Clinical Characteristics of Highly Myopic Patients With Asymmetric Myopic Atrophic Maculopathy–Analysis Using Multimodal Imaging

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Purpose. To evaluate the factors associated with asymmetric myopic atrophic maculopathy (MAM) in highly myopic patients.

Methods. We enrolled highly myopic patients with asymmetric MAM according to the atrophy, traction, and neovascularization (ATN) classification. The results of color fundus photography, optical coherence tomography (OCT), OCT angiography, and corneal visualization Scheimpflug technology (Corvis ST tonometry) were reviewed. The association between inter-eye differences in clinical features and MAM grading was analyzed using logistic regression analysis.

Results. Among the 72 eyes of 36 patients 61.0 ± 9.3 years of age, 9, 33, 17, and 13 eyes had A1, A2, A3, and A4, respectively. The mean axial length was 30.44 ± 1.92 mm, and there was no significant difference between eyes with less severe and more severe MAM. The inter-eye differences in MAM grading were associated with the inter-eye differences in the presence of Bruch's membrane defects ($P = 0.014$), ellipsoid zone disruption ($P = 0.013$), vessel density of the deep retinal layer ($P = 0.022$), foveal avascular zone circularity ($P = 0.012$), foveal avascular zone area ($P = 0.049$), flow area of the choriocapillaris ($P = 0.013$), vessel diameter ($P = 0.045$), and fractal dimension ($P = 0.015$). No Corvis ST parameter was statistically significant. A higher difference in the choriocapillaris flow area ($P = 0.013$; adjusted odds ratio = 1.10 [1.02–1.18]) remained associated with higher inter-eye differences in MAM grading in the multivariable regression.

Conclusions. A smaller choriocapillaris flow area was associated with more severe MAM, suggesting that vascular factors play pivotal roles in MAM.

Keywords: asymmetric myopic atrophic maculopathy, high myopia, pathologic myopia, optical coherence tomography angiography, Corvis ST

Myopic maculopathy is the leading cause of irreversible vision loss in this era, and its development and progression are strongly associated with aging and elongated axial length.[1–9] According to the newly proposed atrophy, traction, and neovascularization (ATN) classification system, myopic maculopathy can be classified into myopic atrophic maculopathy (MAM), myopic neovascular maculopathy (MNM), and myopic tractional maculopathy (MTM).[10] However, the mechanism underlying the development of MAM has not been fully elucidated.[1] The widely accepted "mechanical theory" states that the elongated eyeball and posterior staphyloma lead to the development of myopic maculopathy.[11] Additionally, the "ischemic and vascular theory" also plays a role, wherein decreased retinal and choroidal perfusion worsens the maculopathy.[1]

Newly developed technologies could help investigate the clinical characteristics of highly myopic eyes and the pathophysiology of myopic maculopathy. Optical coherence tomography angiography (OCTA) revealed that the retinal capillary plexus and choriocapillaris vessel density decreased in high myopia patients.[12] When corneal visualization Scheimpflug tonometry (Corvis ST; Oculus, Wetzlar, Germany) was applied, it was revealed that myopic eyes had weakened corneal biomechanical properties and decreased stiffness due to the stretching and elongation of the eyeball.[13–16] Therefore, we further investigated whether these vascular and biomechanical changes were associated with the development and severity of MAM.

In clinical practice, we have observed that some patients develop MAM with a different severity in

each eye. Because aging, gender, and systemic vascular disease have not been risk factors in these situations, we wanted to identify other factors associated with asymmetric inter-eye MAM. Therefore, in this study, we aimed to compare the clinical characteristics between eyes with different severities of MAM, as defined by the ATN classification system, and use multimodal imaging to identify the factors associated with asymmetric MAM.

