Multimodal evaluation of macular function in age-related macular degeneration

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ABSTRACT

Objective To evaluate macular function using multimodality in eyes with age-related macular degeneration (AMD) at various stages.

Methods Macular function in 20 control eyes (20 subjects), 17 eyes (17 patients) with large drusen, 18 eyes (18 patients) with drusenoid pigment epithelial detachment (PED), and 19 eyes (19 patients) with neovascular AMD was examined using a Landolt chart for visual acuity; retinal sensitivity was measured by microperimetry; and focal macular electroretinography (fmERG) was performed. In all of these eyes, retinal morphology was examined using optical coherence tomography.

Results Eyes with neovascular AMD showed morphologic changes in the neurosensory retina as well as marked deterioration of macular function in all parameters measured with a Landolt chart, fmERG, and microperimetry. Eyes with large drusen showed only minimal morphologic changes in the neurosensory retina. In this large drusen group, although retinal sensitivity at the central point was significantly decreased ($P = 0.0063$), the other parameters of macular function were well preserved. In eyes with drusenoid PED, the structure of the neurosensory retina was well preserved, while the foveal thickness was significantly increased ($P = 0.013$). The macular function of these eyes was significantly deteriorated, with the VA, amplitude of the a-wave and b-wave, and retinal sensitivity being markedly decreased. In addition, the area of PED correlated with the latency of the a- wave and b-wave and with the retinal sensitivity within the central 4° or 8° region.

Conclusion Multimodal evaluation demonstrated a significant decrease in macular function in drusenoid PED and in

neovascular AMD.

Keywords: Age-related macular degeneration, Drusenoid pigment epithelial detachment, Drusen, Focal macular electroretinography, Microperimetry

Introduction

Age-related macular degeneration (AMD) is one of the leading causes of visual impairment and an intensive therapeutic target in developed countries [1-6]. Drusen or drusenoid pigment epithelium detachment (PED), which is a prodrome lesion of advanced AMD, does not usually cause a severe loss of visual acuity (VA), but it is the subsequent development of choroid neovascularization (CNV) that so often causes the central visual disturbance. So far, however, visual impairment due to AMD has been evaluated primarily by VA measurement alone. Indeed, VA measurement is essential to evaluate visual function, but it reflects only foveal function. Lesions of AMD, including drusen, CNV, serous retinal detachment, subretinal hemorrhage, and PED, are seen not only beneath the fovea but in the larger macular area, which leads to the macular dysfunction.[7]

To evaluate visual function of the entire macular area, simultaneous use of the focal macular electroretinogram (fmERG) and of microperimetry have recently been reported [8, 9]. The fmERG enables measurement of macular function throughout its entirety, even in patients with poor fixation, by monitoring through an infrared camera and manual adjustment of the stimulus to the macular area [10]. Microperimetry allows functional evaluation of selected points throughout the macular area [11, 12]. During this test, the autotracking function corrects for shifts in the measurement position caused by small, involuntary movements. Recent studies using microperimetry have shown that early or advanced AMD often accompanies the severe reduction in sensitivity of the macular area [13-21]. With the use of microperimetry, Yodoi et al reported a functional reduction in the macular area of eyes with subfoveal polypoidal choroidal vasculopathy (PCV), which is a variant of neovascular AMD [22]. In their report, macular

function improved after photodynamic therapy with concomitant recovery of the subjective symptoms, despite there being no improvement in VA.

Other recent studies with microperimetry or ERG have evaluated macular function in eyes with AMD and have reported that it is impaired—even in eyes with drusen alone [23, 24]. Indeed, each modality has both advantages and limitations. To evaluate visual function effectively, it would be of help to measure retinal function within the macular area using the multimodality approach. So far, however, little information is available on the multimodal evaluation of visual function in eyes with AMD. Therefore, this study was designed to evaluate the macular function using multimodality in eyes with AMD at various stages, including those with large drusen, drusenoid PED, and those with neovascular AMD.

Patients and methods

In this prospective study, we performed multimodal evaluation of macular function in eyes with AMD at various stages; the eyes comprised 17 (17 patients) with large drusen, 18 (18 patients) with drusenoid PED, and 19 (19 patients) with neovascular AMD (8 eyes with typical AMD and 11 eyes with polypoidal choroidal vasculopathy). Eyes with large drusen were judged by the presence of multiple large drusen (>125 μm) within 3000 μm of the center of the macula on fundus photographs. The diagnostic criteria of drusenoid PED were confluent drusen, with a focal area of PED involving the macular area, with a minimum size of 1/2 disc diameter [25], and without CNV detected on ophthalmoscopy or fluorescein and indocyanine green angiography. Neovascular AMD was diagnosed

on the basis of fluorescein and indocyanine green angiography, which showed an exudative change with CNV. In the current study, eyes with central geographic atrophy were excluded. We also recruited 20 eyes (20 subjects) as an age-adjusted control group. The criteria for the eyes, including for the control eyes, were as follows: ≥1.0 VA on a Landolt chart, <10 small drusen (<63 μm) within 3000 μm of the center of the macula on the fundus photograph, normal morphology of the fovea as seen with optical coherence tomography (OCT), and absence of central geographic atrophy or CNV.

This study was approved by the institutional review board of Kyoto University Graduate School of Medicine and adhered to the tenets of the Declaration of Helsinki. Written informed consent for research participation was obtained from each subject before examination.

Each subject underwent a comprehensive ophthalmologic examination, including measurement of best-corrected VA on a Landolt chart, determination of intraocular pressure, indirect ophthalmoscopy, and slit-lamp biomicroscopy with a contact lens. In each subject, 45º digital fundus photographs were obtained using a digital fundus camera (TRC-50LX; Topcon, Tokyo, Japan; 3216 × 2136 pixels) after pupil dilatation and the macular area was examined with a Spectralis HRA+OCT device (Heidelberg Engineering, Heidelberg, Germany). Each patient with large drusen, drusenoid PED, or neovascular AMD underwent fluorescein and indocyanine green angiography with a confocal laser scanning system (HRA-2; Heidelberg Engineering). In each eye, macular function was examined by fundus-monitored microperimetry and fmERG recording.

Retinal sensitivity within the macular area was examined with a fundus-monitored microperimeter (Micro

Perimeter 1 [MP1]; Nidek, Gamagori, Japan). A 4-2-staircase strategy with Goldmann III-sized stimuli was used, and 57 stimulus locations within a 10° radius were examined by microperimetry. Each stimulus was located according to the measurement points on the Humphrey 10-2, with some additional points. The white background illumination was set at 1.27 cd/m^2. The differential luminance, defined as the difference between the stimulus luminance and background luminance, was 127 cd/m^2 at 0-dB stimulation, and the maximum stimulus attenuation was 20 dB. The stimulus duration was 200 milliseconds (ms), and the fixation target varied in size according to the VA of the patient. There were 17 and 37 measurement points within the central circles with radii of 4° and 8°, respectively.

