Eye Shape Deformity Predicts Myopic Maculopathy Progression among Highly Myopic Individuals：A 4-Year Longitudinal Study

Authors: Cong Li, MD[1]*, Huawang Wu, MD, PhD[2,3,4]*, Ou Xiao, MD, PhD[1], Ruilin Xiong, MD, PhD[1], Xinxing Guo, MD, PhD[5], Yanxian Chen, MD, PhD[6], Qiuxia Yin, MPH[1], Mingguang He, MD, PhD[6] †, Zhixi Li, MD, PhD[1] †

Author Affiliations

1. State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangdong Provincial Key Laboratory of Ophthalmology and Visual Science, Guangdong Provincial Clinical Research Center for Ocular Diseases, Guangzhou, China
2. The Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou, 510370, China
3. Guangdong Engineering Technology Research Center for Translational Medicine of Mental Disorders, Guangzhou, 510370, China.
4. Key Laboratory of Neurogenetics and Channelopathies of Guangdong Province and the Ministry of Education of China, Guangzhou Medical University, Guangzhou, 510370, China.
5. Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland
6. School of Optometry, The Hong Kong Polytechnic University, Kowloon, Hong Kong

*Co-first authors †Co-corresponding authors.

Abbreviated Title: Eye shape and myopic maculopathy

Correspondence

Zhixi Li, MD, PhD, State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou 510060, China.
E-mail: lzx11-11@163.com

Funding/Acknowledgement: This work was supported by National Natural Science Foundation of China (82301249); Science and Technology Projects in Guangzhou (SL2024A04J01756); the Fundamental Research Funds of the State Key Laboratory of Ophthalmology (83000-32030003); Guangzhou Municipal Key Discipline in Medicine (2021-2023), Guangzhou High-level Clinical Key Specialty, Guangzhou Research-oriented Hospital; and the Global STEM Professorship Scheme (P0046113).

Conflict of Interest Disclosures: No conflicting relationship exists for any authors.

Key words: myopic maculopathy progression, ocular shape, three-dimensional magnetic resonance imaging, high myopia, cohort study

Summary Statement:
Using 4-year longitudinal data, we observed that highly myopic individuals with eye shape deformity had myopic maculopathy (MM) progression more frequently than those with non-deformed eye shape. Eye shape deformity identified from three-dimensional magnetic resonance imaging is a novel predictor for MM progression, equally as important as axial length.

Word Count: [Abstract: 200 / Text: 2980]
Tables: 3; Figures: 3
Supplemental Digital Content: Tables: 2; Video: 1

Author Contributions:
Conception and design: CL, ZL
Analysis and interpretation: All authors
Data collection: All authors
Obtained funding: ZL, MH, HW
Overall responsibility: ZL, MH

Abstract

Purpose: To determine the impact of eye shape using three-dimensional magnetic resonance imaging (3D MRI) on myopic maculopathy (MM) progression.

Methods: At baseline, 67 participants with high myopia were selected. Eye shape was classified into spheroidal, ellipsoidal, temporally distorted, nasally distorted, conical, and barrel-shape identified from 3D MRI. Spheroidal and ellipsoidal were defined as non-deformity, otherwise others were defined as eye deformity. MM progression was determined through color fundus photography.

Results: Within 4-year follow-up, 17.1% (7/41) of patients with non-deformed eye shape had MM progression, whereas 69.2% (18/26) of patients with eye shape deformity had MM progression. In multivariate analysis, eye shape deformity (Odds ratio [OR], 4.35; 95% confidence interval [CI], 1.10-17.29; p = 0.036) and axial length (AL) of ≥ 28 mm (OR, 12.75; 95% CI, 2.27-71.48; p = 0.004) significantly correlated with MM progression. The predictive discrimination of eye shape alone for MM progression did not differ from AL (area under the curve, AUC: 0.765 versus 0.750, p = 0.486). By incorporating age, sex, AL and eye shape, the prediction model achieved an AUC of 0.862 for discriminating MM progression.

Conclusion: Eye shape deformity assessed by 3D MRI is a novel predictor for MM progression in high myopia.

