Distribution and Severity of Myopic Maculopathy Among Highly Myopic Eyes

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PURPOSE. The purpose of this study was to document the distribution of the severity of myopic maculopathy in a cohort of highly myopic patients and to explore the associated risk factors.

METHODS. A total of 890 Chinese highly myopes aged between 7 and 70 years (median age 19 years) and with spherical refraction −6.00 diopter (D) or worse in both eyes were investigated. All participants underwent detailed ophthalmic examination. Myopic maculopathy was graded into 5 categories according to the International Photographic Classification and Grading System using color fundus photographs: category 0, no myopic retinal lesions, category 1, tessellated fundus only; category 2, diffuse chorioretinal atrophy; category 3, patchy chorioretinal atrophy; category 4, macular atrophy. Category 2 or greater were further classified as clinically significant myopic maculopathy (CSMM).

RESULTS. Data from 884 of 890 right eyes were available for analysis. The proportions of category 1, category 2, category 3, and category 4 were 20.0% (177 eyes), 20.2% (178 eyes), 2.6% (23 eyes), and 0.2% (2 eyes), respectively. The proportion of CSMM increased with more myopic refraction (odds ratio 1.57; 95% confidence interval: 1.46-1.68), longer axial length (odds ratio 2.97; 95% confidence interval: 2.50–3.53), and older age (40–70 years compared to 12–18 years, odds ratio 6.77; 95% confidence interval: 3.61–12.70). However, there was a higher proportion of CSMM in children aged 7 to 11 years than those aged 12 to 18 years (20.9% vs. 11.0%, $P = 0.008$).

CONCLUSIONS. Older age, more myopic refraction, and longer axial length were associated with more severe myopic maculopathy. Although CSMM was uncommon among younger participants, children with early-onset high myopia have a disproportionately increased risk.

Keywords: high myopia, myopic maculopathy, risk factors

In the past 50 years, the prevalence of myopia has risen dramatically, and myopia has become a global public health problem, particularly in East Asia and Southeast Asia.[1–3] In some urban areas, 80% to 90% of young adults have myopia, and up to 20% have high myopia (defined as –6 diopters [D] or worse).[4–7] High myopia often leads to pathologic changes, such as glaucoma, retinal detachment, myopic maculopathy, and myopic optic neuropathy.[8] Of these pathologic changes, myopic maculopathy is the most common[8–11] and is one of the major causes of uncorrectable visual impairment and blindness in the elderly population.[12–15] With the increasing prevalence of myopia, the prevalence of high myopia is also on the rise and is likely to be associated with increasing rates of myopic maculopathy in the near future.[16]

Myopic maculopathy was also termed as "myopic retinopathy" or "myopic macular degeneration" with the associated fundus lesions including tessellated fundus, chorioretinal atrophy, lacquer cracks, choroidal neovascularization (CNV), Fuchs' spot, CNV-related macular atrophy, posterior staphyloma, and optic nerve crescent.[3,9,10,17–20] Although there is no consensus on the classification of myopic maculopathy, the classification system proposed by Avila et al.[18] in 1984 was used in many studies.[11,21–24]

However, Hayashi et al.[20] argued that this widely used classification was not based on the natural history of myopic maculopathy and that certain cases could not be categorized using this system. Recently, based on the long-term clinical observations of myopic maculopathy and its pattern of progression, Ohno-Matsui and colleagues[25] proposed a simplified classification system, named the International Photographic Classification and Grading System for myopic maculopathy. By using this new grading system, Yan et al.[26] investigated the 10-year progression pattern of myopic maculopathy in an older Chinese highly myopic population, and Fang et al.[27] reported the 18-year progression of the myopic maculopathy in a Japanese high myopia cohort. These longitudinal studies demonstrated the practicability of the new grading system and are very helpful for clinicians to understand the disease course and to guide treatment strategy. This new grading system has

the potential to serve as a universal tool for clinical and epidemiological studies of myopic maculopathy.

In this study, we use this new tool to categorize the cases observed in a large-scale high myopia cohort. We describe the distribution of myopic maculopathy and explore associated risk factors among highly myopic eyes.

METHODS

Study Participants

The participants in this study were from the Zhongshan Ophthalmic Center-Brien Holden Vision Institute high myopia cohort study, which were recruited consecutively through the optometry clinic and community screening at Zhongshan Ophthalmic Center in Guangzhou, China. The details of the inclusion and exclusion criteria of the study have been described elsewhere.[28] Briefly, individuals aged between 7 and 70 years, with spherical power −6.00 D or worse in both eyes were invited to participate in the study. The exclusion criteria were any history of refractive or intraocular surgery, media opacity, secondary myopia, complications with autoimmune disease, or any severe systemic problems. In the present study, eyes with coexisting retinal pathology such as multifocal choroiditis and punctate inner choroidopathy were also excluded. The study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of Zhongshan Ophthalmic Center. Written consent was obtained from participants or guardians of participants who were aged younger than 18 years.