The fmERG recording procedure has been previously described in detail [8, 9]. Briefly, after maximal dilatation of the pupils of both eyes, a Burian-Allen bipolar contact lens electrode (Hansen Ophthalmic Laboratories, Iowa City, IA, USA) was placed in the conjunctival sac of each eye under topical anesthesia. A chloride silver electrode was attached to the left earlobe to serve as the ground electrode. The fmERG was elicited by circular stimuli positioned on the macular area, using a prototype of the ER-80 (Kowa, Tokyo, Japan), which consisted of an infrared camera (Kowa) and a stimulation system (Mayo Corporation, Nagoya, Japan). The luminance values of the white stimulus light and the background illumination were 181.5 and 6.9 cd/m^2, respectively. The stimulus within the 7.5°-radius circle was centered on the fovea, as observed through the infrared camera. The fmERG was recorded using 5-Hz rectangular stimuli (100 ms with the light on and 100 ms with the light off). The recording (200 responses) was carried out in triplicate to confirm the reproducibility of the results, so a total of 600 responses were averaged by the signal processor (Neuropack MEB-2204; Nihon Kohden, Tokyo, Japan). The fmERG response was

digitized at 10 kHz with a band-pass filter of 5–500 Hz for the a-wave and the b-wave. The amplitudes of the a- and b-waves were measured from baseline to the peak of the a-wave and from the trough of the a-wave to the peak of the b-wave, respectively. Latency was defined as the time from the beginning of stimulation to the peak of each component.

For the OCT images, the foveal thickness in each eye was determined in the following 2 ways: the distance between the internal limiting membrane (ILM) and the outer border of the RPE or the distance between the ILM and the Bruch membrane. In eyes with drusenoid PED, we also measured the height and area of the PED. For the sequential OCT images, the height of the PED was defined as the maximal distance between the outer border of the RPE and the Bruch membrane (sometimes outside the fovea). For the late-phase indocyanine green angiogram, the area of the PED was measured using software built into the HRA-2. Briefly, drusenoid PED was observed as a dark area on the late-phase indocyanine green angiogram, and the edge of this central dark area was traced manually. The surrounding small dark lesions (drusen) isolated from the central PED were not included.

Statistical analysis was performed using PASW Statistics version 17.0 software (SPSS, Chicago, IL, USA). All values were expressed as means ± standard deviations. The best-corrected VA was measured using a Landolt chart and converted to the logarithm of the minimum angle of resolution (logMAR). To clarify differences from the healthy controls, all mean values between groups were compared using 1-way analysis of variance and post hoc Dunnet tests. Bivariate analysis was done with the Pearson product moment correlation.

Results

Table 1 shows the characteristics of the study populations. Although the controls (82.0 ± 3.2 years) were significantly older than the patients with neovascular AMD (77.3 ± 6.9 years, $P = 0.019$), there was no significant difference in the gender or lens status of groups. In the control group, 13 eyes had small drusen in the macular area and 7 had no drusen. All eyes showed good macular function (Fig. 1).

All functional parameters were measured, with VA, fmERG, and microperimetry showing significant variation between the groups (Table 1). All eyes with neovascular AMD showed marked morphologic changes in the neurosensory retina. In this group, cystoid macular edema was seen in 4 eyes (21%), serous retinal detachment, in 14 eyes (74%), and PED, in 17 eyes (89%); foveal thickness of the neurosensory retina (384 ± 256 μm) was significantly increased compared with the control eyes (224 ± 27 μm) (Fig. 2). Consistent with these morphologic changes, macular function (VA, fmERG, and microperimetry) was significantly deteriorated in the neovascular AMD group (Figs. 3 and 4).

In the large drusen group, all eyes showed multiple large drusen in the macular area; the mean number of drusen measuring 125 to 250 μm was 10.3 ± 4.2 and that of drusen measuring at least 250 μm was 3.1 ± 2.1. These eyes showed minimal morphologic changes in the neurosensory retina. No eyes in this group showed cystoid macular edema, serous retinal detachment, or a vitelliform lesion. Foveal thickness of the neurosensory retina (196 ± 40 μm) was no different from that in the control group (Fig. 2). In this large drusen group, while retinal sensitivity at the central point was significantly decreased, the other parameters of macular function (VA, fmERG, and

microperimetry) were preserved (Figs. 3 and 5).

In the drusenoid PED group, all eyes had drusenoid PED of at least 1/2 disc diameter within the macular area. The mean area of the PED was 4.78 ± 3.74 mm^2 and the mean height was 266 ± 178 μm. In eyes with drusenoid PED, the foveal thickness between the ILM and the Bruch membrane (377 ± 164 μm) was significantly greater than that in the control eyes (224 ± 27 μm, $P = 0.013$). However, the structure of the neurosensory retina was well preserved, and the foveal thickness between the ILM and RPE (200 ± 49 μm) did not differ from that in the control group (Fig. 2). On the other hand, the macular function of these eyes was significantly deteriorated. VA, amplitude of the a-wave and of the b-wave, and retinal sensitivity measured with the MP1 were significantly decreased when compared with the control eyes (Figs. 3 and 6). Table 2 shows the correlation between the size of the drusenoid PED and macular function and between the area of the PED and the latency of the a-wave and the b-wave, and retinal sensitivity within the central 4° or 8°. The height of the PED was negatively correlated with retinal sensitivity within the central 4° and 8° areas (Fig. 7).

Discussion

Eyes with neovascular AMD often have a severe decrease in VA. In addition, because such eyes often show serous retinal detachment, subretinal hemorrhage, retinal edema, or PED in the macular area, they may well have a reduction in function in the macular area. With the use of fmERG, Nishihara et al reported that, in eyes with neovascular AMD, the amplitude of each wave was reduced to 29% to 35% of that of the control eyes [26]. With the

use of microperimetry, Sulzbacher et al [24] and Hautamäki et al [27] reported more recently that retinal sensitivity was markedly decreased within the area of CNV, macular edema, hemorrhage, subretinal fluid, or PED in eyes with neovascular AMD. In our patients with neovascular AMD, cystoid macular edema was seen in 21%, serous retinal detachment was seen in 74%, and PED was seen in 89% of the patients, and thickness of the fovea in the neurosensory retina was significantly increased. In eyes with neovascular AMD, severe macular dysfunction is based on the morphologic changes caused by the exudative change resulting from the CNV.

Eyes with drusen often maintain good VA. However, as the number or size of the drusen increases, they may cause a functional disturbance in the macular area. So far, several electrophysiologic assessments have been performed to study the macular function in eyes with drusen [23, 28-33]. Falsini et al documented an abnormality of the focal ERG threshold in eyes with more than 20 soft drusen [33], although they did not investigate the correlation between each drusen and the local sensitivity loss. With the use of microperimetry, Midena et al reported that retinal sensitivity in eyes with large drusen (>125 μm) was severely deteriorated[16]. Iwama et al reported that eyes with confluent soft drusen often show focal areas with reduced retinal function consistent with irregularity of the RPE line or of the junction between the inner and outer segments of the photoreceptors [34]. In the current study, while retinal sensitivity at the central point was significantly decreased in eyes with large drusen, the other parameters of macular function (VA, fmERG, and microperimetry) were well preserved. Although we did not assess function at each point, retinal function may be focally deteriorated, consistent with the drusen. In addition, the area in which drusen are seen may be involved in the reduction of macular function.