Introduction

Myopic maculopathy (MM) has already become a primary cause of irreversible vision loss and blindness among highly myopic population, especially in East Asia.[1] Projections indicate that approximately 938 million individuals worldwide will develop high myopia (HM) by 2050,[2] suggesting that a considerable number of myopic individuals will suffer from MM-associated visual impairment and thus their quality of life will be affected. Given MM is clinically significant, there is an urgent need for improvement in identifying high-risk individuals, which facilitates early interventions and prevents vision loss.

Previous investigation revealed that emmetropic eyes usually exhibit oblate or spherical, but a shift in eye shape towards an ellipsoid or more nonuniform expansion occurs in axial myopic eyes.[3-5] Although the exact pathogenesis of MM remains elusive, a possible mechanism suggests that excessive increase of axial length (AL) may trigger stress at the posterior pole and cause local alterations of the sclera, retina and choroid that progressively damage the surrounding tissues.[6] Additionally, it was suggested that the MM prevalence increases with longer AL in a nonlinear manner.[7-13] Thus, it may be inferred that aside from AL, abnormal alterations of eye shape can possibly exert pivotal impacts on the occurrence and progression of MM.

With the rapid advance of ocular imaging, high-resolution three-dimensional magnetic resonance imaging (3D MRI) has attracted increasing attention since this technique holds advantages over previous methods such as ultrasound or optical coherence tomography for characterizing eye shape.[14] It enables to image the entire eye both locally and globally, providing a direct assessment of 3D structure of the eye and comprehensive biometric information.[14] Using 3D MRI, very limited cross-sectional studies have investigated the association of MM and eye shape but

yielding inconsistent results. Moriyama et al. reported that no significant correlation was found among chorioretinal atrophy, myopic traction maculopathy (MTM), myopic choroidal neovascularization (CNV), and types of eye shape.[15] Conversely, Ohno-Matsui et al. observed that chorioretinal atrophy, patchy atrophy and CNV occurred more commonly among eyes with irregular curvature.[16] Yu et al. also reported that eyes with MTM tended to present with a less uniform eye shape.[17] Considering the progressive nature of MM, it is essential to conduct longitudinal researches and such endeavors would greatly aid in fully clarifying the relationship between eye shape and MM, whereas relevant information is scarce.

Herein, we aimed to determine the impact of eye shape based on 3D MRI on MM progression in highly myopic individuals using 4-year longitudinal data, and further investigate its potential role as a predictive factor for MM progression.

Methods

Study design and participants

This longitudinal cohort study was conducted in Zhongshan Ophthalmic Center (ZOC), Sun Yat-sen university, China. At baseline, 95 subjects with bilateral HM (-6.00 diopter [D] spherical error or greater) were selected from the Zhongshan Ophthalmic Centre–Brien Holden Vision Institute (ZOC-BHVI) Guangzhou High Myopia Cohort Study by stratified random sampling.[18] Among them, 67 subjects attended the 4-year follow-up and accepted comprehensive ophthalmic examinations. This study was approved by the Ethics Committee of ZOC, adhering to the tenets of the Declaration of Helsinki. Signed informed consent was obtained from all participants before enrollment.

MRI data acquisition and analysis

At baseline, the subjects underwent MRI examination (Achieva X-Series 3T; Philips Medical Systems, Best, the Netherlands) at the Affiliated Brain Hospital of Guangzhou Medical University. The MRI data were obtained with an 8-channel phased-array head-coil. The subjects were instructed to keep both of eyes closed and minimize movement during the scanning. For each subject, high-resolution brain structural images were obtained using a T2-weighted 3D turbo spin-echo (TSE) sequence. The parameters were as follows: repetition time = 2,500ms, echo time = 250ms, flip angle = 90°, TSE factor = 133, SENSE = 2, field of view = 256 mm × 256mm, data matrix = 256 × 256, slice thickness = 1 mm, voxel size = 1 × 1 × 1 mm^3, and 188 sagittal slices covering the whole brain. The scanning time for each subject was approximately 6 minutes. The fat-suppression technique was performed to reduce the fat signals of the orbit, enhancing the contrast between the eyeball and surrounding tissues, and thus being used to reconstruct the morphology of the eyeball. Given that eye movement can influence the quality of MRI images, an experienced neuroradiologist (H.W.) would inspect the morphology of the eyeball after the scanning to ensure no significant motion artifacts. Volume renderings of the images were produced using high-resolution 3D data on a computer workstation (OsiriX 7.0; OsiriX Medical Image Software, Bernex, Switzerland). The edge of the eyeball was manually contoured using OsiriX software, and the tissues outside of the eyeball were carefully removed.

