity and fundus-related microperimetry.

RESULTS. Thirty-seven and 16 eyes were assigned to group A and group B, respectively. Temporal to the fovea, each eye of group B had an absolute scotoma. Topographically, the areas with reduced LIS correlated well with the angiographically hyperfluorescent areas or retinal pigmentations and showed a sharp demarcation from areas with normal LIS. However, within areas with angiographic alterations, at least some test locations exhibited preserved LIS in group B eyes; in 51% of group A eyes, none of those test locations showed abnormal LIS. Group A eyes that showed marked LIS reduction revealed common abnormalities: either hyporeflective spaces between the neurosensory retina and the retinal pigment epithelium in OCT imaging or atrophic areas, both topographically related to the scotoma. Visual acuity was correlated with foveal LIS but not with the LIS temporal to the fovea.

CONCLUSIONS. Long-standing morphologic macular alterations from type 2 IMT are associated with topographically related functional impairment. Eyes with profound parafoveal scotomas can exhibit relatively preserved visual acuity. Therefore, testing for retinal light sensitivity should be included as an additional outcome measure for future interventional studies. (*Invest Ophthalmol Vis Sci.* 2007;48:3788–3795) DOI:10.1167/iovs.06-1272

Type 2 idiopathic macular telangiectasia (IMT) is a rare condition that usually presents in the fifth to seventh decade with slow decrease in visual acuity, difficulty reading, and metamorphopsia.[1,2] Vascular pathology first becomes evident temporal to the fovea but may eventually progress to encompass the whole parafoveal area. Ophthalmoscopic and angiographic findings are parameters for assessing disease progression and stage.

However, the impact of the vascular changes on functional parameters, such as on the light increment sensitivity, is unknown. Whether the angiographic leakage in type 2 IMT is associated with a topographically related functional deficit (scotoma) and whether the fundoscopic findings and the angiographic heterogeneity in size and intensity are reflected by those deficits has not been investigated. Patients with advanced disease stages may report visual deficits despite relatively preserved visual acuity. Location and size of a paracentral scotoma may have little impact on distance vision but may influence other functional parameters, such as reading ability.

We hypothesized that functional deficits are topographically related to the funduscopically and angiographically visible abnormalities and that they progress with later disease stages. Furthermore, we assumed that in accordance with the angiographic findings, scotomas begin and are most pronounced temporal to the fovea. In this context, we expected visual acuity to be better correlated with the foveal than with the parafoveal retinal sensitivity, thus proving microperimetry to be a distinct measurement of functional deficits in type 2 IMT.

Microperimetry is able to quantify macular sensitivity in an exact, fundus-related fashion, thus adding detailed information about the degree and pattern of macular functional alteration, and it allows correlation with a precise location of retinal abnormalities. Microperimetry has been successfully used in the visual function assessment and follow-up of different macular disorders, including age-related macular degeneration, macular holes, and diabetic macular edema.[3–7] In this study, we assessed retinal light increment sensitivity (LIS) in different stages of type 2 IMT by fundus-controlled static threshold microperimetry of the angiographically hyperfluorescent and the adjacent areas. Furthermore, the correlation of visual acuity with foveal and parafoveal LIS, respectively, was determined.

The study was conducted as part of the macular telangiectasia (MacTel) project (www.mactelresearch.org), the first longitudinal international multicenter trial to investigate the natural history of type 2 IMT in a large patient cohort.

PATIENTS AND METHODS

Fifty-eight eyes of 30 patients were examined in a cross-sectional study. All patients were recruited from the retinal disease clinic at the Department of Ophthalmology, University of Bonn. Eyes that underwent previous macular laser photocoagulation or macular surgery were excluded from analysis. All patients underwent complete ophthalmic examination, including best-corrected visual acuity, anterior segment examination, indirect ophthalmoscopy, fluorescein angiography, fundus photography, optical coherence tomography (OCT), and microperimetry. Patients were included if occult or barely visible telangiectasia, often detectable only with fluorescein angiography revealing late phase diffuse hyperfluorescence, were present (according to the criteria established by Gass and Blodi[2]). The study was conducted in accordance with the tenets of the Declaration of Helsinki, and informed consent was obtained from every patient.

Classification of Clinical Stages

The classification of Gass and Blodi, based on a large amount of cross-sectional and longitudinal data, was used.[2] Stage 1 represents early, ophthalmoscopically occult vascular pathology only evident in fluorescein angiography by late phase diffuse parafoveal hyperfluorescence. Mild loss of retinal transparency may be seen in stage 2 before dilated right-angle venules become visible in stage 3. The hallmark of stage 4 is intraretinal pigment clumping that most often develops along the right-angled venules. Neovascular membranes are a late consequence and are the characteristic feature for stage 5 type 2 IMT.

Visual Acuity Testing

Best-corrected visual acuity was measured with standard Early Treatment Diabetic Retinopathy Study (ETDRS) protocols with a modified ETDRS distance chart transilluminated with a chart illuminator (Lighthouse International, New York, NY). Either ETDRS visual acuity or Snellen visual acuity was obtained. These measures were then transformed to logMAR values for statistical evaluation.