Drusenoid PED refers to a fairly well-circumscribed, shallow elevation of the RPE formed by confluent soft drusen, often located in the center of the macula [35]. VA in eyes with drusenoid PED is reported to be relatively good. In fact, in a recent report from the Age-Related Eye Disease Study, baseline VA in eyes with drusenoid PED was ~20/32, with ~90% of eyes having VA better than 20/40 [35]. So far, however, little information is available on the macular dysfunction caused by drusenoid PED. In the current study, VA, amplitude of the a-wave and b-wave, and retinal sensitivity measured with the MP1 were significantly decreased when compared with the control eyes. In addition, the area and height of the PED were correlated with the fmERG and with the retinal sensitivity within the macular area—correlations that are consistent with the previously mentioned report of confluent drusen [34]. Photoreceptor damages, which could be observed as discontinuity of the junction of the inner and outer segments and as presence of hyperreflective foci in the OCT image (Fig. 6) [36, 37], might result in decreased macular function in eyes with drusenoid PED. Falsini et al also discussed that focal ERG sensitivity loss in eyes with drusen might result from photoreceptor drop out [33], as could be slightly seen in the OCT images of eyes with large drusen in our study (Fig. 5).

The prognosis of drusenoid PED was initially thought to be relatively good [38, 39]; however, a recent cohort study reported a high rate of progression to more advanced AMD [35]. Roquet et al documented that presence of metamorphopsia and drusenoid PED of greater than 2 disc diameters were risk factors of CNV occurrence within 2 years [25]. Recently, other research groups have reported results of pilot studies on the early treatment of drusenoid PED without CNV by photodynamic therapy or by antivascular endothelial growth factor therapy [40-43].

Gallego-Pinazo et al successfully treated 6 patients with drusenoid PED using intravitreal ranibizumab.[41] However, Krishnan and Lochhead reported rapid development of geographic atrophy after intravitreal injection of pegaptanib in an eye with drusenoid PED [42]. In a recent report from the Age-Related Eye Disease Study, 19% of eyes with drusenoid PED developed central geographic atrophy and 23% of these developed neovascular AMD [35]. When geographic atrophy develops in the extrafoveal region, VA measurement does not reflect a visual disturbance. The effect of treatment for drusenoid PED remains controversial. Multimodal measurements of macular function would be most helpful to evaluate the treatment efficacy of drusenoid PED.

There are various limitations to the current study. First, the eligible patients and controls in this study were all Japanese, and the genetic background may well have influenced the characteristics of AMD, so our results should be confirmed in another population. Second, the sample size of each group was small, so it is possible that we did not detect small differences between groups. Third, the current study excluded central geographic atrophy, primarily because this is a relatively rare feature of AMD in Japanese patients. Finally, this was a cross-sectional study, so we could not offer any information regarding changes in macular function over time. Further longitudinal studies are necessary to fully elucidate the macular function in eyes with AMD of various stages and to study the treatment effects and the natural course of eyes with AMD, especially those with AMD in the early stage. Multimodal evaluations of the entire macular function should be of great help in these endeavors.

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None

REFERENCES

1. Friedman DS, O'Colmain BJ, Munoz B, Tomany SC, McCarty C, de Jong PT, et al. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol. 2004;122:564-72.

2. Bressler NM. Age-related macular degeneration is the leading cause of blindness. JAMA. 2004;291:1900-1.

3. Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, et al. Global data on visual impairment in the year 2002. Bull World Health Organ. 2004;82:844-51.

4. Ishibashi T and on behalf of the L-JSG. Maintenance therapy with pegaptanib sodium for neovascular age-related macular degeneration: an exploratory study in Japanese patients (LEVEL-J study). Jpn J Ophthalmol. 2013;57:417-23.

5. Yoshida Y, Kohno T, Yamamoto M, Yoneda T, Iwami H, Shiraki K. Two-year results of reduced-fluence photodynamic therapy combined with intravitreal ranibizumab for typical age-related macular degeneration and polypoidal choroidal vasculopathy. Jpn J Ophthalmol. 2013;57:283-93.

6. Yoshizawa C, Saito W, Hirose S, Kitamei H, Noda K, Ishida S. Photodynamic therapy combined with intravitreal bevacizumab and sub-tenon triamcinolone acetonide injections for age-related macular degeneration. Jpn J Ophthalmol. 2013;57:68-73.

7. Tezel TH, Del Priore LV, Flowers BE, Grosof DH, Benenson IL, Zamora RL, et al. Correlation between scanning laser ophthalmoscope microperimetry and anatomic abnormalities in patients with subfoveal neovascularization. Ophthalmology. 1996;103:1829-36.

8. Ogino K, Tsujikawa A, Murakami T, Muraoka Y, Akagi-Kurashige Y, Ishihara K, et al. Evaluation of macular function using focal macular electroretinography in eyes with macular edema associated with branch retinal vein occlusion. Invest Ophthalmol Vis Sci. 2011;52:8047-55.

9. Ogino K, Tsujikawa A, Nakamura H, Miyamoto K, Murakami T, Muraoka Y, et al. Focal macular electroretinogram in macular edema secondary to central retinal vein occlusion. Invest Ophthalmol Vis Sci. 2011;52:3514-20.

10. Miyake Y. Focal macular electroretinography. Nagoya J Med Sci. 1998;61:79-84.

11. Springer C, Bültmann S, Völcker HE, Rohrschneider K. Fundus perimetry with the Micro Perimeter 1 in normal individuals: comparison with conventional threshold perimetry. Ophthalmology. 2005;112:848-54.

12. Rohrschneider K, Springer C, Bültmann S, Völcker HE. Microperimetry--comparison between the micro perimeter 1 and scanning laser ophthalmoscope--fundus perimetry. Am J Ophthalmol. 2005;139:125-34.

13. Ritter M, Bolz M, Sacu S, Deak GG, Kiss C, Pruente C, et al. Effect of intravitreal ranibizumab in avascular pigment epithelial detachment. Eye (Lond). 2010;24:962-8.

14. Parisi V, Perillo L, Tedeschi M, Scassa C, Gallinaro G, Capaldo N, et al. Macular function in eyes with early age-related macular degeneration with or without contralateral late age-related macular degeneration. Retina. 2007;27:879-90.

15. Ozdemir H, Karacorlu M, Senturk F, Karacorlu SA, Uysal O. Microperimetric changes after intravitreal bevacizumab injection for exudative age-related macular degeneration. Acta Ophthalmol 2012;90:71-5.

16. Midena E, Vujosevic S, Convento E, Manfre A, Cavarzeran F, Pilotto E. Microperimetry and fundus autofluorescence in patients with early age-related macular degeneration. Br J Ophthalmol. 2007;91:1499-503.

17. Midena E, Radin PP, Pilotto E, Ghirlando A, Convento E, Varano M. Fixation pattern and macular sensitivity in eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration: a microperimetry study. Semin Ophthalmol. 2004;19:55-61.

18. Landa G, Su E, Garcia PM, Seiple WH, Rosen RB. Inner segment-outer segment junctional layer integrity and corresponding retinal sensitivity in dry and wet forms of age-related macular degeneration. Retina. 2011;31:364-70.

19. Dinc UA, Yenerel M, Gorgun E, Oncel M. Assessment of macular function by microperimetry in intermediate age-related macular degeneration. Eur J Ophthalmol. 2008;18:595-600.

20. Calabrèse A, Bernard JB, Hoffart L, Faure G, Barouch F, Conrath J, et al. Wet versus dry age-related macular degeneration in patients with central field loss: different effects on maximum reading speed. Invest Ophthalmol Vis Sci. 2011;52:2417-24.