Methods

Study Population

In this observational case series, we retrospectively reviewed data of highly myopic patients with an axial length > 26 mm or spherical equivalent < –6.0 diopters (D) who were followed up in clinics for high myopia at the National Taiwan University Hospital from January 2018 to September 2019. Myopic maculopathy was classified according to the ATN classification system.[10] The atrophic component was classified as follows: A0, no myopic retinal lesions; A1, tessellated fundus; A2, diffuse chorioretinal atrophy; A3, patchy chorioretinal atrophy; and A4, macular atrophy, which correspond to the Meta-Analysis for Pathologic Myopia (META-PM) study group classifications from C0 to C4, respectively. Patients with asymmetric atrophic component grading and those with an inter-eye axial length difference of less than 1 mm were included in the analysis. Patients who underwent intraocular surgery other than cataract surgery or had other concurrent retinal diseases were excluded. The study was approved by the Institutional Review Board of National Taiwan University Hospital and carried out in accordance with the tenets of the Declaration of Helsinki. The need for informed consent was waived by the Institutional Review Board.

Ophthalmic Examinations

Medical records of the enrolled patients were retrospectively reviewed. The following information was documented: demographics, ocular biometry measured using the Lenstar LS 900 (Haag-Streit, Koeniz, Switzerland), best-corrected visual acuity, and history of active myopic choroidal neovascularization (CNV). Color fundus photography centered on the macula was performed (CR-DGi Image Viewer; Canon Inc., Tokyo, Japan). The ATN classification and the following features were determined. The tilt of the disc was described as the ratio between the longest and shortest diameters of the disc. Disc torsion was defined as the angle between the disc's long axis and vertical meridian. The vertical meridian was perpendicular to the line connecting the fovea and disc center.[17] The presence of a lacquer crack or Fuchs spots was identified.[18] Posterior staphyloma was defined as local outpouching of the posterior pole identified by an ophthalmoscope. Corneal biomechanical parameters were obtained using Corvis ST tonometry, including A1 and A2 lengths, A1 and A2 velocities, peak distance, highest concavity (HC) radius, HC deformation amplitude, HC deflection amplitude, deformation amplitude (DA) ratio at 2 mm, stiffness parameter (SP-A1), arc length, inversus radius, and maximum whole eye movement.[19]

Optical Coherence Tomography

Standard 10-mm vertical and horizontal scans centered on the fovea were performed using spectral-domain OCT (RTVue RT-100, version 3.5; Optovue, Inc., Fremont, CA, USA). Scans with a signal strength index > 40/100 were selected for analysis. Bruch's membrane defects,[18] the presence of a dome-shaped macula,[20] and disruption of the ellipsoid zone were identified. The subfoveal choroidal thickness was measured using a manual caliper function of a built-in software. The central foveal thickness of the whole, inner, and outer retina was measured. The inner retinal layer was superficial to the inner nuclear layer, and the rest of the retinal layers were defined as the outer retina. The macular radius of curvature within the 10-mm scanning area was measured using Kappa Curvature Analysis for Fiji.[21]

OCTA was performed with the Optovue RTVue XR Avanti with AngioVue OCTA system, using two consecutive B-scans composed of 304 × 304-cross A-scans in approximately 2.6 seconds (70,000 A-scans/s). Scans with a signal strength index < 4/10 were excluded. The AngioVue software has a built-in projection artifact removal algorithm and can perform en face retinal imaging of the superficial layer, deep layer, outer retina, and choriocapillaris. The superficial layer had an inner boundary 3 µm below the internal limiting membrane and an outer boundary 15 µm below the inner plexiform layer. The deep layer had boundaries set at 15 µm and 70 µm below the inner plexiform layer. The choriocapillaris had boundaries set at 30 µm and 60 µm below the retinal pigment epithelium. Auto-segmentation errors were corrected by manually adjusting the contour and location of each segmentation line. The vessel density of the central 3 × 3-mm area of the superficial and deep layers of the retina and the area and perimeter of the foveal avascular zone (FAZ) were measured using built-in software and then recorded. The flow area of the choriocapillaris was calculated within a central 2-mm-diameter circle.

