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Abnormal retinal reflectivity to short-wavelength light in type 2 idiopathic macular telangiectasia

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Abstract

Purpose—Macular Telangiectasia Type 2 (MacTel) is a bilateral, progressive, potentially blinding retinal disease characterized by vascular and neurodegenerative signs, including an increased parafoveal reflectivity to blue light (BLR). Our aim was to investigate the relationship of this sign with other signs of MacTel in multiple imaging modalities.

Methods—Participants were selected from the MacTel Study, based on a confirmed diagnosis and the availability of images. The extent of signs in BLR, fluorescein angiographic, optical coherence tomographic (OCT) and single- and dual-wavelength autofluorescence (DWAF) images were analyzed.

Results—A well-defined abnormality of the perifovea is demonstrated by dual wavelength autofluorescence and blue light reflectance in early disease. The agreement in area size of the abnormalities in DWAF and in BLR images was excellent, for right eyes: $\rho=0.917$ ($p<0.0001$, 95% CI 0.855-0.954, $n=46$) and for left eyes: $\rho=0.952$ ($p<0.0001$, 95% CI 0.916-0.973, $n=49$).

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Other changes are less extensive initially and expand later to occupy that area and do not extend beyond it.

Conclusion—Our findings indicate that abnormal metabolic handling of luteal pigment and physical changes giving rise to increased reflectance are widespread in the macula throughout the natural history of the disease, precede other changes and are relevant to early diagnosis.

Keywords

blue light reflectance; angiography; degeneration; imaging; MacTel; macular pigment; Müller cells; OCT; retina; telangiectasia

Introduction

Macular Telangiectasia Type 2 (MacTel) is a bilateral, slowly progressive retinal disease of unknown pathogenesis, potentially leading to a loss of central vision.¹ Previous clinical and histopathological data suggest a hereditary cause and a central role for retinal Müller cells in the pathogenesis of the disease.²⁻⁴

The phenotype of MacTel is limited to the perifoveal region and is characterized by both vascular and neurodegenerative changes. Color and red-free fundus photographic signs include a loss of retinal transparency, retinal crystals at the level of the internal limiting membrane (ILM) and in later disease pigment plaques in the mid-retina. Fundus fluorescein angiographic (FFA) signs include dilated, blunted and right-angle veins, dilated deep retinal capillaries and hyperfluorescence (early leakage, late staining) but without an increase in retinal thickness. In late disease subretinal neovascularization may occur.⁵⁻⁷

More recent imaging modalities have provided valuable insight into previously little or unknown characteristics of the phenotype (Figure 1). A loss of retinal transparency is considered an early sign in MacTel (driving stage 2 in the severity classification of the disease devised by Gass and Blodi⁸), indeed it may be the first detectable manifestation of the disease. Reflective imaging using short wavelength light ('blue light reflectance imaging', BLR) provides a superior tool for detecting and recording this phenomenon.⁹⁻¹¹

Short-wavelength (488nm, blue) autofluorescence imaging may demonstrate increased signal in the parafoveal region in early disease, and later decreased autofluorescence corresponding to intraretinal perivascular pigment clumps or plaques.⁵ Using dual (488+512nm) wavelength autofluorescence (DWAF) imaging,¹²⁻¹⁴ a redistribution of macular (luteal) pigment (MP) in a specific pattern can be demonstrated. This pattern typically starts with a wedge-shaped depletion of MP just temporal of the foveal center, progressing centripetally to involve the foveal center and finally encompasses an oval area centered on the fovea, with a band of increased MP density along its boundaries.¹⁵⁻¹⁷

In optical coherence tomographic (OCT) images, low-reflecting spaces may be apparent in the inner and outer retina, while later in disease progressive atrophy of the outer retina occurs. Initially this is characterized by a discontinuity (break) in the line commonly attributed to the junctions of the photoreceptor inner and outer segments (or the ellipsoids of the inner segments, IS/OS line or ellipsoid zone, EZ),¹⁸⁻²⁰ with subsequent structural

disorganization and apparent ‘collapse’ of the retinal layers internal to the IS/OS through the IS/OS break towards the retinal pigment epithelium (RPE).^{18, 21, 22} The external limiting membrane (ELM), a thin hyper-reflective line adjacent to the EZ on OCT, is formed by tight junctions between the photoreceptors and Müller cells and its abnormalities may be considered a signal of structural changes in either cell type, its morphology in MacTel has however not been described. Histopathological studies have shown changes limited to the area delineated by BLR and structural changes in Müller cells.

