Natural Course of Myopic Traction Maculopathy and Factors Influencing Progression and Visual Acuity

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Abstract

Background: To describe the natural course of myopic traction maculopathy (MTM) and determine predictive factors for its progression and visual prognosis.

Methods: This retrospective observational study included 113 MTM patients (147 eyes). Best-corrected visual acuity (BCVA) measurements and optical coherence tomography findings were recorded.

Results: Over a mean follow-up of 38.2 ± 11.1 months, 58 of 147 eyes (39.5%) progressed. The progression rate of outer schisis prominently located in the fovea or posterior staphyloma was significantly higher than that of outer schisis prominently located in paravascular areas (P = 0.0006). MTM with partial posterior vitreous detachment during the follow-up progressed more rapidly than MTM without (P = 0.0461). Patients with older age (>65 years), and defects in the ellipsoid zone (EZ) had worse BCVA at the last visit (P = 0.0281, and P = 0.0433). Multiple linear regression analysis showed that BCVA and defects in the EZ at baseline were significantly associated with the final BCVA (P < 0.0001 and P = 0.0259, respectively).

Conclusion: MTM has a high possibility for progression. Outer schisis located predominantly in the fovea or posterior staphyloma or with partial posterior vitreous detachment exhibits rapid progression. The integrity of the EZ is related to visual prognosis.

Background

Myopic traction maculopathy (MTM) refers to a series of pathological changes in the macula in high myopia, including vitreomacular traction, an epimacular membrane, retinoschisis, a lamellar macular hole (LMH) and foveal detachment. Damage to the outer retinal structure or development to foveal detachment and a full-thickness macular hole in the advanced stage can cause visual impairment in MTM, and surgical intervention is recommended to promote anatomical reattachment of the retina and visual recovery. Retinoschisis is a major characteristic lesion of MTM, and the incidence of retinoschisis in high myopia with posterior staphyloma is as high as 31.3%. Retinoschisis can occur in the fovea and extrafovea and in different locations of the intraretinal neural layers due to different dominant pathological factors. However, the mechanism of retinoschisis has not yet been fully elucidated, and many studies have shown that inward and tangential forces produced by partial posterior vitreous detachment (PVD), an epiretinal membrane, arteriosclerosis, and a stiff internal limiting membrane (ILM) and outward traction generated by asynchronous global elongation and posterior staphyloma may play important roles in its pathogenesis.

Recently, several studies have indicated that the progression rate of MTM varies, that paravascular abnormalities and paravascular inner retinoschisis may be associated with the pathogenesis of foveoschisis, and that the severity of retinoschisis in MTM can affect its progression regardless of whether cataract surgery is performed. Poor baseline visual acuity is often found in entire macula-
involved retinoschisis eyes accompanied by a disruption in the ellipsoid zone (EZ)\textsuperscript{16}, and progression of MTM can lead to worse visual outcomes in its natural course\textsuperscript{15}. However, these studies have focused little on identifying the evolution of retinoschisis prominent in different locations caused by different initiation factors, on the role of inner retinoschisis at paravascular arcades and ILM detachment in the progression of MTM, or on the comparison of the baseline factors affecting visual acuity at follow-up in large series.

Thus, we conducted this study to describe the natural course of MTM, to determine the effects of morphological characteristics of retinoschisis by OCT on MTM progression and to assess the risk factors influencing visual prognosis.

**Methods**

**Patients**

This retrospective study recruited patients with MTM who initially visited the Department of Ophthalmology of the Sixth People's Hospital Affiliated to Shanghai Jiao Tong University from June 2014 to March 2018. The inclusion criteria were as follows: 1) axis length $\geq$ 26 mm and refractive error $\leq$ -6.00 D and 2) MTM diagnosed by OCT. The exclusion criteria were as follows: 1) severe cataract affecting the quality of OCT imaging; 2) a full-thickness macular hole at baseline; 3) choroidal neovascularization; and 4) a history of vitreoretinal surgery. The study adhered to the guidelines of the Helsinki Declaration and had the approval of the Ethics Committee of Sixth People's Hospital Affiliated to Shanghai Jiao Tong University, Shanghai, China. The study was registered in the Chinese clinical trial registry (http://www.chictr.org.cn/, Registration number: ChiCTR2000038824). All patients signed written informed consent for participation.