21. Bolz M, Simader C, Ritter M, Ahlers C, Benesch T, Prunte C, et al. Morphological and functional analysis of the loading regimen with intravitreal ranibizumab in neovascular age-related macular degeneration. Br J Ophthalmol. 2010;94:185-9.

22. Yodoi Y, Tsujikawa A, Kameda T, Otani A, Tamura H, Mandai M, et al. Central retinal sensitivity measured

with the micro perimeter 1 after photodynamic therapy for polypoidal choroidal vasculopathy. Am J Ophthalmol. 2007;143:984-94.

23. Falsini B, Serrao S, Fadda A, Iarossi G, Porrello G, Cocco F, et al. Focal electroretinograms and fundus appearance in nonexudative age-related macular degeneration: quantitative relationship between retinal morphology and function. Graefes Arch Clin Exp Ophthalmol. 1999;237:193-200.

24. Sulzbacher F, Kiss C, Kaider A, Eisenkoelbl S, Munk M, Roberts P, et al. Correlation of SD-OCT features and retinal sensitivity in neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci. 2012;53:6448-55.

25. Roquet W, Roudot-Thoraval F, Coscas G, Soubrane G. Clinical features of drusenoid pigment epithelial detachment in age related macular degeneration. Br J Ophthalmol. 2004;88:638-42.

26. Nishihara H, Kondo M, Ishikawa K, Sugita T, Piao CH, Nakamura Y, et al. Focal macular electroretinograms in eyes with wet-type age-related macular degeneration. Invest Ophthalmol Vis Sci. 2008;49:3121-5.

27. Hautamäki A, Oikkonen J, Onkamo P, Immonen I. Correlation between components of newly diagnosed exudative age-related macular degeneration lesion and focal retinal sensitivity. Acta Ophthalmol. doi:10.1111/j.1755-3768.2012.02556.x.

28. Piccardi M, Ziccardi L, Stifano G, Montrone L, Iarossi G, Minnella A, et al. Regional cone-mediated dysfunction in age-related maculopathy evaluated by focal electroretinograms: relationship with retinal

morphology and perimetric sensitivity. Ophthalmic Res. 2009;41:194-202.

29. Li J, Tso MO, Lam TT. Reduced amplitude and delayed latency in foveal response of multifocal electroretinogram in early age related macular degeneration. Br J Ophthalmol. 2001; 85:287-90.

30. Gerth C, Delahunt PB, Alam S, Morse LS, Werner JS. Cone-mediated multifocal electroretinogram in age-related macular degeneration: progression over a long-term follow-up. Arch Ophthalmol. 2006;124:345-52.

31. Feigl B, Brown B, Lovie-Kitchin J, Swann P. Functional loss in early age-related maculopathy: the ischaemia postreceptoral hypothesis. Eye (Lond). 2007;21:689-96.

32. Feigl B, Brown B, Lovie-Kitchin J, Swann P. Cone- and rod-mediated multifocal electroretinogram in early age-related maculopathy. Eye (Lond). 2005;19:431-41.

33. Falsini B, Fadda A, Iarossi G, Piccardi M, Canu D, Minnella A, et al. Retinal sensitivity to flicker modulation: reduced by early age-related maculopathy. Invest Ophthalmol Vis Sci. 2000;41:1498-506.

34. Iwama D, Tsujikawa A, Ojima Y, Nakanishi H, Yamashiro K, Tamura H, et al. Relationship between retinal sensitivity and morphologic changes in eyes with confluent soft drusen. Clin Experiment Ophthalmol. 2010;38:483-8.

35. Cukras C, Agron E, Klein ML, Ferris FL, 3rd, Chew EY, Gensler G, et al. Natural history of drusenoid pigment epithelial detachment in age-related macular degeneration: Age-Related Eye Disease Study Report No. 28. Ophthalmology. 2010;117:489-99.

311 36. Ogino K, Murakami T, Tsujikawa A, Miyamoto K, Sakamoto A, Ota M, et al. Characteristics of optical
312 coherence tomographic hyperreflective foci in retinal vein occlusion. Retina. 2012;32:77-85.
313 37. Bolz M, Schmidt-Erfurth U, Deak G, Mylonas G, Kriechbaum K, Scholda C. Optical coherence
314 tomographic hyperreflective foci: a morphologic sign of lipid extravasation in diabetic macular edema.
315 Ophthalmology. 2009;116:914-20.
316 38. Hartnett ME, Weiter JJ, Garsd A, Jalkh AE. Classification of retinal pigment epithelial detachments
317 associated with drusen. Graefes Arch Clin Exp Ophthalmol. 1992;230:11-9.
318 39. Casswell AG, Kohen D, Bird AC. Retinal pigment epithelial detachments in the elderly: classification and
319 outcome. Br J Ophthalmol. 1985;69:397-403.
320 40. Querques G, Bux AV, Delle Noci N. Foveal geographic atrophy following intravitreal pegaptanib sodium
321 (Macugen) for drusenoid pigment epithelium detachment. Eur J Ophthalmol. 2009;19:890-3.
322 41. Gallego-Pinazo R, Marina A, Suelves C, Frances-Munoz E, Millan JM, Arevalo JF, et al. Intravitreal
323 ranibizumab for symptomatic drusenoid pigment epithelial detachment without choroidal
324 neovascularization in age-related macular degeneration. Clin Ophthalmol. 2011;5:161-5.
325 42. Lee NY, Kim KS. Photodynamic therapy treatment for eyes with drusenoid pigment epithelium detachment.
326 Korean J Ophthalmol. 2008;22:194-6.
327 43. Krishnan R, Lochhead J. Regression of soft drusen and drusenoid pigment epithelial detachment following
328 intravitreal anti-vascular endothelial growth factor therapy. Can J Ophthalmol. 2010;45:83-4.

Figure Legends

Fig. 1 Macular function in a healthy control eye. Retinal sensitivity map obtained by microperimetry (**a**) and focal macular electroretinogram (**b**). White arrowhead = beginning of stimulus; yellow arrow = amplitude of each wave of focal macular electroretinogram

Fig. 2 Foveal thickness of control eyes, eyes with large drusen, eyes with drusenoid pigment epithelial detachment, and eyes with neovascular age-related macular degeneration. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.0001$, compared with control eyes. *P* values were calculated by the Dunnet test. ILM indicates internal limiting membrane; RPE, retinal pigment epithelium; PED, pigment epithelium detachment; AMD, age-related macular degeneration

Fig. 3 Macular function measured with multimodality in control eyes, eyes with large drusen, eyes with drusenoid pigment epithelial detachment, and eyes with neovascular age-related macular degeneration. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.0001$, as compared with control eyes. *P* values were calculated by the Dunnet test. LogMAR indicates logarithm of the minimum angle of resolution; PED, pigment epithelium detachment; AMD, age-related macular degeneration

Fig. 4 Macular function in an eye with neovascular age-related macular degeneration. (**a**). Fundus photograph

shows submacular hemorrhage (0.15 on a Landolt chart, OD). (**b**, **c**) Fluorescein and indocyanine green angiograms reveal subfoveal choroidal neovascularization. Horizontal (**d**) and vertical (**e**) sections obtained with OCT show subretinal fluid. (**f**) Retinal sensitivity map obtained with microperimetry shows a substantial reduction of retinal sensitivity in the macular function. (**g**) Focal macular electroretinogram shows a substantial reduction in amplitude of all waves. Arrowhead = beginning of stimulus