Ophthalmic Examinations

All participants underwent a comprehensive ocular examination. Axial length (AL) was measured using the Lenstar LS900 (Haag-Streit AG, Koeniz, Switzerland) before cycloplegia. If the AL was out of the measurement range (greater than 32 mm), IOL Master (Carl Zeiss Meditec, Jena, Germany) was used. After complete cycloplegia, refraction data were collected with an autorefractor (KR8800; Topcon, Tokyo, Japan). A digital camera (Canon CX-1; Canon Corp., Tokyo, Japan) was used to take 2-field 45° fundus photos (1 macular-centered and 1 optic disc–centered) of both eyes.

Definitions and Classification of Myopic Maculopathy

The International Photographic Classification and Grading System for Myopic Maculopathy was adopted in the analysis of color fundus photos.[25] In this grading system, myopic maculopathy was classified in order of increasing severity into the following five categories: category 0, no myopic retinal degenerative lesions (C0); category 1, tessellated fundus only (C1); category 2, diffuse chorioretinal atrophy (C2); category 3, patchy chorioretinal atrophy (C3); category 4, macular atrophy (C4). Lacquer cracks, myopic CNV, and Fuchs' spot were identified as "plus" lesions. The eyes with C2 or greater were classified as clinically significant myopic maculopathy (CSMM). The grading of fundus photos was performed by two masked, trained ophthalmologists (O.X., X.G.), with agreement ranging from 0.60 to 0.70 for the macular categories. In cases of disagreement, the final decision was adjudicated by a senior ophthalmologist (M.H.).

Statistical Analysis

Stata Version 12.0 (Stata Corporation, College Station, TX, USA) was used for all statistical analyses. Refractive error was determined by spherical equivalence (SE), calculated as spherical refraction + 1/2 cylindrical refraction. Age, SE, and AL were presented as medians with 25th and 75th percentile values because the distributions were skewed. The right eyes were arbitrarily chosen for analysis. For comparison of the participants' ages, SE, and AL among macular categories (C0 to C3), the Kruskal-Wallis rank test was used. Pairwise comparisons of the four groups (C0 to C3) were made using the Mann-Whitney test. C4 was not included in the statistical analysis because there were only two eyes in this category. Age was categorized into the following four groups: 7 to 11 years (early onset), 12 to 18 years (middle school students), 19 to 39 years (young adults), and 40 to 70 years (older adults). Each age group was divided into three subgroups by SE or AL. SE was categorized into the following three groups: −8.00 D$\sim\leq$−6.00 D, −10.00 D$\sim\leq$−8.00 D, and $\leq$−10.00 D. AL was also categorized into the following three groups: <27.0 mm, 27.0$\sim$<29.0 mm, and $\geq$29.0 mm. The distributions of myopic maculopathy grading by different age and SE or age and AL groups were presented as stacked bar graphs, and the proportions of CSMM among different age groups were analyzed using Pearson chi-square tests followed with Bonferroni adjustment for between-group comparisons. To further compare the proportions of CSMM in the SE subgroups, logistic regression was used. Univariate and multivariate logistic regression was performed to calculate the odds ratio (OR) of potential risk factors of CSMM. A $P < 0.05$ was considered statistically significant.

RESULTS

A total of 890 participants were enrolled in the Zhongshan Ophthalmic Center-Brien Holden Vision Institute high myopia cohort study. Among these participants, 6 with coexisting retinal pathology in the right eyes were excluded, and the data from the remaining 884 participants' right eyes were analyzed.

Ocular Characteristics in Different Category of Myopic Maculopathy

The demographic and clinical characteristics of the participants and their right eyes in different categories of myopic maculopathy are summarized in Table 1. A total of 203 (22.9%) right eyes had CSMM. Plus lesions were identified in 21 eyes (2.4%), including 17 lacquer cracks, 2 CNV, and 2 Fuchs spot. Greater severity of myopic maculopathy was associated with older age, greater SE, and longer AL, but not associated with sex.