**Clinical Examinations**

All patients were given a comprehensive ocular examination. Best-corrected visual acuity (BCVA) and refractive error were measured by applying a Snellen chart, and BCVA was then converted to logarithmic minimal angle of resolution (logMAR) units for statistical analysis. Axial length was measured by an IOL-Master, and the presence of posterior staphyloma was observed by B-scan ultrasonography. Spectral domain OCT (SD-OCT) (Heidelberg Engineering, Heidelberg, Germany) was performed on the MTM eyes. Two subtypes of retinoschisis were recorded: outer schisis (occurring in the outer plexiform layer) and inner schisis (occurring in the inner plexiform layer and/or ILM detachment). The central foveal thickness (CFT) was measured and defined as the distance between the hyperreflective band of the ILM and the hyperreflective band of the retinal pigment epithelium through the central fovea and averaging the values measured in the horizontal and vertical A-scans. Then, we determined the most prominent location (upper and lower vascular arcades or their branch vessels, the fovea or the posterior staphyloma) of outer schisis within a diameter of 10 mm centered on the fovea from OCT images, in which the maximum neural thickness (MNT), defined as the distance between the hyperreflective band of the ILM and the
hyperreflective band of the retinal pigment epithelium, was measured. Partial PVD, an epimacular membrane, an LMH and the integrity (intact, partially continuous, or absent) of the EZ were examined by OCT, and based on the definition of Shimada et al\textsuperscript{15}, the progression of MTM was characterized as the height of outer schisis increasing by 100 μm, expansion in the extent of outer schisis, or the development of an LMH, FD or a full-thickness macular hole. MTM improvement was termed a reduction in the height or extent of outer schisis unaccompanied with the development of an LMH, FD or a full-thickness macular hole. Cases that did not meet the standard of progression or improvement were treated as stable. The follow-up time lasted for at least two years. BCVA measurements and OCT examinations were performed in all patients at every visit.

**Statistical Analysis**

Statistical analysis was performed using SAS software version 9.13 (SAS Institute Inc., Chicago, IL). Data are depicted as the mean ± standard deviation (SD). The one-way analysis of variance was used for the comparison of continuous variables, and the chi-square test was used for the statistical analysis of count data. If the sample size in the group was 5, Fisher’s exact test was performed. If the data did not conform to a normal distribution, the Kruskal-Wallis test was performed. We determined the factors influencing BCVA at the last visit using multivariate regression analysis. When $P$ was <0.05, the difference was considered statistically significant.

**Results**

**Baseline Characteristics**

We enrolled 113 patients (147 eyes) with MTM in this study, and the mean follow-up time was 38.2 ± 11.1 months. The baseline characteristics of all patients are listed in Table 1.

**Changes in Morphological Characteristics by OCT**

There were 18, 28, 9, 53 and 39 eyes in stages S0, S1, S2, S3, and S4 of MTM, respectively, at the last visit. In the follow-up period, 58 eyes (39.5%) progressed (Fig. 1 and Fig. 2), 66 eyes (44.9%) remained stable (Fig. 3), and 23 eyes (15.6%) experienced improvement (Fig. 4). A full-thickness macular hole was found in 1 eye, an LMH developed in 4 eyes, and FD developed in 7 eyes. At the last visit, ILM detachment was disrupted or disappeared in 5 eyes that did not experience progression.