Types and assessment of eye shape

We previously defined six distinct types of eye shape in total:[18] 1) spheroidal, presenting symmetry in the temporal and nasal regions without neither evident elongation of the posterior segment nor alteration of the curvature radius; 2) ellipsoidal, presenting symmetry in the temporal and nasal regions with elongation of the posterior segment but no alteration of the curvature radius; 3) conical, presenting symmetry in the temporal and nasal regions with elongation of the

posterior segment and equally steeper than a circle curvature radius, which resembled the "cylindrical" type proposed by prior investigation;[3,16] 4) nasally distorted, presenting asymmetry in the temporal and nasal regions with elongation of the posterior segment and more protruded nasal half; 5) temporally distorted, presenting asymmetry in the temporal and nasal regions with elongation of the posterior segment and more protruded temporal half; 6) barrel shape, presenting symmetry in the temporal and nasal regions with elongation of the posterior segment and flatter than a circle radius of curvature. In the current study, conical, nasally distorted, temporally distorted, and barrel shape represented the eye shape deformity. The procedure for eye shape classification was performed step-by-step. First, an eye was classified into either spheroidal or non-spheroidal from the rotating 3D view both horizontally and vertically. For non-spheroidal eyes, subsequent analysis was conducted in nasal and inferior views to compare the symmetry of the posterior segment curvature and to identify the presence of posterior staphyloma. Posterior staphyloma was defined as an outpouching of a circumscribed region in the posterior segment and displayed a smaller curvature radius compared to surrounding areas. [4,19] The number of protrusions was also documented based on the rotating 3D view. In the eye viewed inferiorly, which best exhibited the contour profile and the symmetry in the temporal and nasal regions of the posterior segment, the eye shape was determined. We have included a brief video presenting the dynamic 3D MRI reconstruction of the eyeball (**see Video, Supplemental Digital Content 1**), which may facilitate to understand the process of identifying eye shape and posterior staphyloma. Two authors (X.G., Y.C.) who had completed a lecture session on evaluating MRI images, with agreements of 0.84 for eye shape and 0.86 for posterior staphyloma, and were unaware of any clinical information about the eyes. The disagreement would be adjudicated by another author (O.X.).

Ophthalmic examinations

Standard 45° color fundus photography (CFP) images, centered on the optic nerve head and macula, respectively, were captured using a digital fundus camera (Canon CX-1; Tokyo, Japan) after pupil dilation. Furthermore, CFP images were screened according to META-PM classification system for MM grading, including “no myopic retinal degenerative lesion” (Category 0), “tessellated fundus” (Category 1), “diffuse chorioretinal atrophy” (Category 2), “patchy chorioretinal atrophy” (Category 3), and “macular atrophy” (Category 4).[20] Also, the “plus” lesions, including myopic CNV, lacquer cracks, Fuch's spot were assessed. The definition of MM progression in this study followed prior researches[21,22]: 1) For the participants classified as Category 0 or Category 1 at baseline, progression to more advanced category or the occurrence of any "plus" lesions was considered; 2) For the participants classified as Category 2 to Category 4 at baseline, any one of the followings was considered, including progression to more advanced category, initial presence of any “plus” lesions, or any evident enlargement of affected areas caused by diffuse/patchy chorioretinal and macular atrophy, which can be identified by graders when comparing each subject's CFP images at baseline and 4-year visit side by side; 3) Enlargement of any “plus” lesions. Alternatively, if no obvious progression was observed, the eye was classified as non-progression. The CFP images were graded by well-trained ophthalmologists with good agreement.[21]

AL was measured using optical low-coherence reflectometry (Lenstar LS900; Haag-Streit AG, Koeniz, Switzerland). When AL exceeded the range of Lenstar measurement (up to 32 mm), AL was measured using partial coherence interferometry (IOL Master; Carl Zeiss Meditec, Oberkochen, Germany). After pupil dilation for both eyes, determined by at least 6 mm in diameter and the absence of a light reflex, refraction data were collected with an autorefractor (KR8800;

Topcon, Tokyo, Japan). Spherical equivalent (SE) was calculated by summing spherical power and half of cylindrical power.