Grading

Two ophthalmologists independently graded the images (color fundus photographs, red-free images, and fluorescein angiography images) that corresponded to ETDRS field 2 according to the classification system introduced by Gass and Blodi.[2] Forty-three color fundus photographs were available for grading. If image quality was low or no color images were taken, grading was accomplished by means of red-free or fluorescein angiography images. Agreement between both graders was estimated using the Cohen κ coefficient of agreement for assessment of interobserver variability. The κ statistic was interpreted using the ranges suggested by Landis and Koch[8]: less than 0, poor agreement; 0 to 0.20, slight agreement; 0.21 to 0.40, fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, substantial agreement; and more than 0.81, almost perfect agreement.

Digital Fluorescein Angiography and Color Fundus Photography

After informed consent was obtained, standard rapid sequence fluorescein angiography was performed starting at the first appearance of fluorescence in the choroidal or retinal circulation. Middle- and late-phase angiographs were taken 2, 5, and 10 minutes after injection of 5 mL fluorescein into an antecubital or other convenient vein. Images were acquired by digital photography (FF450; Carl Zeiss, Oberkochen, Germany) or by confocal scanning laser ophthalmoscopy (cSLO; HRA2; Heidelberg Engineering, Heidelberg, Germany). For the latter, digital images of 768 × 768 pixels at an angle of 30° were obtained

using the continuous- or single-image acquisition mode at a line scan frequency of 8 kHz (maximum, 16 frames/s). For digital image processing, the included software was used (Eye Explorer, software version 1.4.1.0; Heidelberg Engineering). Digital color fundus photographs were taken with a 30° fundus camera (FF450; Carl Zeiss).

Ocular Coherence Tomography

OCT (Stratus OCT scanner, software version 4.0.1; Carl Zeiss Meditec GmbH, Oberkochen, Germany) was performed to visualize the cross-sectional retinal structure with an axial resolution of 10 μm. The scanning protocol used for this study was the Macular Thickness program.

Microperimetry and Monitoring of Fixation Stability

All patients underwent automatic fundus-correlated microperimetry (MP1, software version 1.5.1; Nidek Technologies, Padova, Italy) with dilated pupils (1% tropicamide and 5% phenylephrine). An integrated infrared fundus camera (1392 × 1038-pixel resolution; 45° field of view) allowed real-time fundus imaging on a monitor. The fixation target and stimuli were projected onto the retina by a liquid crystal color monitor. White monochromatic background illumination was set at 4 apostilbs (asb; 1.27 cd/m^2); fixation target illumination was set at 100 asb, and stimulus intensity could be varied on a 1 (0.1 log)–step scale from 0 to 20 dB, where 0 dB represented the brightest luminance of 400 asb (127 cd/m^2).

For this study, the test configuration was as follows: standard red cross as fixation target, 2° in diameter with a thickness of 1 U; Goldmann III stimulus size with 100-ms projection time; and predefined automatic macula test pattern covering the central 16° centered onto the fovea with 53 stimuli that are 2° (inner stimuli) or 4° (outer stimuli; Fig. 1) apart. A 4–2 staircase test strategy was used. Preexamination testing of the individual light sensitivity allowed preselection of the initial stimulus intensity to reduce examination time. Light stimuli were randomly presented during the examination as in standard static perimetry. Results are reported in decibels. A stimulus was projected every 60 seconds onto the optic nerve head area to check for false-positive answers. If cooperation was sufficient, additional stimuli were placed parafoveally to detect smaller scotomas that were not detected by the standard test pattern or to define an evident scotoma more exactly. To allow for better clinical correlation between microperimetric data and retinal details, functional results were displayed on a color digital fundus image, acquired by a charge-coupled device color camera (1392 × 1038 pixels, xenon flash).

During the microperimetry examination, an integrated high-speed image-tracking software compensated for eye movements by continu-
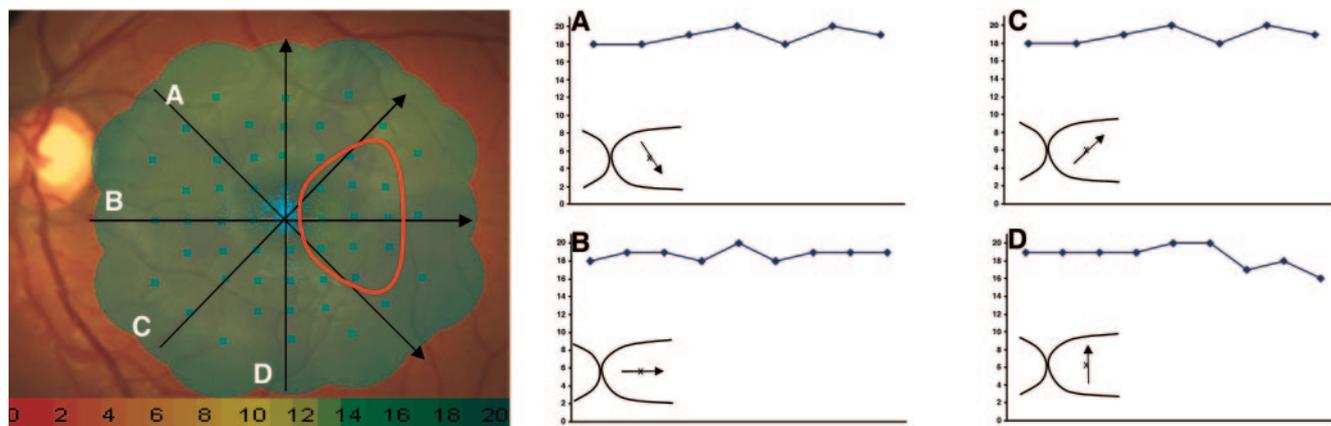