Fiji software[22] was used to process and analyze the en face angiography map of the full retina for calculating the microvascular parameters. The OCTA images were corrected for image magnification using Bennett's formula.[23] The FAZ was marked and the circularity was calculated using the "circularity" function. The 3 × 3-mm angiography maps were converted to 8-bit 304 × 304-pixel images. The default algorithm was used for autothresholding.[24] Then, the skeletonize function was used to create a skeletonized image. The vessel density was calculated as the area occupied by the white pixels (blood vessels) divided by the all area of the binarized image. The skeleton density was calculated as the area occupied by the white pixels (skeletonized blood vessels) divided by the all area of the skeletonized image. The vessel diameter was calculated as the vessel density divided by the skeleton density. The fractal dimension was calculated by the box-counting method to quantify the branching complexity.[25–27] Vessel tortuosity was calculated as an average of the ratio of geodesic distance and the Euclidean distance of each vessel branch.[27]

Statistical Analysis

All statistical analyses were performed using RStudio 3.6.0 (RStudio, Inc., Boston, MA, USA). For descriptive statistics, the mean and standard deviation were calculated for parametric data. For every patient, the eye with lower grade A classification and that with higher grade A classification

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were designated as the less severe eye and more severe eye, respectively. A paired *t*-test, χ^2 test, or Wilcoxon rank-sum test was used to compare the clinical characteristics between the more severe and less severe eyes. To evaluate the factors associated with more significant inter-eye difference MAM asymmetry, patients with an A grading inter-eye difference equal to one were designated as the reference group. Univariate logistic regression analysis was performed to analyze the association with inter-eye differences in certain clinical features and the asymmetric MAM grading. Variables with $P < 0.1$ were included in the multivariable logistic regression analysis. $P < 0.05$ was considered statistically significant.

Results

Seventy-two eyes of 36 patients (seven men and 29 women) were enrolled. The patients' mean age was 61.0 ± 9.3 years. The mean axial length was 30.44 ± 1.92 mm. All patients had a posterior staphyloma. Nine eyes (12.5%) had A1 maculopathy, 33 eyes (45.8%) had A2 maculopathy, 17 eyes (23.6%) had A3 maculopathy, and 13 eyes (18.1%) had A4 maculopathy. In terms of inter-eye difference, 22 patients (61.1%) had one A grading difference, 13 patients (36.1%) had two A grading differences, and one patient (2.8%) had three A grading differences. Thirteen eyes from 11 patients had a history of active myopic CNV diagnosed by fluorescence angiography or OCTA. All of these eyes had received the intravitreal injection of anti-vascular endothelial growth factor. The mean duration from the onset of CNV to the time of data acquisition was 33.7 ± 19.0 months.

Inter-Eye Difference: Eyes With Less Severe MAM Versus Eyes With More Severe MAM

The comparison of clinical characteristics between eyes with less severe MAM and eyes with more severe MAM is presented in Table 1. Axial length and spherical equivalent were not significantly different between these two groups. Eyes with more severe MAM had a smaller macular radius of curvature and more dome-shaped macula, lacquer crack, Fuchs' spots, Bruch's membrane defects, ellipsoid zone disruption, thinner subfoveal choroidal thickness, and thinner retinal thickness at the full and inner layers compared to those of the eyes with less severe MAM. Regarding angiographic parameters, compared to those of eyes with less severe MAM, eyes with more severe MAM had lower FAZ circularity, a smaller choriocapillaris flow area, larger vessel diameter, and lower fractal dimension. No Corvis ST parameter differed between eyes with less severe and more severe MAM.

Factors Associated With Inter-Eye Difference Asymmetric MAM

Table 2 shows the results of the univariable regression analysis for factors associated with asymmetric MAM. None of the Corvis ST parameters was statistically significant. Higher inter-eye differences in MAM grading were associated with more significant differences in terms of the presence of Bruch's membrane defect, ellipsoid zone disruption, vessel density of the deep retinal layer, FAZ circularity, FAZ area, flow area of the choriocapillaris, vessel diameter, and fractal dimension. Multivariable regression analysis showed that the higher inter-eye difference in the flow area of the choriocapillaris ($P = 0.013$; adjusted odds ratio = 1.10 [1.02–1.18]) remained associated with higher inter-eye differences in MAM grading.