Fig. 5 Macular function in an eye with large drusen. (**a**) Fundus photograph shows multiple large drusen in the macular area (1.0 on a Landolt chart, OD). (**b**, **c**) Fluorescein and indocyanine green angiograms reveal no choroidal neovascularization. Horizontal (**d**) and vertical (**e**) sections obtained with OCT show multiple large drusen beneath and affecting the fovea. The junction of the inner and outer segments of photoreceptors (between the arrows) was discontinued. (**f**) Microperimetry shows preserved retinal sensitivity within the macular area except for the fovea. (**g**) Focal macular electroretinogram shows that the amplitude of all of the waves was relatively preserved. Arrowhead = beginning of stimulus

Fig. 6 Macular function in an eye with drusenoid pigment epithelial detachment (PED). (**a**) Fundus photograph of drusenoid PED under the fovea (0.7 on a Landolt chart, OD). (**b**) Fluorescein angiogram reveals no choroidal neovascularization. (**c**) From the late-phase indocyanine green angiogram, the area of drusenoid PED was calculated as 6.26 mm^2. Horizontal (**d**) and vertical (**e**) sections obtained with OCT show drusenoid PED. The height of the

PED was 258 μm. The red arrow indicates hyperreflective foci. (**f**) Retinal sensitivity map obtained with microperimetry shows a marked reduction in retinal sensitivity consistent with drusenoid PED. (**g**) In the focal macular electroretinogram, the amplitude of each wave was reduced to 60% - 75% of normal amplitudes. Arrowhead = beginning of stimulus

Fig. 7 Scattergram of the size of the drusenoid pigment epithelial detachment and macular functions measured with focal macular electroretinogram or microperimetry. PED indicates pigment epithelium detachment

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TABLE 1. Background, foveal thickness, and macular function of control eyes, eyes with large drusen, eyes with drusenoid pigment epithelial detachment, and eyes with neovascular age-related macular degeneration.

	Controls	**Large Drusen**	**Drusenoid PED**	**Neovascular AMD**	***P* value**
Sex (male/female)	16/4	11/6	18/0	16/3	0.054
Phakia/pseudophakia	14/6	9/8	13/5	12/7	0.627
Age, y	82.0 ± 3.2	80.7 ± 5.2	78.9 ± 5.0	77.3 ± 6.9	0.040
Visual acuity, logMAR	-0.07 ± 0.07	0.05 ± 0.14	0.16 ± 0.18	0.42 ± 0.42	< 0.0001
Foveal thickness, µm					
ILM to RPE	224 ± 27	196 ± 40	200 ± 49	384 ± 256	< 0.0001
ILM to Bruch membrane	224 ± 27	231 ± 36	377 ± 164	533 ± 263	< 0.0001
Amplitude of fmERG, µV					
a-wave	1.73 ± 0.65	1.35 ± 0.49	1.21 ± 0.67	0.87 ± 0.58	0.0005
b-wave	3.14 ± 0.89	2.55 ± 0.91	2.20 ± 1.09	1.37 ± 1.04	< 0.0001
Latency of fmERG, ms					
a-wave	23.18 ± 1.28	23.67 ± 1.58	24.39 ± 1.77	25.76 ± 3.39	0.040
b-wave	42.05 ± 2.27	45.44 ± 3.87	45.22 ± 3.71	48.87 ± 7.38	0.0005
Retinal sensitivity, dB					
center point	14.78 ± 3.52	9.94 ± 3.86	3.82 ± 3.43	5.37 ± 6.31	< 0.0001
within 4°	16.50 ± 2.01	13.35 ± 3.57	6.83 ± 4.39	5.78 ± 6.27	< 0.0001
within 8°	16.13 ± 2.10	13.66 ± 3.32	9.19 ± 3.94	6.76 ± 6.23	< 0.0001

PED pigment epithelium detachment, *AMD* age-related macular degeneration, *fmERG* focal macular electroretinogram, *ILM* internal limiting membrane, *RPE* retinal pigment epithelium

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TABLE 2. Correlation between size of drusenoid pigment epithelium detachment and macular function.

	Area of Drusenoid PED		**Height of Drusenoid PED**	
	r	*P* value	*r*	*P* value
Visual acuity in logMAR	0.058	0.820	0.432	0.074
Amplitude of fmERG				
a-wave	-0.427	0.077	-0.118	0.642
b-wave	-0.445	0.067	-0.312	0.207
Latency of fmERG				
a-wave	0.635	0.006	-0.090	0.732
b-wave	0.530	0.029	0.100	0.702
Retinal sensitivity				
center point	-0.472	0.056	-0.423	0.091
within 4°	-0.682	0.003	-0.625	0.007
within 8°	-0.761	0.0004	-0.533	0.028

PED pigment epithelium detachment, *logMAR* logarithm of the minimum angle of resolution, *fmERG* focal macular electroretinogram