Statistical analysis

In this study, the right eye was used for statistical analysis due to the high correlation between both eyes of each participant. Comparison of baseline clinical characteristics between included participants and participants who did not attend the 4-year follow-up was performed using Pearson's chi-square test or Fisher's exact test, where appropriate, as was comparison of baseline and follow-up clinical characteristics between deformed eyes and non-deformed eyes. The characteristics of MM in eyes with and without protrusion or staphyloma was analyzed using Fisher's exact test. Logistic regression analysis was employed to determine potential risk factors of MM progression. The area under the curve (AUC) was used to assess the predictive ability of discerning MM progression, and the likelihood ratio test was used to compare these models. All analyses were performed using Stata 14.0 (StataCorp, College Station, TX, USA), with the statistical significance threshold established at a two-sided $p < 0.05$.

Results

In total, 67 eligible participants with the mean age of 32.6 ± 14.7 years attended the 4-year visit and were included in the analysis. Of them, 35 (52.2%) participants were female. Compared with the participants who did not attend the follow-up, the included participants had no significant differences in the distribution of age, sex, AL, SE, MM category, eye shape, staphyloma, and protrusion at baseline (all $p > 0.05$) (**see Table S1, Supplemental Digital Content 2**).

As shown in **Table 1**, the proportions of spheroidal, ellipsoidal, conical, nasally distorted, temporally distorted, and barrel shape were 35 (52.2%), 6 (9.0%), 12

(17.9%), 8 (11.9%), 3 (4.5%) and 3 (4.5%) among 67 participants at baseline, respectively. A total of 21 (31.3%) participants had MM level ≥ Category 2. And more severe MM (≥ Category 2) occurred more frequently in deformed eyes (61.5%) compared to eyes with non-deformed shape (12.2%) ($p < 0.001$). During 4-year follow up, 17.1% (7/41) of patients with non-deformed eye shape had MM progression, whereas 69.2% (18/26) of patients with deformed eye shape at baseline had MM progression ($p < 0.001$). **Figure 1.** presents the typical examples of eye shape based on 3D MRI and corresponding MM progression.

In **Table 2,** we found that patients without staphyloma on MRI had milder category of MM (C0/C1) more frequently than patients with staphyloma at baseline ($p < 0.001$). During 4-year follow-up, the patients with pre-existing staphyloma had MM progression more frequently than those without staphyloma ($p < 0.001$). **Figure 2.** presents the typical examples of eyes with/without staphyloma and corresponding MM progression. Similarly, during 4-year follow-up, the patients without protrusion at baseline had MM progression less frequently than those with protrusion ($p < 0.001$) (**see Table S2, Supplemental Digital Content 3**).

In **Table 3**, the multivariate analysis showed that MM progression was significantly associated with eye shape deformity (Odds ratio [OR], 4.35; 95% confidence interval [CI], 1.10-17.29; $p = 0.036$) and AL of ≥ 28 mm (OR, 12.75; 95% CI, 2.27-71.48; $p = 0.004$) but not with age (OR, 4.55; 95% CI, 0.73-28.47; $p = 0.105$) and sex (OR, 1.39; 95% CI, 0.38-5.13; $p = 0.619$). When adjusting for age, sex and AL, the presence of posterior staphyloma significantly correlated with MM progression (OR, 11.56; 95% CI,1.73-77.07; $p = 0.011$).

As shown in **Figure 3**, the AUCs for discriminating MM progression using eye shape (Model 1) and AL (Model 2) alone were 0.765 (95% CI: 0.657-0.873) and 0.750 (95%

CI: 0.651-0.848), respectively. No significant difference in predictive efficacy was observed between Model 1 and Model 2 (p = 0.486). By incorporating age, sex, AL and eye shape, the prediction Model 3 achieved an AUC of 0.862 (95% CI: 0.763-0.962).