The aim of the present study in search of clues to the pathogenesis of the disease and of signs permitting an early diagnosis, was to investigate the characteristics of abnormal retinal reflectivity to short-wavelength light and its relationship with other vascular and neurodegenerative clinical signs of MacTel detectable in multiple imaging modalities including autofluorescence, fluorescein angiographic, OCT and DWAF imaging.

Participants and Methods

Participants

Eyes of participants with a confirmed diagnosis from one site of the MacTel Study, an international multicenter prospective natural history observational study of MacTel⁵ were chosen for this study. The site was selected on the basis of the availability of a wide range of imaging modalities including blue-light reflectance (BLR), autofluorescence (AF), fundus fluorescein angiographic (FFA), dual-wavelength autofluorescence (DWAF) and OCT images. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the local institutional review board/ethics committee. Prior to enrolment in the study, written, informed consent was obtained from each participant following an explanation of the nature of the study.

Imaging

Images were recording in compliance with a standardised operating protocol by trained and certified image acquisition specialists. Blue light reflectance images were acquired using either a Heidelberg Retina Angiograph II or a Heidelberg Spectralis SLO system (Heidelberg Engineering GmbH, Heidelberg, Germany) using the ‘red free’ setting (utilizing a 488nm blue laser for illumination of the retina). Single-wavelength autofluorescence images were acquired using the same excitation wavelength, with a barrier filter for reflected light at <520nm. The distribution of macular pigment was recorded by dual-wavelength autofluorescence method using a Heidelberg Retina Angiograph Classic scanning laser ophthalmoscope system (Heidelberg Engineering GmbH, Heidelberg, Germany). This method has been described previously.¹²⁻¹⁴ Briefly, two series of autofluorescence images of the fundus were recorded using monochromatic excitation lights of 488nm and 514nm wavelength respectively, through a barrier filter for returning light at <560nm. Individual images within each sequence were aligned using anatomic (mainly vascular) landmarks and averaged to improve the signal-to-noise ratio. A map of relative densities characteristic of macular pigment content was calculated from each corresponding pixel pair within the two averaged images. In our study 10-16 individual images were averaged at each wavelength prior to calculating the macular pigment density maps. Spectral domain OCT volume scans

of the retina were acquired using Heidelberg Spectralis OCT systems (Heidelberg Engineering GmbH, Heidelberg, Germany). Raster volume scans covered a retinal area of at least 15×10 degrees in size, centered on the fovea, with a maximum B-scan interval of 30 microns. The transverse imaging module of the Heidelberg Eye Explorer (HEYEX) software was used for creating en face images of the EZ and ELM layers following manual inspection and where necessary correction of the automated segmentation of these specific layers provided by HEYEX.

Phenotyping

Images of all modalities (en face OCT of the EZ, of the ELM, early and late FFA, AF, DWAF and BLR) were aligned to attain exact correspondence primarily using I2K Retina version 1.3.8 (DualAlign™ LLC) and collected in multi-layered PSD image files in Adobe Photoshop (version CS6, Adobe Systems Inc., San Jose, California, USA). The extent of the abnormality in the ELM was delineated based on the points of clear visibility of the ELM and both adjacent layers nearest to the retinal abnormality (typically a ‘collapse’) from to vantage points, the standard B-scan perspective and one at 90 to it (in the Y-Z plane) using a dedicated 3D imaging software package (Amira v5.3, FEI Inc, Hillsboro, Oregon, USA). Orthogonal maps (in the x-y, a.k.a. the ‘en face’ plane) of the boundary markers were exported to Photoshop and aligned manually to the common geometry of the other imaging modalities. All image alignments were inspected and corrected manually as necessary in Adobe Photoshop. The extent of abnormalities in each imaging modality was delineated and measured (expressed in pixels) manually and their relative areas and locations within the plane of the retina were compared.