Discussion

The underlying mechanism of MAM is still debated. The increased axial length and associated posterior staphyloma were shown to predispose the development of MAM.[3,5,7–9,28] This mechanical theory is widely accepted, wherein stretching of the ocular coat induces choroidal attenuation, Bruch's membrane rupturing, and retinal pigment epithelium (RPE) degeneration.[1] On the other hand, the vascular theory has been proposed,[1] wherein the decreased choroidal volume and thickness caused by axial elongation fail to meet the metabolic demand of the retina, which causes subsequent macular degeneration.[10,29] Some systemic conditions, such as aging, gender, and hypertension, were also related to the development and progression of myopic maculopathy.[2–4,9,28,30,31] Clinically, we observed that some patients without significant anisometropia in both eyes had different MAM severities. In this situation, the elongated axial length was not the only contributing factor. To determine the contributing factors in these patients, patients without significant inter-eye differences in axial length were enrolled to evaluate the roles of mechanical and vascular factors in MAM. The confounding effects of systemic factors were controlled by the intra-individual comparison.

In this study, all eyes had a posterior staphyloma, predisposing them to the development of MAM. The eyes with more severe MAM had a steeper macular curvature; however, the increased inter-eye differences in axial length and macular curvature were not associated with more asymmetric MAM. In a previous study, among eyes with posterior staphyloma and a comparably elongated axial length, eyes with MTM had the steepest macular curvature compared to eyes with MNM and controls.[32] Therefore, the role of a posterior staphyloma may be distinct in different types of myopic maculopathy. A steeper macular curvature, associated with more significant anteroposterior traction, contributed to the development of MTM. A shallower macular curvature with more tangential expansion resulted in diffuse choroidal thinning and subsequent CNV.[32] Therefore, the steeper macular curvature, considered to be a mechanical factor, might not be a key factor in the formation of asymmetric MAM.

During axial elongation and the development of myopia, the biomechanical properties and rigidity of the sclera are altered.[1,10] To date, there is no well-established measure to evaluate scleral biomechanics in vivo. However, the dynamic corneal response to Corvis ST could represent the coupling effect of scleral and corneal properties. The reduced rigidity of scleral tissue in myopic eyes may decrease the limitation on corneal deformation and result in decreased corneal stiffness.[33] Previous studies identified several affected parameters, such as increased A2 velocity, HC peak distance, HC deformation amplitude, DA ratio, SP-A1, and smaller HC radius, to be associated with a higher negative refractive error.[13–16,34] To our knowledge, this study is the first to compare corneal biomechanical properties between eyes with different severities of MAM. Because aging and systemic conditions also cause changes in the corneal biomechanical properties, the intra-individual comparison could eliminate the influence of these confounding factors.[35,36] We observed that eyes with more severe MAM did not have more

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Table 1. Comparison of Clinical Characteristics Inter-Eye Difference With Less and More Severe MAM