Discussion

To our knowledge, this study firstly explored the association of eye shape identified from 3D MRI and MM in a longitudinal design. Over 4-year follow up, we found that 17.1% of patients with non-deformed eye shape had MM progression, whereas 69.2% of patients with eye shape deformity had MM progression. Moreover, eye shape deformity and AL of ≥ 28 mm were significant risk factors of MM progression. The AUC for predicting MM progression when eye shape considered as a single risk factor was 0.765, showing no significant difference in predictive efficacy with AL alone (AUC: 0.750, p = 0.486). Based on age, sex, AL, and eye shape, the prediction model showed a good performance for discriminating MM progression, with an AUC of 0.862.

Due to limited studies or cross-sectional designs, the association of eye shape and MM has yet to be fully elucidated. Moriyama et al. reported that no significant correlation was detected among chorioretinal atrophy, CNV and types of eye shape.[15] Conversely, in other studies, the researchers observed that MM occurred more commonly in eyes with less-uniform shape or irregular curvature.[16,17] Using longitudinal data, this study advanced previous studies for further explaining the association between abnormal alterations in eye shape and MM. We observed that patients with eye shape deformity had MM progression more frequently than those with non-deformed eye shape. Moreover, patients with eye shape deformity showed 4.35-fold higher risk of MM progression compared to the patients with non-deformed eye shape when adjusting for age, sex and AL. Several lines of evidence

revealed that emmetropic eyes usually display oblate or spherical, but axial myopic eyes tend to undergo a shift in eye shape towards an ellipsoid or more nonuniform expansion.[4,5,15] Our results indicated that eye shape may play an important role in MM progression.

We firstly demonstrated that eye shape deformity could serve as a potent predictor for MM progression, equally as important as AL. Previous studies have demonstrated that AL is a well-established risk factor for MM progression.[21,23,24] In this study, we found that eye shape deformity had an AUC of 0.765 for discriminating MM progression when considered as a single risk factor, which did not differ from AL alone (AUC: 0.750). Furthermore, by incorporating age, sex, AL and eye shape, the prediction model showed a good performance for discerning MM progression, with an AUC of 0.862. Given that MM is an extremely complex disease, our findings indicate that eye shape assessed by 3D MRI may be an increment to aid in the early diagnosis and monitoring of this condition in highly myopic individuals, especially in the precision clinic settings.

In this longitudinal study, we found that patients with an AL of ≥ 28 mm at baseline had 12.75-fold higher risk of MM progression compared to those with an AL of less than 28 mm. Notably, although previous studies have suggested that MM prevalence increases with longer AL, such relationship is nonlinear.[7-13] Asakuma et al. reported that the prevalence of MM significantly increased from 0.1% in eyes with an AL < 26 mm to 53.7% in eyes with an AL of ≥ 28 mm.[8] Similarly, Liu et al. reported that the prevalence of diffuse chorioretinal atrophy significantly increased from 3.6% in eyes with an AL of less than 26.50 mm to 62.8% in eyes with an AL of ≥ 28.50 mm.[7] From a practical viewpoint, our findings supported the significance of AL of 28 mm in the management of HM and provided rationale to monitor MM progression. In the other prospective study, baseline AL of 28.15 mm or greater was found to be correlated

with the continuing axial elongation in highly myopic adults,[25] adding further evidence to support our findings.

The 3D MRI is a non-invasive and valuable tool for directly detecting the posterior staphyloma.[4] Although previous studies suggested a link between posterior staphyloma and MM,[4,26] few studies have investigated the impact of posterior staphyloma on MM using 3D MRI in a longitudinal design. We prospectively observed that the eyes with pre-existing staphyloma had MM progression more frequently than those without staphyloma during 4-year follow-up. Meanwhile, the presence of posterior staphyloma significantly correlated with MM progression when adjusting for age, sex and AL. Our findings highlighted the necessity for vigilant monitoring of staphyloma among highly myopic individuals.