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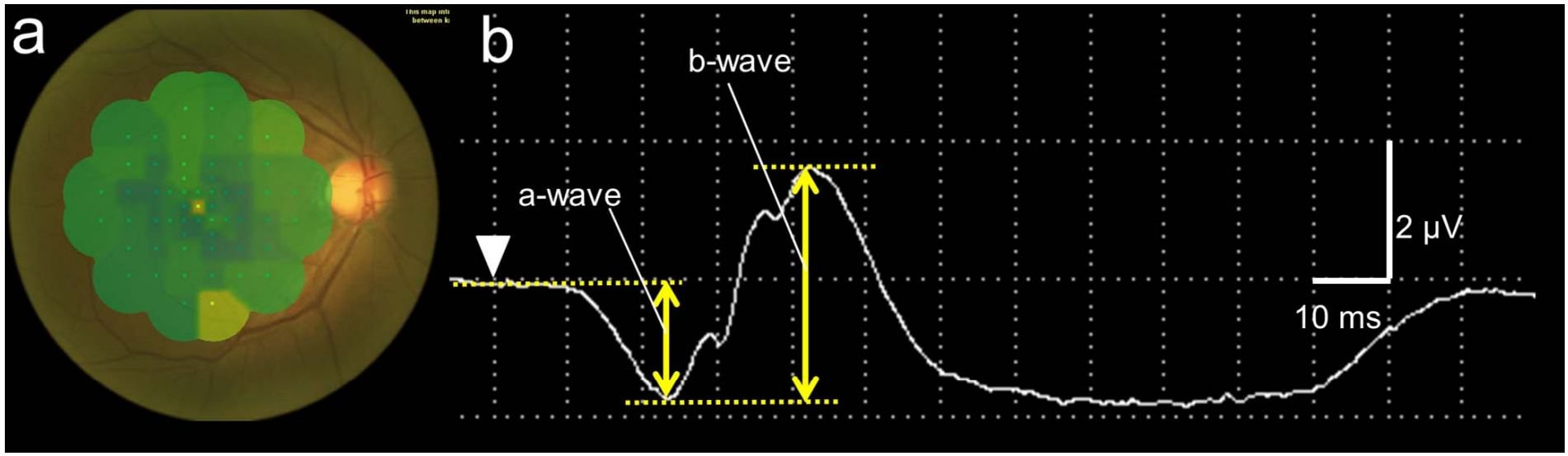
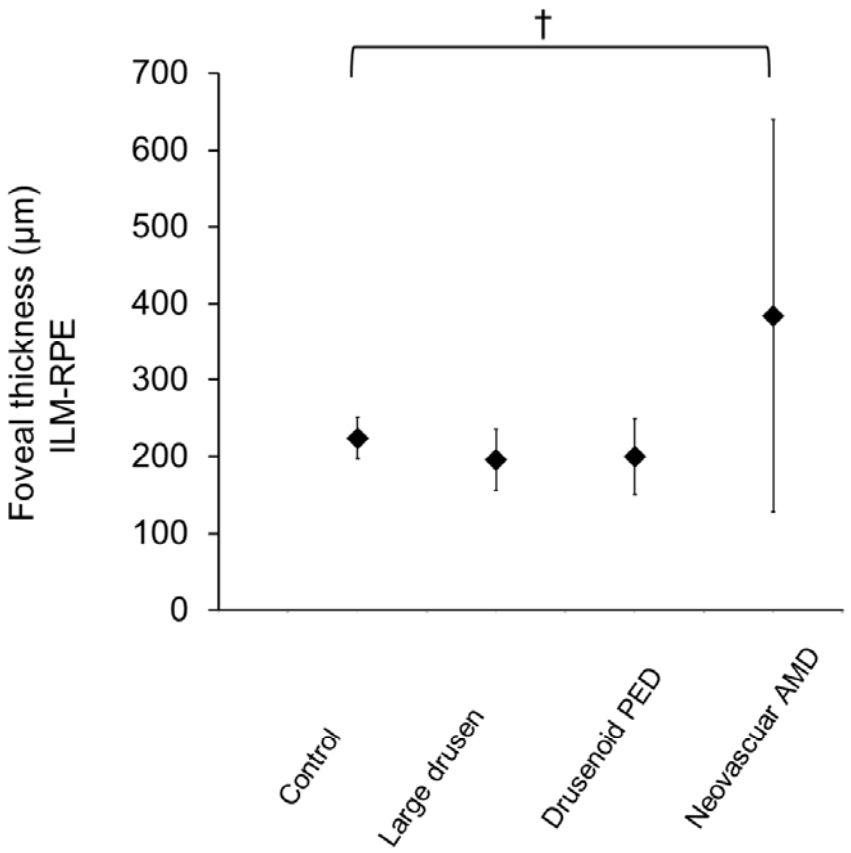


Fig. 1


†
Foveal thickness (μm)
ILM-RPE
700
600
500
400
300
200
100
0
Control
Large drusen
Drusenoid PED
Neovascuar AMD

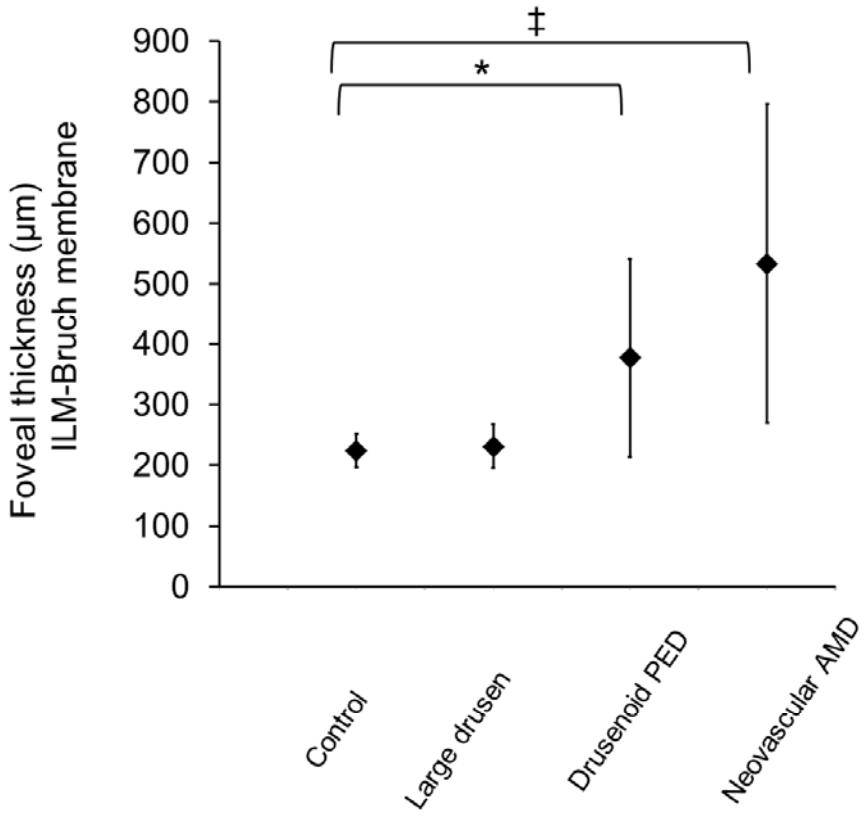

‡
*
Foveal thickness (μm)
ILM-Bruch membrane
900
800
700
600
500
400
300
200
100
0
Control
Large drusen
Drusenoid PED
Neovascular AMD