Due to their relatively low resolution and grainy quality, duplicates of layers containing DWAF images were created and a Gaussian filter was applied to reduce high frequency noise prior to delineation of the abnormal area. The distribution pattern of luteal pigment in healthy eyes demonstrates a peak at the foveal center and progressively decreases towards a plateau value in the peripheral retina. Concentration levels may vary, but the gradient is consistently towards the periphery. The boundary of the abnormal area in MacTel eyes was defined as the collection of points at which luteal pigment density starts to decline *towards* the foveal center.

The term ‘MacTel area’ (introduced by M. Fruttiger, unpublished communications) is defined as the region delimited by the outer boundary of increased reflectivity to short-wavelength light in well established disease (complete ellipse).

Grading and measurements were performed by one grader masked to the identity and clinical data of the patients. To reduce the risk of bias, delineation of lesion boundaries was performed in one imaging modality at a time across the whole available sample. Data necessary for calibration of true retinal image size (axial length and refractive power of the eye) were not available, however most analyses were limited to the relative lateral extent and topographic position of lesions within each eye.

Statistical Methods

The relationships of lesion extent in different imaging modalities was assessed by calculating Spearman's rank correlation coefficient. Spearman's ρ was calculated from grading data ranked in order of severity; calculations were based on the differences between the ranks of corresponding values of the independent and the dependent variable. The value of ρ may range between 1, indicating a perfect correlation and -1 , indicating a perfect inverse (negative) correlation. A p value of <0.05 was accepted as statistically significant. All analyses were conducted using commercially available statistical software (SAS version 9.3; SAS Institute, Cary, NC, USA and MedCalc for Windows, version 12.5, MedCalc Software, Ostend, Belgium).

Results

Full image sets of all imaging modalities were available of 106 eyes of 53 patients (32 women, 21 men), ranging in age between 30-82 years, (mean=61 years, SD=10.6 years) of a quality sufficient for a multimodal analysis.

In all uncomplicated MacTel cases, the BLR hyper-reflective pattern was confined to an oval area centered on the fovea, with the longest axis in the horizontal meridian (corresponding approximately to the parafoveal region), always presenting in the temporal part and covering varying degrees of the remaining area. The central foveal area (corresponding to the foveal pit, and in DWAF images to the central luteal pigment peak) appeared in BLR images dark at varying intensities. We measured the approximate horizontal and vertical diameters of the outer boundary of the BLR hyperreflective area in well-established cases (full ellipse), measurements are presented in Table 1.

Ten eyes of eight patients were excluded from the main analyses and analyzed separately due to very extensive lesions not directly attributable to the primary MacTel disease. In one eye a large area of subretinal fluid was present, which did not diminish either the BLR, DWAF or ELM signals; the visibility of the EZ was however impaired. In two eyes, a highly reflective epiretinal membrane (ERM) was present obscuring the boundary of the BLR pattern. The ERMs were constricting, causing retinal folds, the DWAF pattern was in both cases well detectable, although in one its shape was distorted. In six eyes of four patients a subretinal neovascular (NV) complex extending outside the MacTel area was present. Whereas small NV lesions do not seem to affect the visibility of either the BLR or DWAF signals, as the area size of the NV approaches that of the BLR/DWAF signal, first the BLR then the DWAF signals are attenuated or lost. The detectability of the DWAF signal was consistently better than that of the BLR signal, except in one case with subretinal hemorrhage larger than the parafoveal 'MacTel' area (from a small neovascular lesion), which improved the visibility of the BLR signal by providing a dark background, while obfuscating the DWAF signal.

In good quality BLR images, the area of increased reflectivity appeared to be present at variable intensities. In 30 eyes (28%) the whole "MacTel" area was evenly hyper-reflective. In 55 eyes, (52%) the high level BLR hyper-reflectivity was high temporally and superiorly but did not involve the full 'MacTel' area; in these a lower but clearly detectable level of

increased reflectivity appeared to ‘complete’ the oval pattern (typically inferiorly or inferonasally, see Figure 2 top panel, image A). Images in which this lower level was not visible (11 eyes, 10%) or questionable (14 eyes, 13%) were of low quality and the visibility of the main pattern was also consistently low. The central foveal area containing in DWAF images the central peak of luteal pigment density appeared in BLR images dark at variable levels.