This study had some limitations. First, this study had a relatively small number of patients for each eye shape category. Second, 29.5% of participants from a tertiary eye care hospital were lost to the 4-year follow-up. Nevertheless, no significant differences in the distributions of age, sex, AL, SE, MM category, eye shape, staphyloma and protrusion at baseline were found between the included participants and those who did not attend follow-up, which may reduce potential selection bias. Third, it should be acknowledged that the ocular shape assessed by the T2-weighted 3D MRI actually reflected the contour of the intraocular fluid instead of the outer coat of the eyeball that is the sclera. Fourth, although MRI holds advantage of offering a more direct assessment of the overall eye shape, its feasibility as a routine examination is limited due to practical and financial constraints. Fifth, although this longitudinal study suggested that eye shape deformity can be used to predict MM progression, the association of changes in eye shape and MM progression has not been confirmed and necessitates further investigation.

Conclusion

In summary, we found that patients with eye shape deformity at baseline had MM progression more frequently than patients with non-deformed eye shape during 4-year follow up. The presence of posterior staphyloma was significantly associated with MM progression. Eye shape deformity assessed by 3D MRI, equally as important as AL, is a novel predictor of MM progression. Our findings may offer considerable insights into the monitoring and management of HM.

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Figure Legends

Figure 1. Typical examples of eye shape by three-dimensional magnetic resonance imaging (3D MRI) and corresponding myopic maculopathy progression. Eye shape is spheroidal by 3D MRI (A1), the macula displays the absence of myopic maculopathy at baseline (A2) and remains stable at 4-year follow-up (A3). Eye shape is ellipsoidal (B1), the macula displays diffuse atrophy at baseline (B2) and progresses to patchy atrophy at 4-year follow-up (B3). Eye shape is conical (C1), the macula displays diffuse atrophy at baseline (C2) and progresses to patchy atrophy at 4-year follow-up (C3). Eye shape is nasally distorted (D1), the macula displays patchy atrophy at baseline (D2) and obvious enlargement of its affected area is observed at 4-year follow-up (D3). Eye shape is temporally distorted (E1), the macula displays diffuse atrophy at baseline (E2) and first appearance of lacquer cracks is observed at 4-year follow-up (E3). Eye shape is barrel-shaped (F1), the macula displays diffuse atrophy at baseline (F2) and progresses to macular atrophy at 4-year follow-up, accompanied by the enlargement of lacquer cracks (F3).

Figure 2. Typical examples of eyes with/without staphyloma and corresponding myopic maculopathy progression. In the image viewed inferiorly, one large staphyloma can be seen in the posterior segment of the eye (A1). The macula displays diffuse atrophy and lacquer cracks at baseline (A2), and the enlargement of lacquer cracks was observed at the 4-year visit (A3). The staphyloma can be seen in the posterior segment of the eye (B1). The macula displays diffuse atrophy and lacquer cracks at baseline (B2), and obvious enlargement of diffuse atrophy and lacquer cracks was observed at the 4-year visit (B3). One distinct staphyloma can be seen in the posterior segment of the eye (C1). The macula displays diffuse atrophy at baseline (C2), and obvious enlargement of diffuse atrophy and development of lacquer cracks were observed at the 4-year visit (C3). No staphyloma can be seen in the posterior segment of the eye (D1). The macula displays the absence of myopic maculopathy at baseline (D2), and remains stable at

the 4-year visit (D3). No staphyloma can be seen in the posterior segment of the eye (E1). The macula displays tessellated fundus and diffuse atrophy at baseline (E2), and remains stable at the 4-year visit (E3).

Figure 3. Receiver operating characteristic curves of the prediction models for discriminating the progression of myopic maculopathy. Model 1 included eye shape based on three-dimensional magnetic resonance imaging (3D MRI) alone and achieved an area under the curve (AUC) of 0.765. Model 2 included axial length (AL) alone and achieved an AUC of 0.750. Based on age, sex, AL, and eye shape, the Model 3 achieved an AUC of 0.862.

Supplemental Digital Content

Supplemental Digital Content 1. wmv

The brief video presenting the dynamic three-dimensional magnetic resonance imaging (3D MRI) reconstruction of the eyeball, which may facilitate to understand the process of identifying eye shape.

Supplemental Digital Content 2. docx

Table S1. Comparison of baseline clinical characteristics of included participants and non-included participants.

Supplemental Digital Content 3. docx

Table S2. The characteristics of myopic maculopathy among eyes with different number of protrusions based on three-dimensional magnetic resonance imaging (3D MRI).