Myopic Maculopathy in Different Age and SE or AL

Figure 1 shows the distribution of myopic maculopathy grading by age and SE. CSMM was not common in the younger age group, 7 to 39 years (18.7%), particularly for mild and moderate high myopia (−6.00 to −10.00 D) and was significantly increased in the 40 to 70 years age group (58.3%). However, CSMM was more common in those aged 7 to 11 years when compared with those aged 12 to 18 years (20.9% vs. 11.0%, $P = 0.008$). In adults aged 40 to 70 years and with SE between −6.00 D to −8.00 D, only 9.1% had CSMM. This proportion increased to 40.8% for those with SE between −8.00 D to −10.00 D (odds ratio [OR] 6.87; 95% confidence interval [CI]: 0.77–61.7, $P = 0.085$) and further soared up to 75.8% for those with SE $\leq$−10.00 D (OR 31.42; 95% CI: 3.69–267.6, $P = 0.002$), including 17.2% with patchy chorioretinal atrophy or macular atrophy. Similar variation was also observed on the distribution of myopic macular grading by age and AL (Fig. 2).

TABLE 1. Characteristics of the High Myopic Eyes in Different Levels of Myopic Maculopathy

| Variables | Category of Myopic Maculopathy* | | | | | | | |
	C0	C1	C2	C3	C4†	Total	P
No. of eyes (%)‡	504 (57.0)	177 (20.0)	178 (20.2)	23 (2.6)	2 (0.2)	884	
Age, y; median (P25, P75)	15.8 (13.2, 21.6)	23.5 (17.2, 33.9)	26.4 (16.9, 40.4)	34.0 (27.4, 47.7)	48.3, 54.7	18.5 (14.2, 27.6)	<0.001
Sex							
Male, n (%)	237 (47.0)	81 (45.8)	85 (47.7)	7 (30.4)	0	410 (46.4)	0.467
Female, n (%)	267 (53.0)	96 (54.2)	93 (52.3)	16 (69.6)	2 (100)	474 (53.6)	
SE (D), median (P25, P75)§	−8.13 (−9.25, −7.25)	−9.25 (−12.19, −8.00)	−13.13 (−16.50, −10.25)	−18.25 (−20.50, −16.13)	−20.88, −9.75	−8.88 (−11.50, −7.63)	<0.001
AL (mm), median (P25, P75)‖	26.8 (26.1, 27.5)	27.5 (26.7, 28.4)	29.0 (28.0, 30.3)	30.4 (29.1, 31.3)	31.2, 27.7	27.3 (26.4, 28.3)	<0.001

P25, 25th percentile; P75, 75th percentile.
* C0, normal; C1, tessellated fundus; C2, diffuse chorioretinal atrophy; C3, patchy chorioretinal atrophy; C4, macular atrophy.
† Data from 2 participants are given.
‡ The right eyes of the participants were analyzed in the study.
§ Six eyes could not be measured using an autorefractor (out of the measurement range).
‖ Four missing values (3 eyes had AL out of the measurement range, 1 data missed).

Risk Factors for Myopic Maculopathy

Table 2 shows the logistic regression analysis for the risk factors of CSMM. In the univariate regression, greater myopia, longer AL, and age (7–11 years and ≥19 years) were risk factors for CSMM. The multivariate model 1 (age, sex, and SE as independent variables) and model 2 (age, sex, and AL as independent variables) showed that when compared with normal and tessellated fundus, the odds of developing CSMM increased by 1.57 times for each diopter increase in myopic SE (P < 0.001; model 1) and by 2.97 times for each millimeter increase in AL (P < 0.001; model 2) after adjusting for age and sex. Using the group aged 12 to 18 years as a reference, highly myopic participants in older groups (≥19 years) and the youngest group (7–11 years) had a significantly higher risk of suffering CSMM. In model 2, female sex was a risk factor for CSMM (OR 1.92; 95% CI: 1.25–2.95, P = 0.003), but this effect was not present in model 1 after adjusting for age and SE (OR 0.93; 95% CI: 0.61–1.42, P = 0.747).

DISCUSSION

This study systematically investigated the severity of myopic maculopathy in a Chinese high myopia cohort using the newly developed international classification and grading system. CSMM was seen in 22.9% of highly myopic eyes. Diffuse chorioretinal atrophy (C2) was the predominant category of myopic maculopathy. Older age, longer AL, and more myopic refraction were associated with more severe grading of myopic maculopathy. Interestingly, very young individuals (7–11 years old) with early-onset high myopia had a higher risk of diffuse chorioretinal atrophy than the juvenile high myopia group (12–18 years old).