	Less Severe Eye	More Severe Eye	*P*
Axial length (mm), mean ± SD	30.39 ± 1.89	30.49 ± 1.97	0.349*
Spherical equivalent (D),† mean ± SD (range)	–14.63 ± 5.10 (–21.25 to –6.00)	–15.01 ± 5.27 (–23.00 to –6.00)	0.088‡
Central corneal thickness (µm), mean ± SD	549.9 ± 43.3	551.9 ± 44.3	0.418*
Macular radius of curvature (mm), mean ± SD	5.10 ± 2.18	4.19 ± 1.33	**0.011***
Disc tilt ratio, mean ± SD	1.55 ± 0.29	1.59 ± 0.41	0.535*
Disc torsion (°), mean ± SD	15.9 ± 16.6	14.3 ± 11.7	0.226*
Diameter of peripapillary atrophy (mm), mean ± SD	4.57 ± 1.09	4.83 ± 1.31	0.146*
Dome-shaped macula, *n* (%)	7 (19.4)	15 (41.6)	**0.002**§
Lacquer crack, *n* (%)	9 (25)	19 (52.8)	**0.028**§
Fuchs spot, *n* (%)	5 (13.9)	25 (69.4)	**<0.001**§
Bruch's membrane defect, *n* (%)	1 (2.8)	24 (66.7)	**<0.001**§
Ellipsoid zone disruption, *n* (%)	8 (22.2)	24 (66.7)	**0.002**§
History of active choroidal neovascularization, *n* (%)	4 (11.1)	9 (25.0)	0.220§
Duration of choroidal neovascularization (mo), mean ± SD	22.0 ± 12.5	38.9 ± 19.6	0.416*
Subfoveal choroidal thickness (µm), mean ± SD	74.4 ± 45.4	44.6 ± 31.1	**<0.001***
Central retinal thickness (µm), mean ± SD	266.8 ± 35.7	237.0 ± 66.3	**0.036***
Central inner retinal thickness (µm), mean ± SD	74.0 ± 13.5	59.2 ± 16.6	**<0.001***
Central outer retinal thickness (µm), mean ± SD	192.8 ± 29.4	178.1 ± 59.7	0.218*
OCTA parameters, mean ± SD			
Superficial retinal vessel density (%)	39.2 ± 6.7	37.0 ± 6.5	0.070*
Deep retinal vessel density (%)	43.5 ± 8.1	40.0 ± 9.9	0.066*
Foveal avascular zone area (mm2)	0.312 ± 0.329	0.437 ± 0.451	0.266*
Foveal avascular zone perimeter (mm)	2.200 ± 0.925	2.784 ± 1.334	0.070*
Foveal avascular zone circularity	0.857 ± 0.107	0.773 ± 0.131	**0.008***
Flow area of choriocapillaris (mm^2)	2.03 ± 0.25	1.74 ± 0.37	**<0.001***
Vessel diameter	2.01 ± 0.12	2.11 ± 0.16	**<0.001***
Fractal dimension	1.81 ± 0.01	1.80 ± 0.02	**0.003***
Vessel tortuosity	1.26 ± 0.07	1.28 ± 0.06	0.207*
Corvis ST parameters, mean ± SD			
A1 length (mm)	2.12 ± 0.31	2.16 ± 0.33	0.565*
A1 velocity (m/s)	0.15 ± 0.02	0.15 ± 0.02	0.750*
DA ratio at 2 mm	4.52 ± 0.56	4.45 ± 0.50	0.314*
SP-A1	114.8 ± 18.0	115.9 ± 22.8	0.545*
HC radius	6.81 ± 1.08	6.73 ± 1.03	0.561*
HC deformation amplitude (mm)	1.22 ± 0.16	1.23 ± 0.15	0.896*
HC deflection amplitude (mm)	1.10 ± 0.15	1.11 ± 0.13	0.753*
Arc length (mm)	–0.17 ± 0.08	–0.16 ± 0.04	0.733*
Peak distance (mm)	5.36 ± 0.31	5.37 ± 0.29	0.923*
A2 length (mm)	1.83 ± 0.38	1.70 ± 0.51	0.311*
A2 velocity (m/s)	–0.31 ± 0.06	–0.31 ± 0.06	0.644*
Inversus radius (1/mm)	0.17 ± 0.04	0.16 ± 0.03	0.561*
Maximum whole eye movement	0.29 ± 0.08	0.29 ± 0.07	0.823*

Significant *P*-values are shown in bold.
* Paired *t*-test.
† Data for pseudophakic patients were excluded.
‡ Wilcoxon signed-rank test.
§ χ^2 test.

weakened corneal biomechanical properties. Although the development of Bruch's membrane defect may weaken the outer coat of the eyeball, it could be offset by the formation of fibrotic tissue following the occlusion of choroidal vessels.[10] Previous studies have reported that a decrease in choroidal thickness rather than scleral thickness was associated with the severity of MAM.[1] Together, these observations imply that scleral alteration plays an important role in axial elongation and myopia progression; however, choroidal thinning and ischemic change may be more pivotal in the pathogenesis of MAM.