**Risk Factors for Progression**

We divided the patients into three groups, progressive, stable and improved, to explore the possible risk factors affecting progression (Table 2). When we determined the influence of the subgroup, subtype and location of retinoschisis on progression, 24 eyes with S0 at baseline were excluded. The progression rate in eyes with outer schisis most prominently located in the fovea or staphyloma (51.4%) was significantly higher than that in eyes in which outer schisis was located in the vascular arcades (22.6%) ($P = 0.0006$).
Eyes with partial PVD during the follow-up had a higher proportion of progression (58.1%) than those without PVD (31.7%) \((P = 0.0461)\). In contrast, age, axial length, presence of posterior staphyloma, epimacular membrane, subgroup or subtype of schisis were not different among the three groups \((P > 0.05)\).

**Changes in BCVA and Predictive Factors for Visual Acuity**

LogMAR BCVA at the last follow-up was worse than that at baseline in all patients \((P = 0.0420)\), in patients who were older than 65 years, and in patients with defects in the EZ \((P=0.0281, \text{ and } P = 0.0433, \text{ respectively})\) (Table 3). In the multiple linear regression analysis, logMAR BCVA \((P < 0.0001)\) and a defect in the EZ at baseline \((P = 0.0259)\) were significantly correlated with logMAR BCVA at the last follow-up (Table 4).

**Discussion**

Our study found that 58/147 eyes (39.5%) with MTM progressed over the 2-year follow-up period, and eyes with retinoschisis prominently located in the fovea or posterior staphyloma were prone to progression. Vitreoretinal traction may be one of the risk factors for progression, and the integrity of the EZ was considered to be a main factor affecting visual prognosis.

The progression rate of MTM or retinoschisis varies, ranging between 11.6% and 68.9%, according to different standards\(^{14,15}\). Gaucher et al\(^{14}\) found that 68.9% (20/29 eyes) of the eyes with foveoschisis progressed with enlargement of retinal cleavage and/or visual decline during a mean follow-up period of 31.2 months. In our retrospective study, 48/123 eyes (39.0%) with MTM progressed based on the criteria of morphological changes of MTM described by Shimada et al\(^{15}\), even when 24 S0 eyes were excluded at baseline, which was much higher than that reported by Shimada et al\(^{15}\) (11.6%). The different progression rates may be related to the difference in age, the status of vitreomacular traction, the involved location and area of schisis or the follow-up period in these studies.

Our results showed that eyes with outer schisis prominently located in the fovea or posterior staphyloma had a higher risk of progression than those in which outer schisis was located in the vascular areas. The mechanism of retinoschisis is complicated, and the growth of the eyeball is considered an initial factor in the pathogenesis of foveoschisis\(^{18}\). Shinohara et al\(^{19}\) suggested that posterior staphyloma may act as the main cause of retinoschisis located within the area of the posterior staphyloma by ultrawide-field swept-source OCT, and outer and inner retinoschisis located in vascular arcades may be caused mainly by vitreous adhesion in the blood vessels of the retina and the tractional force of the retinal arterioles\(^{20}\). However, after reaching the loose outer retina through the transmission of intraretinal tissues, the inner traction may become weak, and the inner retina may play a “shock-absorbing”-like role, while outward traction is direct and persistent, which may be the reason why outer retinoschisis at the blood vessel develops more slowly than that in the fovea. In our series, almost all cases of inner schisis were confined to the paravascular area adjacent to the superior or inferior temporal vascular arcades, which may result
from tangential traction of the retinal arterioles. The presence of inner schisis did not significantly promote the progression of outer schisis in different locations regardless of the presence of ILM detachment, revealing that the retina itself may play a secondary role in the occurrence and development of outer schisis. In this study, MTM with partial PVD during follow-up was more likely to progress. Shinohara et al\textsuperscript{19} also proposed that the posterior vitreous extensively adhered to the retinal surface, exerting persistent inward traction in eyes of retinoschisis, which may contribute to the development of retinoschisis without posterior staphyloma. Additionally, we found that the stage of schisis had no significant influence on the risk of progression. Shimada et al\textsuperscript{15} and Cheng et al\textsuperscript{16} suggested that the status of S4 eyes was unstable and had a high risk for deterioration. Cai et al\textsuperscript{12} also believed that as long as the schisis involved the fovea, regardless of whether it extended to the entire macula, the possibility of progression was relatively high. Therefore, attention should be paid to each stage of MTM, especially in eyes with vitreomacular adhesion, and appropriate interventions should be given before MTM develops. Meanwhile, we observed that eyes in which ILM detachment was disrupted or disappeared did not progress. In foveoschisis, Müller cells and astrocytes proliferate to produce tangential stress to separate the intraretinal tissues\textsuperscript{10}. Once ILM detachment is disrupted, tangential stress is released, and the splitting cavity may shrink or even completely disappear.