Fig. 2

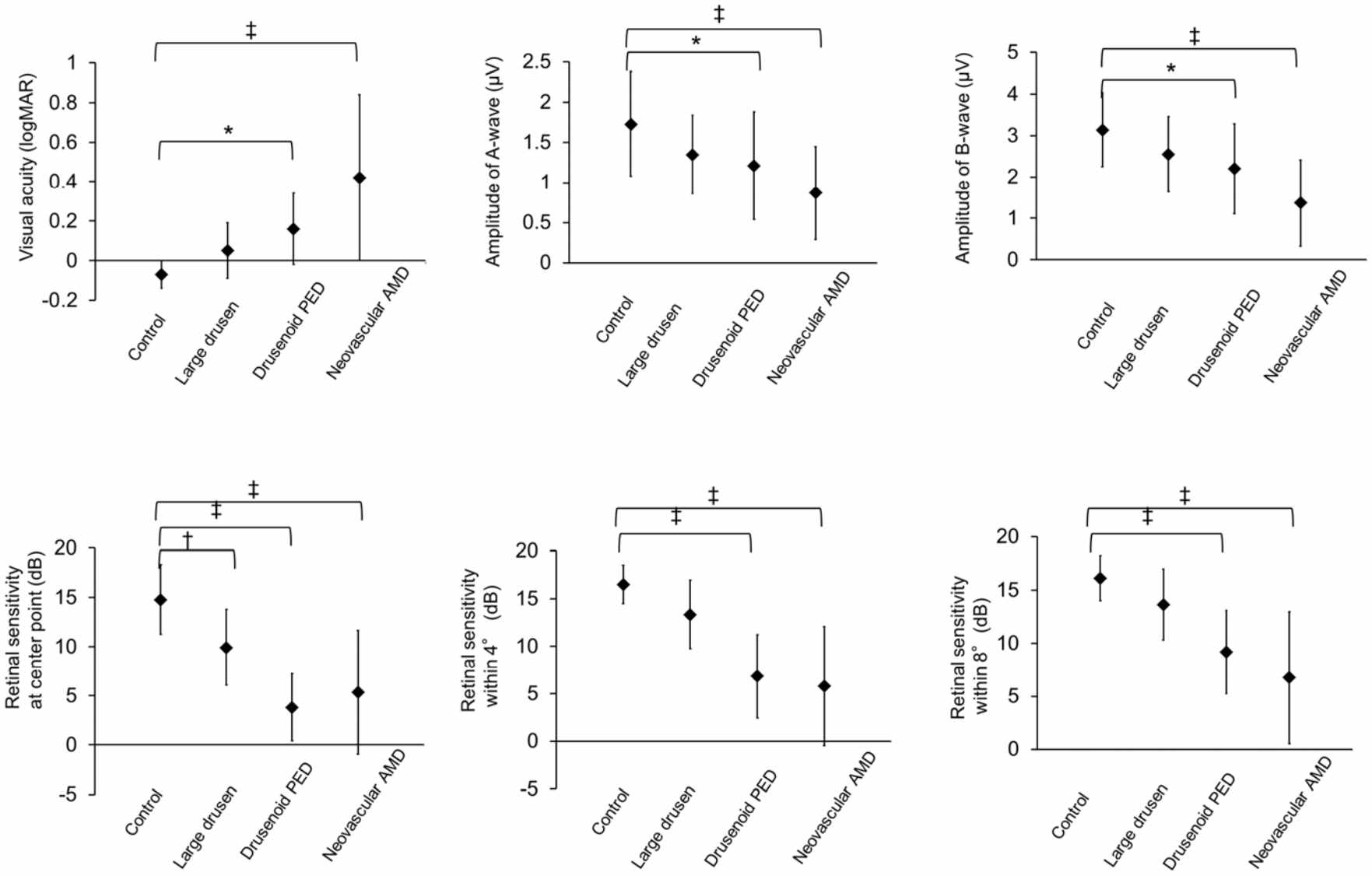

Visual acuity (logMAR)
1
0.8
0.6
0.4
0.2
0
-0.2
‡
*
Control
Large drusen
Drusenoid PED
Neovascular AMD
Amplitude of A-wave (μV)
2.5
2
1.5
1
0.5
0
‡
*
Control
Large drusen
Drusenoid PED
Neovascular AMD
Amplitude of B-wave (μV)
5
4
3
2
1
0
‡
*
Control
Large drusen
Drusenoid PED
Neovascular AMD
Retinal sensitivity at center point (dB)
20
15
10
5
0
-5
‡
‡
†
Control
Large drusen
Drusenoid PED
Neovascular AMD
Retinal sensitivity within 4° (dB)
20
15
10
5
0
-5
‡
‡
Control
Large drusen
Drusenoid PED
Neovascular AMD
Retinal sensitivity within 8° (dB)
20
15
10
5
0
‡
‡
Control
Large drusen
Drusenoid PED
Neovascular AMD