The detectability of the pattern in BLR images was influenced by several factors, including obscuring lids and lashes, tear film anomalies (short break-up time, lipid droplets), crystalline lens and vitreous opacities. Obscuring technical factors included defocus, uneven field illumination and over-exposure. The pattern brightness appeared to be affected by directionality and to some extent by the type of SLO machine used (HRA or Spectralis). These phenomena may warrant a further systematic analysis. In this study however, the outcome measure was the lateral extent of the BLR hyperreflectivity (and not the intensity of the hyperreflectivity) and this was possible to measure in all images.

We assessed the inter-grader repeatability of measurements of the BLR hyperreflective area in well-established disease (complete ellipse) by calculating the intraclass correlation coefficient (ICC), investigating absolute agreement between two graders for all measurements, in a two-way model (n=18 eyes). The ICC was for single measures 0.9656 (95%CI 0.9065 to 0.9872) and for average measures 0.9825 (95%CI 0.9510 to 0.9936).

The detectability of the DWAF signal was consistently better than that of the BLR signal although this did not impede the analysis.

The concordance in area size of luteal pigment abnormality in DWAF images and the area of increased reflectivity to blue light (BLR) was excellent, for right eyes: $\rho=0.917$ ($p<0.0001$, 95%CI 0.855-0.954, n=46) and for left eyes: $\rho=0.952$ ($p<0.0001$, 95%CI 0.916-0.973, n=49). The mean (BLR) relative area of intersection was in right eyes 88% and in left eyes 87%. Removing neovascular cases from the analysis did not significantly affect the correlation.

The lateral extent of abnormalities in all other imaging modalities was smaller in area and located within the area occupied by the BLR/DWAF abnormality.

Single wavelength (blue) AF images provided a sharp boundary of a hyper-autofluorescence towards the foveal center (as well as very clear hypo-AF anomalies corresponding to brown pigment plaques in the mid-retina), however towards the periphery, the boundary was too indistinct to delineate in 28 of a total of 96 cases (29%).

The correlation between DWAF and AF lesion area was $\rho=0.441$ ($p<0.0091$, 95%CI 0.121-0.678, n=34) for right eyes and $\rho=0.554$ ($p<0.0009$, 95%CI 0.253-0.745, n=34) for left eyes. The AF abnormality occupied on average 53% of the DWAF abnormality in right eyes and 49% in left eyes.

The correlation between the BLR hyper-reflective area and the area of leakage/staining in the late-phase FFA was $\rho=0.772$ ($p<0.0001$, 95%CI 0.620-0.868, n=46) for right eyes and

$\rho=0.737$ ($p<0.0001$, 95%CI 0.575-0.843, $n=49$) for left eyes. The FFA abnormality occupied on average 50% of the BLR hyper-reflective area in both right and left eyes.

The correlation between the BLR hyper-reflective area and the area of a break in the EZ (IS/OS layer) was $\rho=0.631$ ($p<0.0001$, 95%CI 0.418-0.779, $n=46$) for right eyes and $\rho=0.593$ ($p<0.0001$, 95%CI 0.374-0.749, $n=49$) for left eyes. The EZ (IS/OS) break extent was on average 15% of the BLR hyper-reflective area in right eyes and 12% in left eyes.

The correlation in area size and location of the ELM abnormality and the EZ (IS/OS) break was very good, $\rho=0.989$ ($p<0.0001$, 95%CI 0.980-0.994, $n=46$) for right eyes and $\rho=0.978$ ($p<0.0001$, 95%CI 0.961-0.987, $n=50$) for left eyes. In 32 of 46 right eyes, the area of the EZ break was larger than that of the ELM abnormality (on average by 36% of the ELM area, median difference 18%), in 8 eyes it was smaller (on average by 10%, median 3%), in 6 eyes the two areas were the same. In 32 of 50 left eyes, the area of the EZ disruption was larger than that of the ELM lesion (by a mean 40%, median 14%), in 7 eyes it was smaller (on average by 5%, median 2%), in 11 eyes the two areas were the same. The magnitude of differences was affected by a few outliers (see scatter plot in supplemental Figure S1).

The characteristics and distribution of area measurements are shown in Table 2 and Figure 3. Agreement between right and left eyes is shown in Table 3. All changes were situated within the area delineated by DWAF and blue light reflectance (see supplemental Figure S2).

Discussion

Type 2 idiopathic macular telangiectasia - as the name suggests - was long considered a primarily vascular disease. However, new imaging modalities including OCT, DWAF and BLR imaging have revealed numerous neurodegenerative signs of the disease and contributed to a paradigm shift in the hypothesis of its pathogenesis.