In this study, patients who were older than 65 years, who had EZ defects at the first visit had poor final BCVA, and further multiple linear regression analysis showed that first-visit visual acuity and EZ defects are factors affecting visual prognosis. The interruption or absence of reflection EZ in the outer retina of retinoschisis may represent the abnormal energy metabolism of the elongated mitochondria of the photoreceptors, which means that visual function is impaired. Damage to EZ is not uncommon in patients with retinoschisis. Sayanagi et al\textsuperscript{21,22} reported that the incidence of EZ defects in foveoschisis is between 29\% and 38\%. Studies on the influencing factors of vision recovery after vitrectomy for foveoschisis have confirmed that the recovery of the EZ has a significant correlation with postoperative vision recovery\textsuperscript{23,24}. Cheng et al\textsuperscript{16} reported that 6/14 (42.9\%) patients with retinoschisis who had $\geq 2$ lines of vision loss in their natural courses had EZ disruption at the first visit. We speculate that some elderly patients had a long course of schisis, and the baseline EZ was not intact or even absent, the photoreceptors were damaged severely over time, which subsequently caused poor vision. Even in pseudophakic eyes, the improvement in their visual function was not satisfactory after cataract surgery.

Our study has some limitations. First, the occurrence and development of cataracts in some elderly patients who experienced a long follow-up time inevitably affected visual acuity, and an electrophysiological examination may be required as a good supplement to evaluate visual function and prognosis. Second, the exertion of centrifugal vertical and tangential forces may cause an increase in the height and expansion of the extent of retinoschisis, respectively. In future studies, if we can increase the sample size, quantify the extent of the schisis, supplement the criteria for the progression of MTM, and further explore the equivalence of the impact of the expansion of the extent and the increase in height of the schisis on the progression of MTM, it may be of some significance to investigate its pathogenesis.
In summary, MTM had a high progression rate during the follow-up. MTM progression was related to the location of retinoschisis. Vitreomacular traction may play an important role in the natural course of MTM. Defects in the EZ have a negative influence on visual prognosis. MTM with schisis prominent in the fovea or posterior staphyloma and with obvious vitreomacular traction should be regularly followed, morphological changes in the outer retina should be considered, and surgical intervention should be carried out once the disease worsens.

**Abbreviations**

MTM: myopic traction maculopathy; EZ: ellipsoid zone; LMH: lamellar macular hole; PVD: posterior vitreous detachment; ILM: internal limiting membrane; BCVA: best-corrected visual acuity; Log MAR: logarithmic minimal angle of resolution; SD-OCT: Spectral domain OCT; CFT: central foveal thickness; MNT: maximum neural thickness; SD: standard deviation.

**Declarations**

**Ethics approval and consent to participate:** The study adhered to the guidelines of the Helsinki Declaration and had the approval of the Ethics Committee of Sixth People's Hospital Affiliated to Shanghai Jiao Tong University, Shanghai, China (Approval NO.: 2020-073). The study was registered in the Chinese clinical trial registry (http://www.chictr.org.cn/, Registration number: ChiCTR2000038824). All patients signed written informed consent for participation.

**Consent for publication:** All presentations of case reports have consent for publication.

**Availability of data and materials:** The data used and analyzed during the current study are available from the corresponding author on reasonable request. The data supporting our findings can also be found in the Chinese clinical trial registry (http://www.chictr.org.cn/, Registration number: ChiCTR2000038824).