There is an increased risk of developing CSMM with higher myopia. In our Chinese high myopia cohort, we observed that even in the older adult group (40–70 years), participants with SE between −6.00 D to −8.00 D had a negligible level of CSMM. This proportion increased to 40.8% and 75.8% for those with SE −8.00 D to −10.00 D and SE −10.00 D or worse, respectively. Although the P value for the −8.00 D to −10.00 D subgroup was not statistically significant, the pattern of dose response in this study suggests that highly myopic patients with SE −8.00 D or worse appear to have a clinically increased risk of developing CSMM and therefore SE −8.00 D could be a more appropriate cutoff for pathologic myopia when compared with SE −6.00 D. This cutoff was also chosen as a definition for "pathologic myopia" by the recent International Classification System.[25]

Previous studies showed that myopic maculopathy was uncommon in highly myopic children.[29–31] We found similar results: around 13% of participants aged between 7 to 18 years developed diffuse chorioretinal atrophy (C2). The relatively lower proportion of CSMM and less severe lesions among the school-aged children can be explained by the fact that the duration of the eye ball stretching is not long enough to cause substantial retinal damage.[29–31] In the Beijing Eye Study and Fang's long-term observation of the myopic maculopathy, the progression of myopic maculopathy was associated with older age and longer AL.[26,27] Our results were consistent with the previous studies.

Interestingly, early-onset high myopia cases (group aged 7–11 years) had a higher proportion of diffuse atrophy. Because the prevalence of high myopia is very low in this age group as reported by previous epidemiological studies,[1,4,32,33] early-onset high myopia could be genetic in origin and is different from the acquired high myopia, which is environmentally
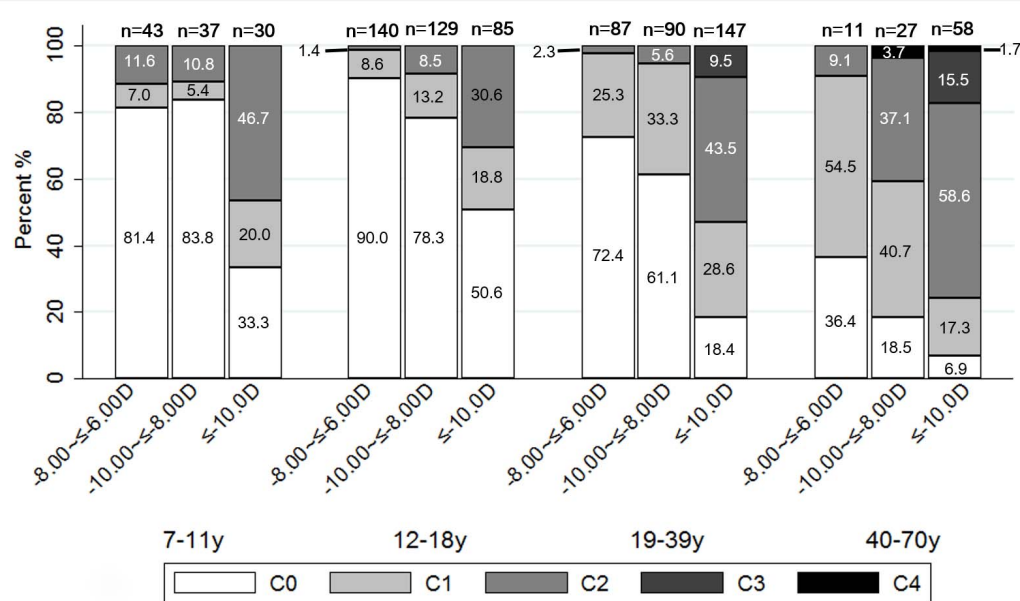
FIGURE 1. Distribution of myopic maculopathy grading according to age and SE.

driven and usually occurs after 11 years of age.[1] The disproportionately higher rate of CSMM in the group aged 7 to 11 years may be a unique clinical characteristic of early-onset high myopia. After entering adolescence (12–18 years old), the prevalence of acquired high myopia increased and diluted the rate of CSMM seen in the early-onset myopia cases. However, with aging and the progression of high myopia, the rate of CSMM increased again, as shown in our study.

In a 20-year longitudinal case series study, Yokoi et al.[34] reported that the presence of peripapillary diffuse atrophy in childhood may be an indicator for the development of advanced CSMM later in adulthood. In the 18-year follow-up