FIGURE 1. Interpolated sensitivity map of a subject with normal eyes. *Blue dots* visualize fixation stability during the total examination time. The *red frame* represents the area analyzed for the minimal LIS temporal to the fovea. Testing points on the four connecting lines are plotted in the diagrams on the right.

ously (25 times/s) tracing the position of the patient's fixation, with a time delay of only 4 ms. This ensured exact spatial correlation between the anatomic landmarks and the perimetric sensitivity maps.[9] Furthermore, the software used this information to precisely correct the stimuli projection locations to compensate for eye movements during the examination. If the software were to lose tracking, projection of the stimuli would have been discontinued until tracking was reestablished. Therefore, even in patients with unstable fixation, exact localization of stimuli is achieved.[9]

Stability of fixation was categorized according to the classification made by Fujii et al..[10] Fixation stability was classified depending on the recorded fixation points within a 2° or 4° diameter circle centered in the gravitational center of all fixation points, respectively, regardless of the position of the foveal center. Fixation was defined as *stable* when more than 75% of the fixation points were located within the 2° diameter circle, *relatively unstable* when less than 75% of the fixation points were located within the 2° diameter circle but more than 75% of the fixation points were located within the 4° diameter circle, and *unstable* when less than 75% of the fixation points were located within the 4° circle.

Analysis of Perimetric Results

For statistical data analysis, individual testing points of the standard macular pattern were used that lie on a horizontal, vertical (nine testing points each), or diagonal connecting line (seven testing points) centered on the fovea (Fig. 1). The positions in right eyes were converted to those for left ones for concordance of the location of the testing points. It was shown in Springer et al.[11] that the highest sensitivity values are achieved in the central part of the visual field and that sensitivity decreases slightly toward the periphery. There is no difference for locations nasal and temporal to the fovea.[11] Results of a

large cohort of subjects with normal vision of different ages have recently been published.[9]

According to Rohrschneider et al.[12], a reduction in the LIS was categorized as an *absolute scotoma* when one or more stimulus was not seen with the brightest stimulus (0 dB, equivalent to an increased stimulus intensity of 20 dB). It was categorized as a *relative scotoma* when a circumscribed area of reduced LIS could be found and as *generally reduced differential light sensitivity* when the threshold values were reduced to the same threshold level in the whole area examined. The macular sensitivity of the encircled testing area (red frame in Fig. 1) was analyzed with regard to the minimal LIS temporal to the fovea. This region was chosen because of the predominant angiographic pathology in that area.

Statistical Analysis

Visual acuity calculations were made using the logMAR (logarithm of the minimum angle of resolution) scale. Nonparametric testing was used for correlation of visual acuity and LIS measurements (Spearman rho) and for comparison of LIS in the two patient groups at individual testing points (Kolmogorov-Smirnov) and of age distribution (Mann-Whitney U test). The significance level was set at 0.05. Statistical calculations were performed using SPSS (Statistical Package for the Social Sciences, version 13.0; SPSS Inc., Chicago, IL).

RESULTS

Descriptive data of the patients included in this study are shown in Table 1. In two patients (patients 4 and 10), microperimetry data were available from only one eye. Four eyes

TABLE 1. Summary of Patients with Type 2 Idiopathic Macular Telangiectasia Examined by Microperimetry

Patient	Sex	Age (y)	Right Eye				Left Eye			
			VA	Central LIS	Minimal LIS Temporally	Grading	VA	Central LIS	Minimal LIS Temporally	Grading
1	M	66	20/100	6	10	A	20/25	18	14	A
2	M	57	20/200	10	0	B	20/20	20	16	A
3	M	63	20/50	12	12	A	20/25	20	8	A
4	M	58	20/40	16	0	B	20/400	MP not available		B, PDT
5	F	58	20/32	14	0	A	20/63	8	0	B, LT
6	F	66	20/200	0	0	B	20/25	12	10	A
7	M	70	20/63	16	8	A	20/40	18	12	A
8	F	68	20/25	18	0	A	20/80	14	0	B, LT
9	M	72	20/40	12	12	B, LT	20/40	18	14	A
10	F	70	20/40	10	6	A	20/200	MP not available		B, LT
11	F	66	20/500	0	0	B	20/100	4	0	A
12	M	53	20/32	20	0	B	20/100	0	0	B, LT
13	M	58	20/25	18	14	A	20/40	18	12	A
14	F	64	20/63	20	0	A	20/32	20	8	A
15	M	64	20/32	10	0	B	20/32	10	0	B
16	F	56	20/25	14	14	A	20/20	20	16	A
17	F	59	20/32	16	14	A	20/25	20	16	A
18	M	62	20/200	2	0	B	20/40	14	0	B
19	F	64	20/40	16	16	A	20/20	18	16	A
20	F	70	20/80	6	8	A	20/50	4	8	A
21	F	53	20/50	14	18	A	20/40	20	12	A
22	F	81	20/80	6	0	A	20/25	12	14	A
23	M	66	20/32	8	0	B	20/63	10	0	B
24	F	51	20/63	8	4	A	20/80	0	0	A
25	F	58	20/63	16	16	A	20/63	12	0	A
26	F	63	20/40	10	12	A	20/25	16	4	A
27	M	71	20/32	12	0	B	20/25	14	0	B
28	M	67	20/80	10	0	A	20/50	16	14	A
29	M	65	20/40	16	0	B	20/63	8	0	B
30	F	58	20/40	16	14	A	20/63	14	0	Macular hole

Seven eyes were excluded (marked in gray). LT, previous laser treatment; PDT, previous photodynamic therapy; MP, microperimetry; VA, visual acuity.

were not included in the data analysis because of previous macular laser treatment (Table 1) and in one eye because of previous macular hole surgery (patient 30; OS). The following data analysis refers to the resultant study cohort of 53 eyes with type 2 IMT.