**Competing interests:** The authors declare that they have no competing interests.

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**Authors' contributions:** Conceived and designed the experiments: SL, QW. Performed the experiments: SL, XW, XC. Analysed the data: SL, TL, CL. Contributed reagents/materials/analysis tools: BL, YC. Wrote the paper: SL. Discussion of the results and critical review of the manuscript: SL, QW. All authors read and approved the final manuscript.

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Tables

Table 1 Demographics and Baseline Characteristics of Patients with Myopic Traction Maculopathy
| Variable                                      | Value                      |
|----------------------------------------------|----------------------------|
| No. of subjects                              | 113                        |
| No. of eyes                                  | 147                        |
| Sex, male/female                             | 38/75                      |
| Age (years), mean ± SD (range)               | 64.6 ± 9.35 (34 to 83)     |
| Refractive error (D), mean ± SD (range)      | -11.6 ± 3.87 (-6.0 to -23) |
| (phakic eyes, n=89)                          |                            |
| Axial length (mm), mean ± SD (range)         | 29.3 ± 1.74 (26.00 to 36.03)|
| BCVA in Snellen equivalent                   | 20/40±20/80-20/1000-20/20  |
| BCVA in logMAR, mean ± SD                    | 0.41±0.37                  |
| Posterior staphyloma (n)                     | 112                        |
| Pseudophakic eyes(n)                         | 58                         |
| Follow-up duration (months)                  | 38.2 ± 11.1 (24 to 71)     |
| Mean ± SD (range)                            |                            |
| Schisis group (n)                            |                            |
| S0                                           | 24                         |
| S1                                           | 29                         |
| S2                                           | 11                         |
| S3                                           | 52                         |
| S4                                           | 31                         |
| The most prominent location of the outer schisis (n) |                |
| Paravascular                                 | 53                         |
| Fovea or posterior staphyloma                | 70                         |
| Schisis subtype (n)                          |                            |
| Outer schisis                                | 75                         |
| Outer and inner schisis                      | 48                         |
| Partial PVD (n)                              | 39                         |
| Epimacular membrane (n)                      | 71                         |
| Factor                  | Value                  |
|------------------------|------------------------|
| LMH (n)                | 26                     |
| CFT (µm)               | 272.3 ± 118.7 112 - 732.5  |
| MNT (µm)               | 420.2 ± 132.2 206 - 711  |
| Defect of EZ (n)       | 21                     |

SD, standard deviation; D, diopter; LogMAR, logarithm of the minimal angle of resolution; PVD, posterior vitreous detachment; LMH, lamellar macular hole; EZ, ellipsoid zone; CFT, central foveal thickness.

a 24 eyes with S0 stage were excluded.

Table 2 Factors Associated With Evolution of Myopic Traction Maculopathy
| Factor                                      | Progressed | Stable | Improved | P value  |
|--------------------------------------------|------------|--------|----------|----------|
| Age (years), mean ± SD                     | 64.7±10.0  | 64.5±9.2| 61.6±7.1 | 0.1012*  |
| Axial length (mm), mean ± SD               | 29.4±1.4   | 29.3±1.8| 29.4±2.2 | 0.0559*  |
| Posterior staphyloma                       |            |        |          | 0.4642** |
| Present                                    | 43         | 50     | 19       |          |
| Absent                                     | 15         | 16     | 4        |          |
| Schisis subgroup (n)                        |            |        |          | 0.5490** |
| S1                                         | 11         | 11     | 7        |          |
| S2                                         | 4          | 6      | 1        |          |
| S3                                         | 23         | 18     | 11       |          |
| S4                                         | 10         | 17     | 4        |          |
| Schisis subtype (n)                        |            |        |          | 0.2317** |
| Outer schisis                              | 34         | 27     | 14       |          |
| Outer and inner schisis                    | 14         | 25     | 9        |          |
| The most prominent location of outer schisis (n)* |            |        |          | 0.0006** |
| Paravascularar                             | 12         | 26     | 15       |          |
| Fovea or posterior staphyloma              | 36         | 26     | 8        |          |
| Epimacular membrane during a follow-up (n) |            |        |          | 0.5788** |
| Present                                    | 35         | 38     | 11       |          |
| Absent                                     | 28         | 23     | 12       |          |
| Partial PVD during a follow-up(n)          |            |        |          | 0.0461** |
| Present                                    | 25         | 11     | 7        |          |
| Absent                                     | 33         | 55     | 16       |          |
| LMH (n)                                    |            |        |          | 0.3893** |
| Present                                    | 11         | 13     | 2        |          |
| Absent                                     | 47         | 53     | 21       |          |
SD, standard deviation; PVD, posterior vitreous detachment; LMH, lamellar macular hole.