study by Fang et al.,[27] they also proposed that diffuse chorioretinal atrophy occurs primarily in the peripapillary and extends to the macula. However, in their study, the majority of participants with diffuse atrophy at baseline were already adults, which may show different patterns from childhood myopia.[34] In our study, the majority of the diffuse chorioretinal atrophy identified in younger children and teenagers was in the peripapillary region. Further long-term observation of the children in our cohort would help validate the finding from Yokoi et al. It may also serve as a tool to predict the development of pathologic myopia based on their clinical features in childhood.
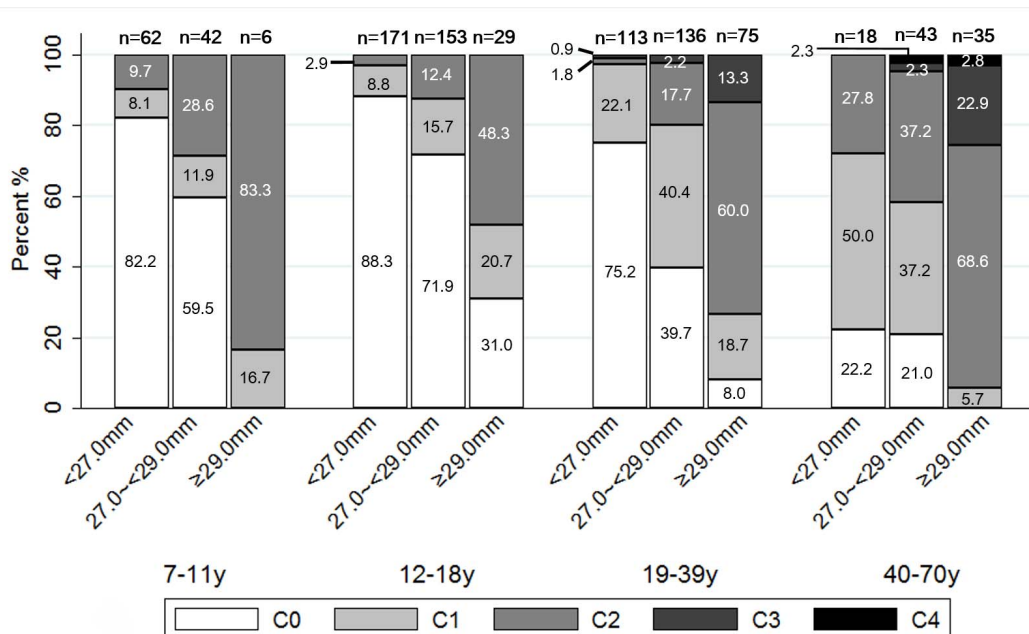

FIGURE 2. Distribution of myopic maculopathy grading according to age and AL.

TABLE 2. Multivariate Logistic Regression Analysis of Risk Factors for CSMM

| | With CSMM | | | | | |
| | Univariate | | Multivariate Model 1* | | Multivariate Model 2† | |
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Age, y						
7–11	2.13 (1.12–3.77)	0.009	2.42 (1.26–4.66)	0.008	4.15 (2.12–8.12)	<0.001
12–18	Reference		Reference		Reference	
19–39	2.87 (1.90–4.35)	<0.001	1.23 (0.73–2.09)	0.441	1.59 (0.95–2.66)	0.080
40–70	11.31 (6.69–19.11)	<0.001	6.77 (3.61–12.70)	<0.001	6.96 (3.66–13.24)	<0.001
Sex						
Male	Reference		Reference		Reference	
Female	1.06 (0.77–1.45)	0.730	0.93 (0.61–1.42)	0.747	1.92 (1.25–2.95)	0.003
SE (−1D)	1.57 (1.47–1.68)	<0.001	1.57 (1.46–1.68)	<0.001	–	–
AL (1 mm)	2.83 (2.43–3.31)	<0.001	–	–	2.97 (2.50–3.53)	<0.001

* Adjusted for age, sex, and SE.
† Adjusted for age, sex, and AL.

The major strengths of our study include the use of a new standardized myopic maculopathy grading scheme and the large sample size of highly myopic participants aged 7 to 70 years. This study cohort was recruited from the optometry service, rather than retinal clinic in ophthalmology unit in the public hospital, and therefore the severity of the cases should be representative of high myopia in general clinical settings. The limitation of this study should be mentioned. First, the cross-sectional study design may not be able to take cohort effects into consideration. Further longitudinal data would help us understand the causal effect and confirm the risk factors for myopic maculopathy. Second, due to the limited field of the two color fundus photographs per eye, posterior staphyloma, which has been reported relevant to myopic maculopathy, was not assessed in this study. Third, we only included Chinese in this high myopia cohort, thus the characteristic of myopic maculopathy observed in this study may not be applied to other races.

In conclusion, our results support the hypothesis that the development of myopic maculopathy in acquired high myopia is time dependent and increases in severity with age attributable to the axial elongation of the eyeball (worse myopic SE).[20] Older age, higher myopic SE, and longer AL were risk factors for more severe myopic maculopathy. Early-onset high myopia (7–11 years old) seems to have a higher risk of developing diffuse atrophy or more severe lesions and may have different etiology in comparison with the later onset cases.

Acknowledgments

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