Evaluation of the grading of the five stages according to Gass and Blodi[2] showed a moderate agreement ($\kappa = 0.52$) for the analysis of all 53 eyes. If the eyes were grouped into two categories (group A, eyes classified as stages 1–3; group B, eyes classified as stages 4–5), agreement between the two graders was almost perfect ($\kappa = 0.95$). There was only a slight agreement within group A ($\kappa = 0.27$) but a moderate agreement within group B ($\kappa = 0.60$). Further analysis considers stages 1 to 3 as group A ($n = 37$) and stages 4 to 5 as group B ($n = 16$). In four patients, one eye was staged as group A and the fellow eye as group B, respectively.

There was no sex predilection (14 men, 16 women). Patient ages ranged from 51 to 81 years (mean, 63 years; SD, 7 years). There was no difference in mean age among patients with bilateral group A or group B disease after excluding patients whose eyes had disease at two different stages (62.1 vs. 62.7 years; $P = 0.804$; Mann-Whitney U test).

ETDRS best-corrected visual acuity was assessed in 34 eyes, and Snellen visual acuity was assessed in 19 eyes. Overall, median visual acuity was 20/40 (20/500–20/20). Median visual acuity was equal in both subgroups (20/40; group A patient range, 20/100–20/20; group B patient range, 20/500–20/25), and statistically there was no significant difference in distribution of visual acuity ($P = 0.428$, Kolmogorov-Smirnov Z test).

Mean microperimetric examination time per eye was 15 minutes 16 seconds ± 5 minutes 58 seconds; for group A it was 13 minutes 48 seconds ± 5 minutes 33 seconds, and for group B it was 18 minutes 40 seconds ± 5 minutes 39 seconds. Mean number of testing points was 66 ± 11 for all eyes or 65 ± 10 and 68 ± 14 for group A and group B, respectively. Thus, mean time needed per testing point was 14 seconds for all eyes, 13 seconds for group A, and 16 seconds for group B. Springer et al.[11] found a shorter examination time per testing point in subjects with normal eyes despite using a 4–2-1 strategy and a higher number of testing points (70). However, perimetric determination of a scotoma is time consuming, and decreased fixation stability often results in loss of tracking, which may lead to longer examination times. The tracked time was on average 86.5% (63.3%–99.1%) of the total examination time in all patients and 87.5% and 84.5% in group A and group B, respectively.

Fixation was classified as stable in 76% and as relatively unstable in 24% within group A and as stable in 63%, relatively unstable in 25%, and unstable in 13% in group B. The less stable fixation in group B patients may be explained by deeper and larger paracentral scotomas in this subgroup. Moreover, the scotoma enclosed the fovea more frequently in those patients.

If an area had reduced LIS, the functional deficit correlated well with an angiographically hyperfluorescent area and showed a relatively sharp demarcation from areas with normal LIS. The reverse, however, was not true: angiographic late-phase hyperfluorescence was not generally associated with LIS reduction. In addition, in eyes with an area of parafoveal hyperfluorescence that encompassed the nasal

region, LIS was considerably higher or within normal limits in the nasal area compared to the temporal area. Two eyes showed overall diminished LIS. In the periphery of the 16° visual field, LIS at 8° eccentricity was significantly lower in
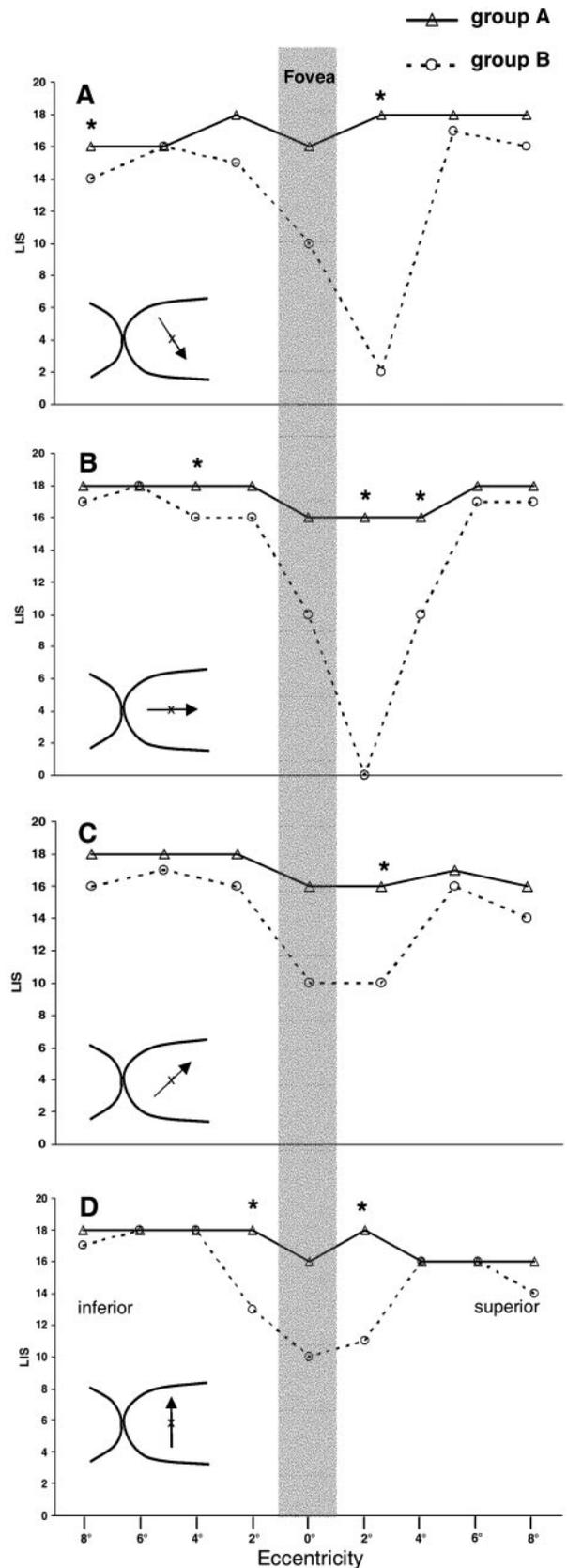