a 24 eyes with S0 stage were excluded

*, Significant difference among group means for age and axial length via one-way analysis of variance ($P<0.05$)

**, Significant difference among three groups for the other factors via chi-square test ($P<0.05$)

Table 3 Comparison of visual acuity at first and last visits with different baseline characteristics
| Characteristics          | BCVA at First Visit | BCVA at Last Visit | P value* |
|-------------------------|--------------------|--------------------|----------|
|                         | Mean ± SD, logMAR  | Mean ± SD, logMAR  |          |
| All patients            | 0.40±0.37          | 0.52±0.48          | 0.0420   |
| Age                     |                    |                    |          |
| ≥65years                | 0.48±0.38          | 0.66±0.51          | 0.0281   |
| <65years                | 0.34±0.36          | 0.41±0.43          | 0.3255   |
| Axial length            |                    |                    |          |
| ≥30mm                   | 0.42±0.43          | 0.59±0.57          | 0.1762   |
| <30mm                   | 0.39±0.34          | 0.49±0.43          | 0.1187   |
| Posterior staphyloma    |                    |                    |          |
| Present                 | 0.42±0.37          | 0.56±0.51          | 0.0761   |
| Absent                  | 0.34±0.39          | 0.42±0.38          | 0.2909   |
| Lamellar macular hole   |                    |                    |          |
| Present                 | 0.71±0.48          | 0.91±0.58          | 0.2365   |
| Absent                  | 0.34±0.31          | 0.44±0.42          | 0.0640   |
| CFT                     |                    |                    |          |
| ≥300μm                  | 0.53±0.43          | 0.69±0.56          | 0.2966   |
| <300μm                  | 0.35±0.33          | 0.45±0.43          | 0.0532   |
| EZ                      | Intact or partially continuous | 0.34±0.31          | 0.42±0.37 | 0.0974 |
|                         | Defect             | 0.73±0.48          | 1.01±0.61 | 0.0433 |

LogMAR, logarithm of the minimal angle of resolution; CFT, central foveal thickness; EZ, ellipsoid zone.

* Significant difference between the group means at the first and last visit via Kruskal-Wallis test (P<0.05)

Table 4 Multiple Linear Regression Analysis of Baseline Characteristics Associated with Visual Acuity at Final Visit
| Characteristics            | Standardized estimate | $P$ value* |
|---------------------------|-----------------------|------------|
| Age (years)               | 0.07584               | 0.1506     |
| Axial Length (mm)         | 0.03997               | 0.4146     |
| BCVA (LogMAR)             | 0.69692               | <0.0001    |
| Posterior Staphyloma      | 0.02664               | 0.5909     |
| LMH                       | -0.00257              | 0.9675     |
| Schisis Subgroup          | 0.08479               | 0.2121     |
| Schisis Subtype           | -0.04117              | 0.4722     |
| CFTμm                      | 0.04227               | 0.5282     |
| Defect of EZ              | -0.12775              | 0.0259     |

LogMAR, logarithm of the minimal angle of resolution; CFT, central foveal thickness; EZ, ellipsoid zone.

* Significant difference via multiple linear regression analysis ($P<0.05$)