One of these neurodegenerative signs, a 'graying of the foveal area' was mentioned as a sign of parafoveal telangiectasia as early as 1978 by Gass et al.²³ This sign was later described as a 'loss of retinal transparency' and alone is the sole criterion of stage 2 in the severity classification of the disease devised by Gass and Blodi in 1993.⁸ Charbel-Issa et al. demonstrated that this area exhibits an abnormally increased reflectivity to short wavelength (488nm) light and can be visualized best using a confocal scanning laser ophthalmoscope.^{9, 10} Jindal et al. noted that the intensity appeared to fade with continuous light exposure and is restored following dark adaptation.²⁴ M. Fruttiger noted that all typical signs of MacTel appear to be located within an area defined by the outer boundary of increased reflectivity to blue light and suggested the term 'MacTel area' as occurred in our cases.

Our findings show that in the vast majority with early disease a well-defined area is apparent on the basis of hyper-reflectivity as seen on blue light reflection and a deficit of luteal pigment as recorded by dual wavelength autofluorescence. There was variation of intensity of reflectivity in the area as seen on blue light reflectance with the densest being in the temporal macula. It is well established that the phenomenon is intensified by dark adaptation²⁴. Thus in those in which the area was not totally outlined, it is conceivable that it

would have been complete following a short time in darkness. One limitation of our study is that the light exposure (bleaching) status of the eye at the time of BLR imaging was not recorded.

The area of abnormality as seen on single wavelength autofluorescence, and fluorescein angiography was limited to the temporal macula in early disease and expands to occupy the whole area as defined by blue light reflectance as the disorder progresses.²⁵ Deficits in the outer retinal lines as seen on OCT appear to occur later, starting temporal to the fovea and expands over time to fill the MacTel area. The progression of outer retinal changes becomes distorted in late disease by subretinal neovascularization with or without contraction by scar tissue in later disease. The progression of these changes appears to be sequentially from temporal to the fovea, to nasal, superior and lastly inferior to the fovea. Notable is the absence of extension outside the area defined early by blue light.

These findings are relevant to early diagnosis that is important in the quest for early diagnosis when attempting to generate pedigrees as is crucial for genetic studies. Dual wavelength autofluorescence or blue light reflectance appear to be equally sensitive. However, the former is not widely available such that blue light is the more useful. Important is the influence of dark adaptation on this finding²⁴ and if a clinician is in doubt as to whether or not the abnormality exists, placing the patient in the dark for 10 minutes or so might help in decision making.

These observations are also important to concepts as to the pathogenesis of disease. They indicate that abnormal metabolic handling of luteal pigment is widespread in the macula even in early disease. It has been shown that Müller cells are involved in the disease process^{3, 4} and it is possible that Müller cells are involved in the metabolism of luteal pigments. There is evidence that Müller cell are involved in metabolism of other retinoids.²⁶

It is also evident that the retinal region affected by disease is defined early in its progress by blue light reflection and dual wavelength. Other changes follow to occupy the whole of that area but do not expand beyond it. This indicates that a specific susceptibility exists that is limited to the MacTel area that presumably can be related to a metabolic attribute limited to this area. This may be related to the metabolic interdependence between Müller cells and photoreceptor cells.²⁷ That Müller cell dysfunction is associated with photoreceptor cell loss is well illustrated in rodents.^{28, 29} Interestingly these rodents develop outer retinal vascularization consistently.²⁷

The only clinically recognized entity that resembles MacTel is seen in Sjögren-Larsson syndrome.²⁵ Evidence has been sought of genetic similarity between the two disorders but none has been found. It is conceivable that certain forms Müller cell dysfunction may cause retinal disease that may be confined to the macula, regardless of the underlying cause.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

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Summary statement

MacTel affects a well-defined region of the macula, indicating localized susceptibility. Our findings indicate that abnormal metabolic handling of luteal pigment and physical changes giving rise to increased reflectance are widespread in the macula throughout the natural history of the disease, precede other changes and are relevant to early diagnosis.