FIGURE 2. Summary of the microperimetric examination results. Each *triangle* and *circle* represents the median LIS of the corresponding individual testing points along the axis, as specified in the schematic fundus within each diagram. The *continuous line* with *triangles* represents group A, and the *dashed line* with *circles* represents group B. *Asterisks* indicate testing points with a statistically significant difference between group A and group B eyes, respectively.
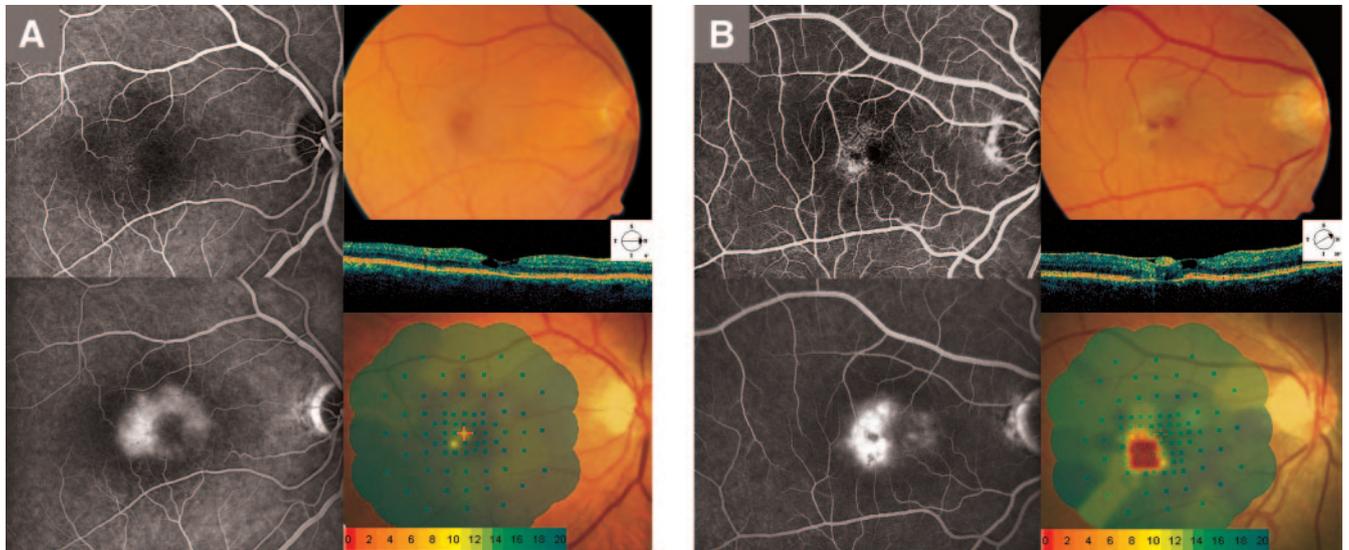
FIGURE 3. (**A**, **B**) Early- (*upper left*) and late-phase (*lower left*) fluorescein angiography, color fundus image (*upper right*), OCT (*middle right*), and interpolated microperimetric sensitivity map (*lower right*). The optic nerve head on the microperimetry map does not reflect the true color proportions. (**A**) Patient 3, OD. Group A (Gass and Blodi classification, stage 2). Retinal graying is seen funduscopically, and small crystalline deposits are located temporal to the fovea. In the early angiographic phase, ectatic capillaries can be seen temporal to the fovea, and leakage in the late phase is parafoveal. Leakage is more intense suprafoveally than infrafoveally. In OCT imaging, hyporeflective spaces are confined to the inner and middle retinal layers. Microperimetry shows only a minor decrease in retinal sensitivity foveally and temporally inferiorly to the fovea. (**B**) Patient 12, OD. Group B (Gass and Blodi classification, stage 4). There is retinal pigment clumping temporal to the fovea, parafoveal graying, crystalline deposits, and a macular pseudohole. Angiographic leakage is more pronounced than in (**A**), and OCT imaging shows intraretinal hyperreflective structures in the area of pigment clumping. Microperimetry shows a total and sharp demarcated scotoma in the parafoveal quadrant temporal inferior to the fovea.

the upper tested fundus region than in the inferior region (*P* < 0.001, Wilcoxon signed rank test; Fig. 2D). This finding is in accordance with the findings by Springer et al.[11] but has not been explained thus far.