This study found that the asymmetric presence of Bruch's membrane defect was associated with a more significant inter-eye difference in MAM grading. The Bruch's membrane was thought to be the primary structure responsible for stabilizing the shape of the eye.[10,37] During the process of axial elongation, the Bruch's membrane extends posteriorly and results in choroidal thinning. Meanwhile, the Bruch's membrane opening present at the optic nerve head also enlarges to release tension, causing gamma zone peripapillary atrophy.[37] When the stretching of Bruch's membrane exceeds the extensile force it can withstand, the Bruch's membrane ruptures at the macular area.[38] Although the Bruch's membrane defect formation is largely caused by mechanical stretching, the loss of RPE and choriocapillaris and decreased choroidal perfusion in highly myopic eyes also make the Bruch's membrane more vulnerable to fragmentation.[39] Linear Bruch's membrane defects appeared as lacquer cracks on a fundus photograph, and they may only present as RPE discontinuities and hyperreflective lines on

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Table 2. Univariable Regression Analysis of Factors Associated with Asymmetric MAM

	Odds Ratio (95% Confidence Interval)	*P*
Age	1.01 (0.94–1.09)	0.711
Gender*	1.23 (0.21–6.63)	0.811
Axial length (mm)	5.40 (0.71–50.58)	0.115
Central corneal thickness (µm)	0.99 (0.93–1.01)	0.571
Macular radius of curvature (mm)	1.15 (0.76–1.86)	0.494
Tilt ratio	1.14 (0.06–18.46)	0.924
Disc torsion (°)	0.94 (0.85–1.01)	0.191
Diameter of peripapillary atrophy (mm)	1.00 (0.99–1.01)	0.730
Dome-shaped macula (%)	2.00 (0.48–8.50)	0.337
Lacquer crack (%)	0.70 (0.15–2.90)	0.629
Fuchs spot (%)	1.80 (0.46–7.53)	0.403
Bruch's membrane defect (%)	15.6 (2.45–309.07)	**0.014**
Ellipsoid zone disruption (%)	6.67 (1.60–33.00)	**0.013**
History of active choroidal neovascularization (%)	2.50 (0.54–12.40)	0.243
Duration of choroidal neovascularization (mo)	1.06 (0.98–1.20)	0.218
Subfoveal choroidal thickness (µm)	1.01 (0.99–1.03)	0.245
Central retinal thickness (µm)	1.01 (0.99–1.02)	0.258
Central inner retinal thickness (µm)	1.05 (1.01–1.11)	0.058
Central outer retinal thickness (µm)	1.00 (0.99–1.02)	0.531
Superficial retinal vessel density (%)	1.06 (0.85–1.35)	0.595
Deep retinal vessel density (%)	1.20 (1.04–1.44)	**0.022**
Foveal avascular zone area (mm^2)	1.07 (1.01–1.15)	**0.049**
Foveal avascular zone perimeter (mm)	4.51 (1.50–34.80)	0.053
Foveal avascular zone circularity	1.01 (1.01–1.03)	**0.012**
Flow area of choriocapillaris (mm^2)	1.09 (1.04–1.21)	**0.013**
Vessel diameter	1.13 (1.02–1.31)	**0.045**
Fractal dimension	1.43 (1.14–2.11)	**0.015**
Vessel tortuosity	1.13 (0.97–1.36)	0.129

Significant *P*-values are shown in bold.
* Female gender was designated as the reference group.

choroidal and scleral tissue on OCT. With widening and progression, they can be detected as disruption of the RPE–Bruch's membrane complex.[40] It has been reported that the planar Bruch's membrane defects are caused by the remnants of CNV or result from the coalescence of patchy atrophic lesions.[41,42] Therefore, in our study, the eyes with evident Bruch's membrane defects were associated with a more severe MAM status.