Figure 1. Aligned multimodal images of a MacTel eye with very early disease

A: 488nm (blue) reflectance image, **B:** dual-wavelength autofluorescence image (DWAF), **C:** single wavelength (488nm) fundus autofluorescence image, **D:** infrared image, **E** and **F:** early and late phase fluorescein angiograms, **G:** IR image with the en face view of the Ellipsoid Zone superimposed, **H:** IR image with the en face map of the External Limiting Membrane (ELM) superimposed. An eye with very early mactel disease from an asymmetrical case, demonstrating essentially no sign of mactel and only a few diabetes-related microaneurysms in the FFA. The FAF, DWAF images appear essentially normal, demonstrating the peak of luteal pigment density at the foveal center, that decreases towards the periphery. The dark central area in the EZ map corresponds to the rod-free center of the fovea externa with very high packing density of cones, where the EZ signal is normally weaker. The fellow eye (not shown) demonstrates all typical signs of MacTel.

Figure 2. BLR imaging in MacTel and multimodal correlates

Aligned multimodal images of a relatively early case (top panel) and a later-stage MacTel eye, bottom panel. A: blue light reflectance images, B: dual wavelength (488+514nm) autofluorescence images, C: single (488nm, blue) autofluorescence images, D: early phase FFA images, E: late-phase FFA images, F: topographic maps of the EZ (IS/OS layer). The small, round, hyper-reflective area close to the fovea in the BLR image in the top panel is an artifact due to internal reflections within the lens system of the Spectralis SLO system.

Figure 3. Correlation of lesion extent in multimodal images of type 2 MacTel

Top row: BLR vs DWAF area in (A) right and (B) in left eyes. Second row: DWAF area vs single wavelength blue light AF area, in right (C) and in left eyes (D). NB: in 28/96 eyes the AF lesion was not possible to delineate due to an indistinct peripheral boundary. Third row: BLR hyper-reflective area vs late FFA area, in right (E) and in left eyes (F). Bottom row: BLR hyper-reflective area vs EZ (IS/OS) break area, in right (G) and in left eyes (H). All data shown are expressed in $\times 1000$ pixels (proprietary units).

Table 1

Approximate dimensions of the BLR hyperreflective area in established disease.

variable	Right eyes					Left eyes				
	mean	SD	min	max	n	mean	SD	min	max	n
horizontal diameter	3082	332	2543	3931	35	3045	427	2103	4375	30
vertical diameter	2355	268	1773	2906	35	2320	335	1774	3291	30
V/H ratio	0.77	0.06	0.66	0.91	35	0.77	0.09	0.67	1.11	30

Diameter measurements are expressed in microns. n signifies the number of eyes. Measurements reported were made in eyes in which the hyperreflective pattern was a full ellipse. It should be noted that the axial length or refractive power of each eye were not taken into account. The scale bar provided in the Heidelberg SLO infrared image was used for calibration of pixel size.

Table 2

Descriptive characteristics of the clinical signs measured.

variable	Right eyes					Left eyes				
	mean	SD	min	max	n	mean	SD	min	max	n
BLR	5.020	1.708	1.515	8.840	46	4.498	1.828	0.000	8.886	49
DWAF	4.759	1.758	1.413	8.969	46	4.278	1.744	0.000	8.298	50
FAF	2.642	1.576	0.268	6.299	34	2.079	1.279	0.000	4.498	34
FFA early	1.095	1.246	0.000	4.995	46	0.806	0.865	0.000	3.457	50
FFA late	1.855	1.414	0.000	5.674	46	1.677	1.076	0.000	4.755	50
EZ (IS/OS)	2.590	1.696	0.000	7.064	46	2.352	1.429	0.000	6.997	50
ELM	0.929	1.088	0.000	4.128	46	0.669	0.773	0.000	3.287	50

For easier reference, area values are expressed in mm²

n signifies the number of eyes.

Table 3

Bilateral symmetry of lesions in multiple imaging modalities.

	p	p	95%CI	n
BLR hyperreflective area	0.822	<0.0001	0.694 0.899	44
DWAF luteal pigment loss area	0.815	<0.0001	0.686 0.895	45
early FFA	0.671	<0.0001	0.470 0.806	45
late FFA	0.698	<0.0001	0.509 0.823	45
EZ (IS/OS) break area	0.523	<0.0002	0.272 0.708	45

It should be noted, that the accuracy of comparisons between fellow eyes may be limited by possible differences in axial length, which were not recorded.