Eyes of group A exhibited a well-preserved LIS (Fig. 3A shows a typical example) within the parafoveal region, but the median LIS of the individual testing points showed a tendency to be diminished at the fovea and the temporal parafovea (Figs. 2B, 2C). Including additionally placed testing points, 18 eyes (49%) had LIS of 10 dB or lower; seven of those eyes had absolute scotoma temporal to the fovea. Two of those 18 eyes showed overall diminished LIS and were excluded from further
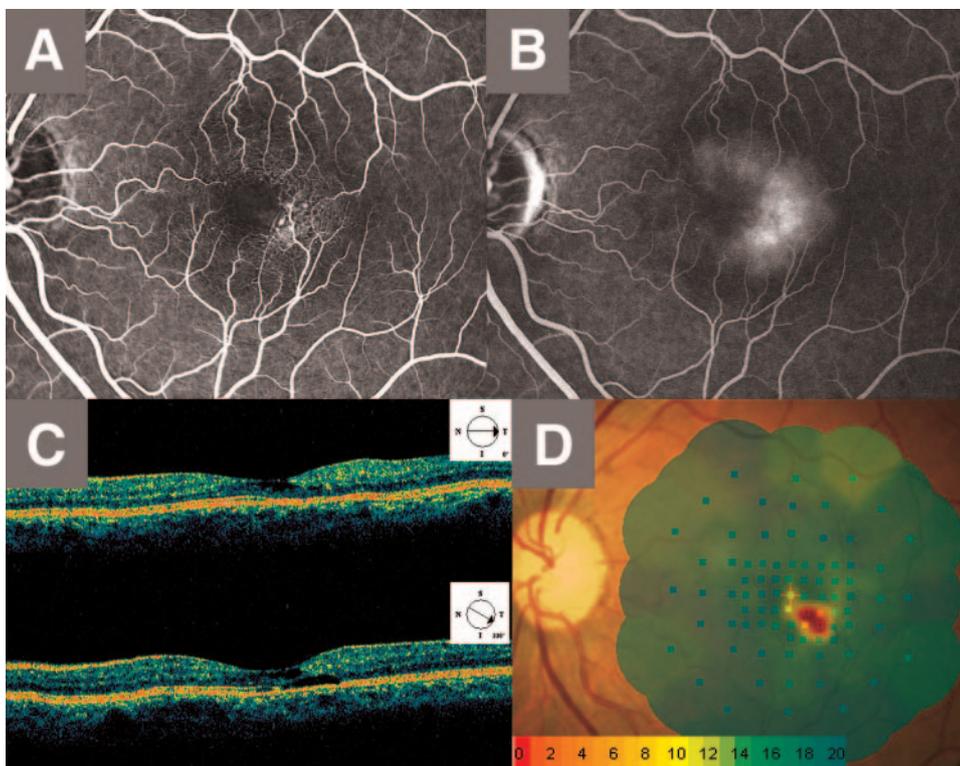

FIGURE 4. Patient 25, OS, group A. Early (**A**) and late (**B**) fluorescein angiography. OCT imaging (**C**) through the area of the scotoma (*lower* OCT) reveals a hyporeflective space between the neurosensory retina and the retinal pigment epithelium that is not present in the horizontal (*upper*) OCT image. Within that area, the interpolated microperimetric sensitivity map (**D**) shows a deep and well-defined small scotoma temporal and inferior to the fovea. The optic nerve head on the microperimetry map does not reflect the true color proportions.
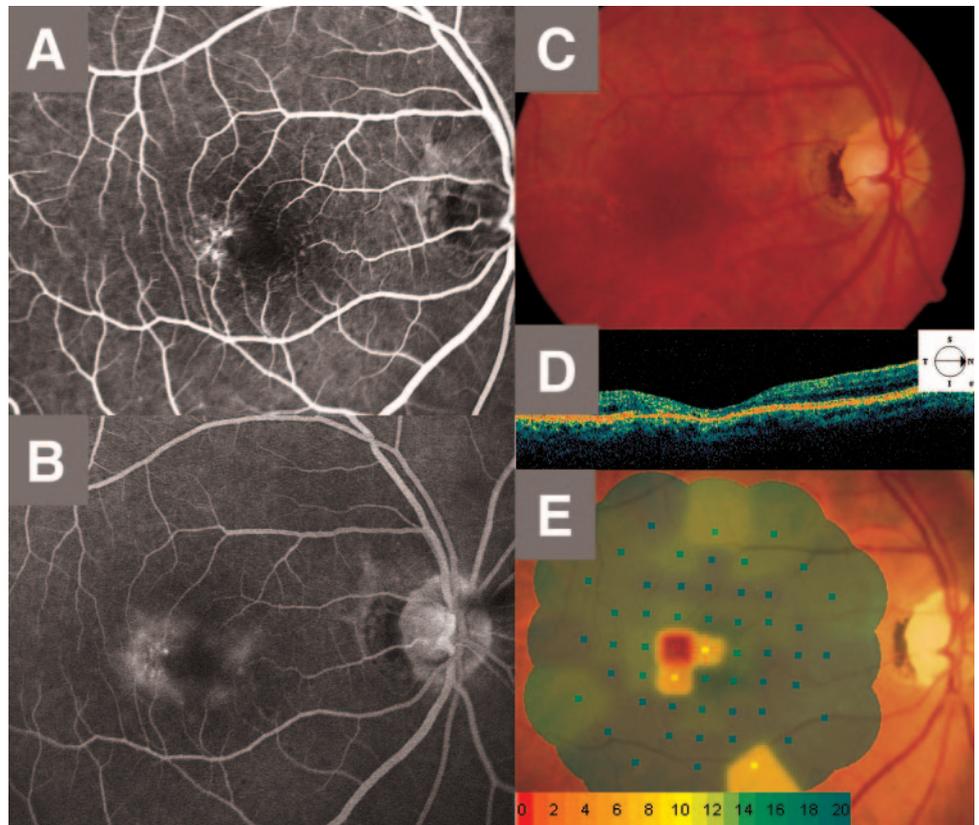
FIGURE 5. Patient 28, OD, group A. Early (**A**) and late (**B**) fluorescein angiography. Color fundus image (**C**) shows small pigment epithelial defects temporal to the fovea. OCT image (**D**) exhibits an atrophic central neurosensory retina. The interpolated microperimetric sensitivity map (**E**) reveals a deep scotoma temporal to the fovea. The optic nerve head on the microperimetry map does not reflect the true color proportions.