Choroidal thinning is typically associated with aging, elevated blood pressure, elongated axial length, and posterior staphyloma.[10] Significant regional choroidal thinning and impaired perfusion may predispose the local scleral curvature change and has been observed at the edge of the posterior staphyloma.[43,44] Markedly and diffusely thinned choroid failed to provide adequate blood supply to the retinal tissue and caused the development of MAM; however, the choroidal thickness did not thoroughly reflect the functional status of the choroidal blood flow. With OCTA, several studies have demonstrated that decreased perfusion of the choriocapillaris in myopic eyes and flow impairment become more significant with increasing MAM severity.[12,45] In our study, the inter-eye difference in MAM grading was not associated with choroidal thickness but was correlated with the flow area of the choriocapillaris. Although the causal relationship between MAM and decreased flow area of the choriocapillaris could not be confirmed using our cross-sectional data, a previous study has reported that choroidal thinning preceded MAM progression.[10] Therefore, the vascular and ischemic factors of the choroid may greatly contribute to the development and progression of MAM.

It was revealed that myopic eyes had retinal thinning and decreased vessel density due to axial elongation. These degenerative changes in pathologic myopia affected the choroid and outer retina first.[10,12,46] Accordingly, the deep retinal capillary plexus may be more vulnerable than the superficial retinal capillary plexus. MAM eyes had a more profound decrease in the deep retinal capillary plexus compared to simple highly myopic eyes.[46] In this study, the inter-eye difference of the deep, but not superficial, retinal vessel density was correlated with asymmetric MAM grading. Moreover, we observed decreased FAZ circularity and vessel branching complexity, and enlarged FAZ area was related to the asymmetric severity of MAM. Vascular dropout seemed to become more prominent with MAM progression. Although both mechanical stretching and ischemia contributed to the development of MAM, microvasculature alteration, especially choroidal circulation, seemed more crucial in these eyes without significant anisometropia. Our findings echo those of previous studies that have proposed that myopic-related vascular changes and ischemia play more important roles in MAM and MNM, whereas tractional force makes a greater contribution to MTM.[1,32,47] Moreover, our intra-individual comparison eliminated the systemic factors affecting blood perfusion, highlighting the importance of vascular theory.

This study has several limitations. Because of the retrospective design, this study could not clarify whether the vascular factors predisposed to the asymmetric MAM or if it was the result of higher stage of maculopathy, especially in A4 eyes; however, 80% of eyes were classified as A1 to A3. Our findings at least supported the notion that mechanical factors have less association with asymmetric MAM compared to vascular factors. To elucidate the causal relationship between vascular factors and asymmetric MAM,

longitudinal observation that collects clinical features at baseline and determines which factors are associated with future development of asymmetric MAM is necessary. We tried to control the contributing effect of axial length in the development of MAM by enrolling patients with inter-eye axial length differences of less than 1 mm. However, a 1-mm difference in axial length may still increase the risk of MAM. Because the axial length was not significantly different between eyes with less severe and more severe MAM, and all of the eyes had staphyloma, this criterion was still reasonable. Due to the retrospective and cross-sectional nature of the study, the past CNV activity could not be analyzed precisely, but it was also a possible factor for asymmetric MAM. Finally, the segmentation of OCTA may be incorrect in eyes with MAM. We tried to adjust the segmentation manually and excluded cases with poor-quality scans, which also limited the number of cases in our cohort.

In conclusion, in patients without significant anisometropia, the eyes with impaired blood perfusion were prone to more severe MAM. Although the causal relationship between MAM and impaired perfusion requires further clarification with longitudinal follow-up, microvasculature alteration and ischemia play important roles in the development and progression of asymmetric MAM. The underlying factors causing inter-eye asymmetric blood perfusion also require further investigation in future studies.

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