Fig. 3

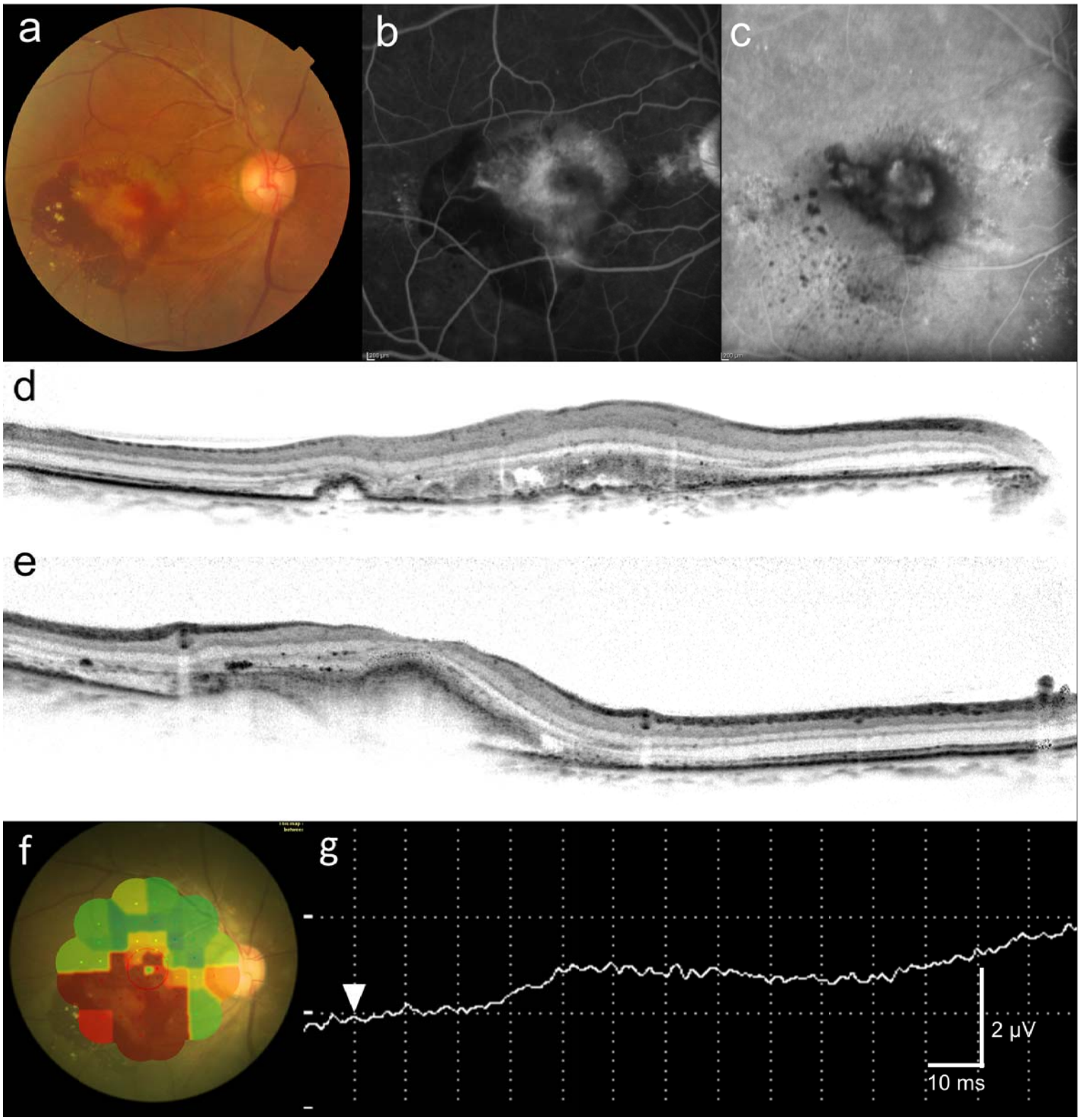


Fig. 4

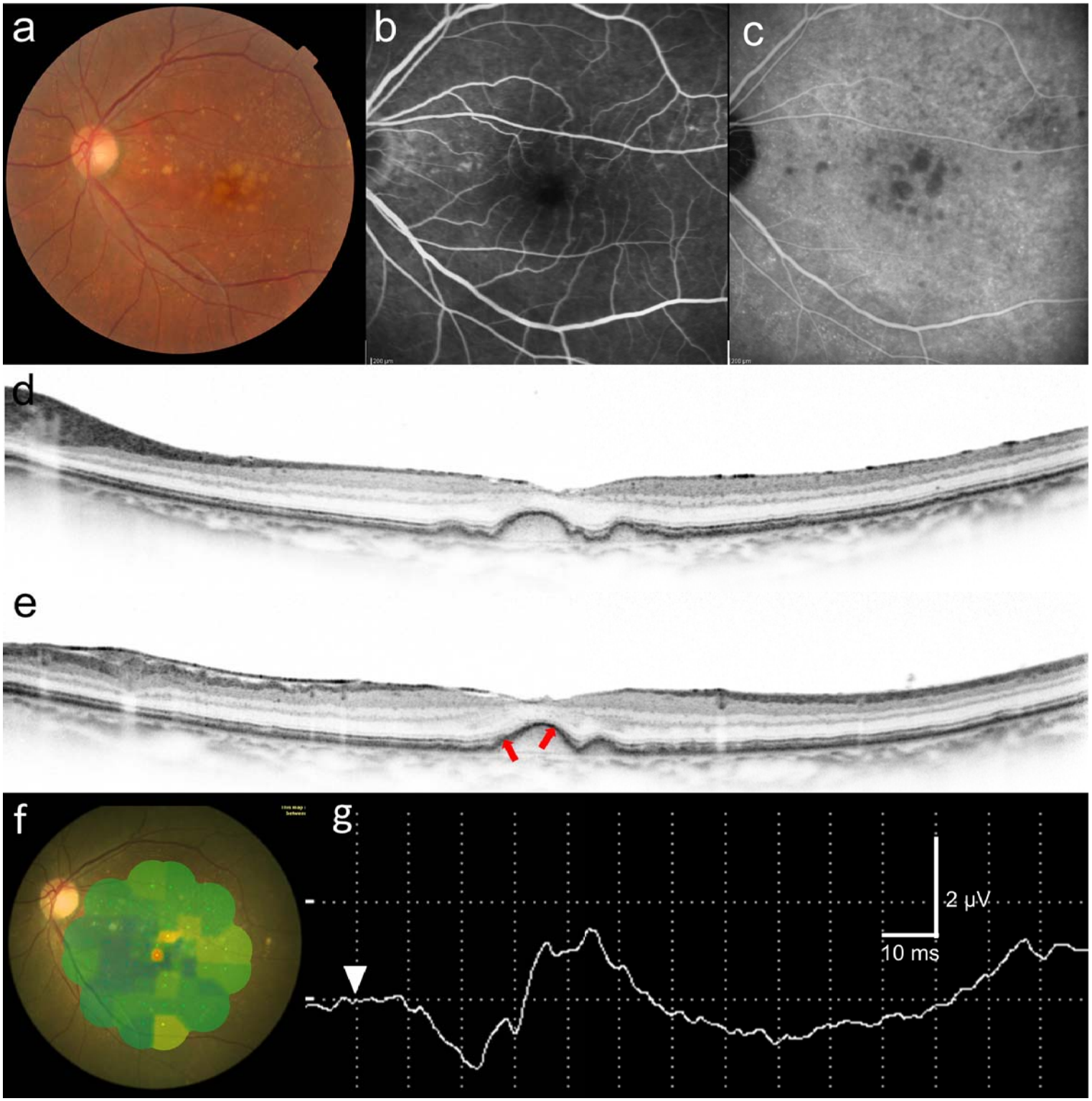


Fig. 5

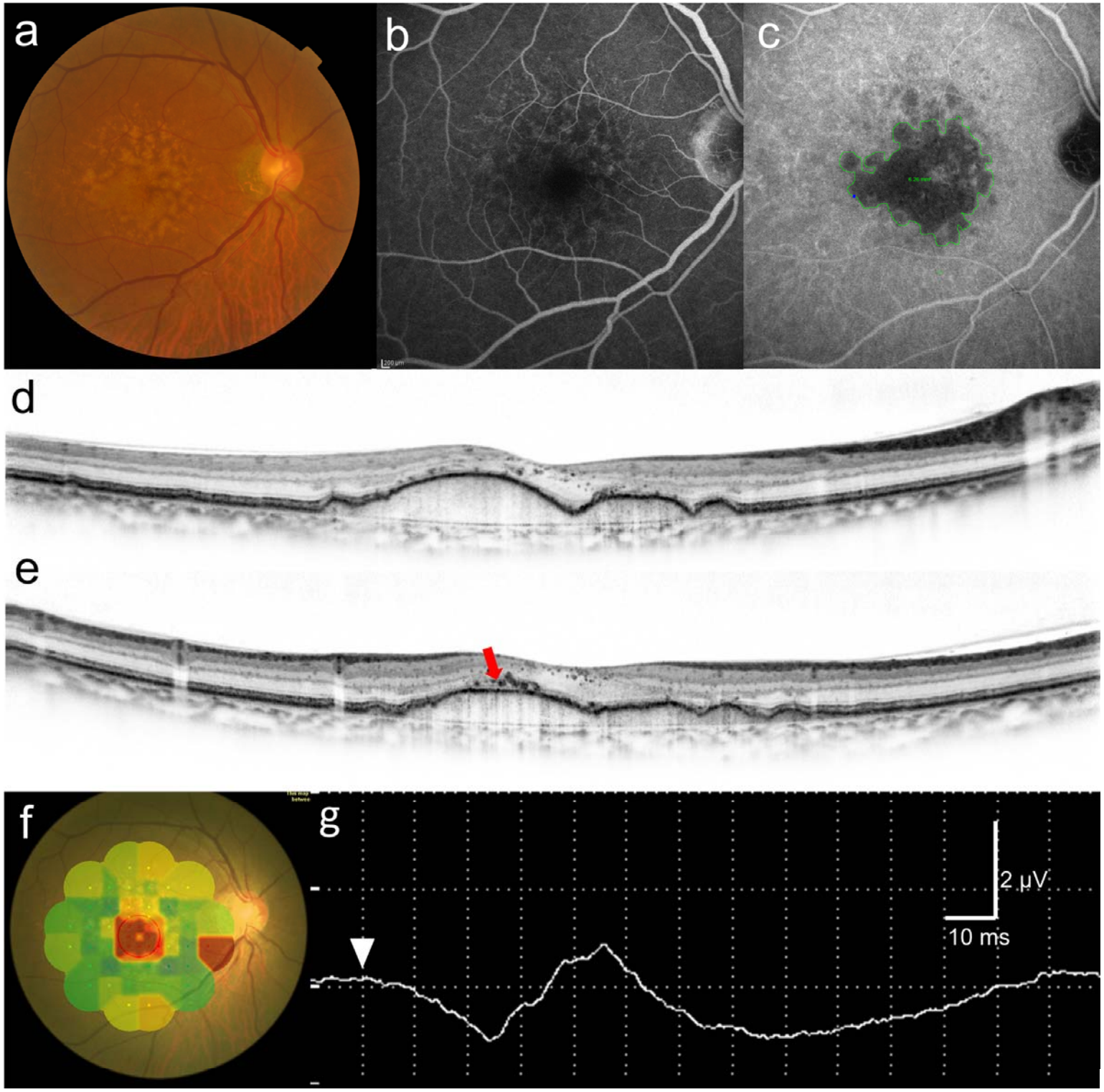


Fig. 6