analysis. Post hoc analysis revealed three distinctive features in the remaining 16 eyes with marked parafoveal LIS reduction: 10 showed hyporeflective spaces topographically related to the scotoma between the neurosensory retina and the retinal pigment epithelium (i.e., in the photoreceptor layer) in OCT imaging (Fig. 4), two showed pigment epithelial and neurosensory atrophy in the area of the scotoma (Fig. 5), and one showed a lamellar macular hole. Three eyes did not show further obvious differences compared with other group A eyes except for above-average leakage. These changes were not seen in eyes with a higher LIS temporal to the fovea except for 3 (of 21) eyes that showed small hyporeflective spaces in the photoreceptor layer.

In group B, median LIS was reduced at the fovea and at 2° parafoveal eccentricity and was most pronounced temporal and temporal inferior to the fovea. There was only a tendency toward LIS reduction in the nasal parafoveal region. Temporal to the fovea, LIS was also reduced at 4° eccentricity. Each group B eye had an absolute scotoma in at least one location temporal to the fovea, which always was associated with retinal pigment clumping or a vascular membrane. Of the 16 eyes of group B, three had a disruption of the outer retinal layer and two had a lamellar macular hole. A vascular membrane was observed in two eyes and was suspected in two other eyes. At 2° eccentricity in the vertical axis, LIS above the fovea was slightly lower than below the fovea. Despite this minor difference, the capillary leakage had a predi-

TABLE 2. Descriptive Statistics of the Microperimetric Findings along the Horizontal Axis

	Horizontal Eccentricity								
Percentile	−8°	−6°	−4°	−2°	0°	2°	4°	6°	8°
Group A (*n* = 37)									
Minimum	6	14	12	8	0	0	4	10	10
5	11, 4	14	13, 8	11, 6	3, 6	0	7, 6	11, 8	10
25	16,5	16	16	16	11	11	14	16	16
50	18	18	18	18	16	16	16	18	18
75	20	20	20	20	18	18	19	20	20
95	20	20	20	20	20	20	20	20	20
Maximum	20	20	20	20	20	20	20	20	20
Group B (*n* = 16)									
Minimum	6	14	10	0	0	0	0	12	12
5	6	14	10	0	0	0	0	12	12
25	14	16	14,5	10	6,5	0	0,5	14	16
50	17	18	16	16	10	0	10	17	17
75	18	18	18	18	14	0	14	18	20
95	20	20	18	20	20	8	18	20	20
Maximum	20	20	18	20	20	8	18	20	20

lection for the suprafoveal region if leakage progressed over the vertical line centered onto the fovea (Fig. 3A). Descriptive statistics of all microperimetric findings along the horizontal axis (Fig. 2B) are provided in Table 2.

There was a significant correlation between logMAR and foveal LIS in both groups (group A: $r = -0.609$, $P < 0.01$; group B: $r = -0.645$, $P < 0.01$; Spearman rho). However, in group A patients, the correlation between visual acuity and the lowest LIS temporal to the fovea was weaker ($r = -0.451$, $P < 0.01$, Spearman rho), whereas in group B patients the correlation was nonexistent because the minimal LIS, independent of visual acuity, was 0.

DISCUSSION

Visual acuity has been the standard parameter for assessing functional deficits in patients with type 2 IMT despite mirroring only one aspect of macular function. However, the macular abnormality in type 2 IMT is mainly located parafoveally. Therefore, visual acuity, which is dependent on foveal function, may not represent the functional parameter of choice to evaluate macular dysfunction in these patients.

This study shows that type 2 IMT may lead to a parafoveal scotoma with good topographic correspondence to the angiographically and ophthalmoscopically visible alterations. If a scotoma is present, it generally shows a sharp demarcation from normal retinal sensitivity. However, early in the course of the disease in group A eyes, LIS could be preserved despite angiographic leakage. Similarly, group B eyes typically had an absolute scotoma temporal to the fovea, whereas nearby angiographically similar areas could show preserved retinal LIS. It is assumed that the pathologic condition in type 2 IMT starts temporal to the fovea, progresses parafoveally, and involves the nasal area in later disease stages. Indeed, the LIS reduction in group B eyes followed this sequence with a medium reduction above and below the fovea and the least LIS reduction nasal to the fovea. These findings suggest a model of the time course of morphologic and functional alterations: angiographic leakage precedes functional consequences, and only chronic retinal alterations may lead to a reduction of LIS. The observed predilection of angiographic leakage for the suprafoveal compared with the infrafoveal region has not, to our knowledge, been reported previously and must be validated in larger cohorts of patients.

To simplify the classification of type 2 IMT, Yannuzzi et al.[13] suggested limiting the subclassification to a nonproliferative and a proliferative stage. They argued that nonproliferative stages are anatomically similar and that major functional deficits would occur once proliferations have appeared. In contrast, we herein present microperimetric evidence that distinct functional deficits may be present parafoveally, even in nonproliferative stages. For such a discrimination based on visual function, microperimetry may be essential. We found within group A eyes that it may be impossible to discriminate eyes with or without paracentral scotomas exclusively by conventional diagnostics (ophthalmoscopy and angiography).

The finding that visual acuity was correlated with foveal LIS but was uncorrelated with the deepest scotoma temporal to the fovea also refers to the parafoveal predilection of the functional impairment. Given that LIS reduction temporal to the fovea may be present despite preserved visual acuity (Table 1) and that the most advanced LIS reduction is generally located parafoveally (Fig. 2), microperimetric testing might enable functional deficits to be revealed earlier than visual acuity testing. Such parafoveal scotomas may be significant in the daily activities of patients with type 2 IMT because paracentral scotomas may lead to reading difficulty.[14] Therefore, our find-

ings might also explain the reduced reading capability reported by patients with type 2 IMT despite the relatively preserved visual acuity.

The overall well-preserved LIS of group A eyes makes a common grouping reasonable in terms of functional impairment. Post hoc analysis of the patient subgroup with marked LIS reduction temporal to the fovea revealed two pathophysiologically plausible peculiarities.

The first was that OCT imaging revealed hyporeflective spaces between neurosensory retina and retinal pigment epithelium that were topographically related to the scotoma. These recently described lesions[15,16] within the outer retina could result from atrophic damage to the photoreceptors, from photoreceptor disruption, or from neurosensory detachment from the retinal pigment epithelium. Hyporeflective spaces in more superficial neurosensory retinal layers do not seem to affect LIS to the same extent. Therefore, deeper hyporeflective spaces might represent a different course or a more advanced stage of disease. Hyporeflective spaces of the outer retina were present in only 14% of group A eyes without deeper scotoma and in 19% of group B eyes. The former showed less pronounced lesions. Small distinct scotomas resulting from such minor lesions could have been missed because of insufficient spatial resolution of the microperimetric testing. The low percentage in group B eyes could indicate that deep hyporeflective spaces disappear in later disease stages and therefore represent a transitional disease manifestation. In a study using ultra–high-resolution OCT, Paunescu et al.[16] found photoreceptor disruption, which was easy to miss in conventional OCT3 imaging, in 84% of eyes with type 2 IMT and reported a correlation between that and visual acuity. Thus far it is unknown whether this finding represents a precursor of the defects in the outer retina, whether they occur in a certain subgroup, and to which extent they are correlated with disease progression. However, given our OCT findings, fast, uninvasive OCT imaging could indicate functional deficits in type 2 IMT.

The second finding in group A eyes with pronounced LIS reduction was the presence of pigment epithelial and neurosensory atrophy that was identifiable ophthalmoscopically and angiographically as a window defect. It was previously reported that pigment epithelial and neurosensory atrophy in patients with macular dystrophy may lead to absolute scotomas in microperimetry.[17]

Group A eyes with pronounced parafoveal LIS reduction that did not obviously show one of the described abnormalities (3 of 16) could be attributed to thus far unidentified explanations. However, the OCT findings could be overlooked because OCT imaging in our setting only detected parafoveal changes along the six scanned axes. Additional studies comparing results from OCT imaging with findings in microperimetry are needed for clarification. It may be that OCT3 technology cannot map small defects, such as those in the photoreceptor layer, that would still be of functional relevance. Furthermore, it remains to be determined whether alterations detected by the OCT3 mapping software are of any functional significance.

Each group B eye had an absolute scotoma at least temporal to the fovea that was always in good topographic correlation with retinal pigment clumping or vascular membranes. Deep scotomas showed a relatively sharp demarcation not only to the angiographically inconspicuous retina but also to the adjacent and angiographically similar areas. These circumscribed functional deficits, which highlight the localized pathology of the disease, remain to be explained. The preferred localization of the scotoma temporal inferior to the fovea may be explained by an orthostatic effect on exudated fluid.

Assigning patients to group A or group B resulted in better interobserver agreement than using the classification proposed by Gass and Blodi,[2] perhaps because of the smooth transition

and difficult discrimination of early signs of disease, such as right-angle venules or loss of retinal transparency. Therefore, the Gass and Blodi[2] classification, based on angiographic and funduscopic findings, may not be feasible for grading in future studies. A recently proposed classification by Yannuzzi et al. also does not consider functional deficits other than visual acuity.[13] Moreover, treatment with intravitreal bevacizumab, an anti-VEGF therapy, has recently been shown to result in a decrease in angiographic leakage.[18] It may be hypothesized that functional treatment effects would best be monitored by microperimetry since the parafovea shows the strongest functional alterations. We suggest including microperimetry as a further outcome measure in future clinical trials. The microperimetric findings may also be of value for future classifications of the disease.

In summary, our microperimetric findings in patients with type 2 IMT show that macular sensitivity significantly decreases temporal to the fovea and that LIS deteriorates in eyes at more severe stages. Longitudinal microperimetric data to be assessed in the MacTel study will give further insight into the pathophysiology and natural history of the disease.

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