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Progression of Myopic Maculopathy during 18-Year Follow-up

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Purpose: To examine the progression pattern of myopic maculopathy.

Design: Retrospective, observational case series.

Participants: Highly myopic patients who had been followed up for 10 years or more.

Methods: Using fundus photographs, myopic features were differentiated according to Meta-analysis of Pathologic Myopia (META-PM) Study Group recommendations.

Main Outcome Measures: Progression pattern of maculopathy.

Results: The study included 810 eyes of 432 patients (mean age, 42.3±16.8 years; mean axial length, 28.8±1.9 mm; mean follow-up, 18.7±7.1 years). The progression rate of myopic maculopathy was 47.0 per 1000 eye-years. Within the pathologic myopia (PM) group (n = 521 eyes), progression of myopic maculopathy was associated with female gender (odds ratio [OR], 2.21; $P = 0.001$), older age (OR, 1.03; $P = 0.002$), longer axial length (OR, 1.20; $P = 0.007$), greater axial elongation (OR, 1.45; $P = 0.005$), and development of parapapillary atrophy (PPA; OR, 3.14; $P < 0.001$). Diffuse atrophy, found in 217 eyes without choroidal neovascularization (CNV) or lacquer cracks (LCs) at baseline, progressed in 111 (51%) eyes, leading to macular diffuse atrophy (n = 64; 64/111 or 58%), patchy atrophy (n = 59; 53%), myopic CNV (n = 18; 16%), LCs (n = 9; 5%), and patchy-related macular atrophy (n = 3; 3%). Patchy atrophy, detected in 63 eyes without CNV or LCs at baseline, showed progression in 60 eyes (95%), leading to enlargement of original patchy atrophy (n = 59; 59/60 or 98%), new patchy atrophy (n = 29; 48%), CNV-related macular atrophy (n = 13; 22%), and patchy-related macular atrophy (n = 5; 8%). Of 66 eyes with LCs, 43 eyes (65%) showed progression with development of new patchy atrophy (n = 38; 38/43 or 88%) and new LCs (n = 7; 16%). Reduction in best-corrected visual acuity (BCVA) was associated mainly (all $P < 0.001$) with the development of CNV or CNV-related macular atrophy and enlargement of macular atrophy.

Conclusions: The most frequent progression patterns were an extension of peripapillary diffuse atrophy to macular diffuse atrophy in diffuse atrophy, enlargement of the original atrophic lesion in patchy atrophy, and development of patchy atrophy in LCs. Main risk factors for progression were older age, longer axial length, and development of PPA. *Ophthalmology 2017;■:1–15 © 2017 by the American Academy of Ophthalmology*

Pathologic myopia (PM) is a major cause of irreversible visual impairment worldwide and in particular in East Asian countries.[1–5] In the Tajimi Study,[1] myopic macular degeneration was the leading cause of blindness in Japanese residents 40 years of age and older. In the Beijing Eye Study,[2] degenerative myopia was the major cause of irreversible low vision and blindness. In studies on European[3] and Latin-American[4] populations, myopic macular degeneration ranked as the third most frequent cause of blindness. A recent study of 4582 Chinese American adults 50 years of age or older revealed that the primary cause of visual impairment and blindness was myopic retinopathy.[5]

Longitudinal changes of myopic maculopathy were examined in 3 investigations.[6–8] Two population-based studies[6,7] applying the same definition of myopic maculopathy (i.e., presence of staphylomas, lacquer cracks [LCs], Fuchs spot, myopic choroidal thinning and atrophy) reported a progression rate of myopic maculopathy of 17.4% in an Australian population (the Blue Mountains Eye Study[6]) and of 11% in a Chinese population (the Beijing Eye Study[7]) during 5-year follow-up periods. Retrospectively analyzing the progression pattern in 806 highly myopic eyes of 429 patients with a follow-up of more than 5 years, Hayashi et al[9] found a progression rate of 40%.

Because these previous studies applied different definitions of PM, before the Meta-analysis of Pathologic Myopia (META-PM) Study Group[10,11] proposed a new classification system for myopic maculopathy and because the previous studies either were cross-sectional investigations or had only a relatively short follow-up, we conducted the present study to assess the progression patterns of myopic maculopathy during a follow-up period of more than 10 years. We applied the international photographic classification and grading system for myopic maculopathy developed by the META-PM study.

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Methods

This retrospective observational case series study included patients with high myopia who had been examined and followed-up for at least 10 years in the High Myopia Clinic of the Tokyo Medical and Dental University. The procedures applied in the study were approved by the Ethics Committee of Tokyo Medical and Dental University, adhering to the tenets of Declaration of Helsinki. Signed informed consent documentation was obtained from all participants. High myopia was defined as a refractive error of less than −8.0 diopters (D) or an axial length of 26.5 mm or more. In individuals younger than 5 years, high myopia was defined by a myopic refractive error of less than −4.0 D, and in children 5 to 8 years of age, high myopia was defined by a myopic refractive error of less than −6.0 D.[12] The exclusion criteria were other retinal or choroidal disorders, such as diabetic retinopathy; retinal vascular diseases, including retinal vein occlusions and age-related macular degeneration; poor quality of fundus photographs; and a history of vitreoretinal surgery.

All study participants underwent a detailed ophthalmologic examination at baseline and at each follow-up visit. The examinations included measurements of best-corrected visual acuity (BCVA) using a Landolt C chart, biometry for determination of axial length, fundus examination in medical mydriasis, fluorescein angiography, and color fundus photography. Before 2001, 35-mm slide color films were used to record the fundus images (30° or 50° view). These films were converted into digital photographs. After 2001, digital color fundus photographs were obtained (TRC 50DX retinal camera [Topcon Medical Systems Co, Tokyo, Japan] or VX-10i fundus camera [Kowa Co, Nagoya, Japan]). Axial length was measured by A-scan ultrasonography (Ultrascan; Alcon, Fort Worth, TX) before 2008. Each measurement was repeated 5 times, and the average value was used for the statistical analyses. From 2008 onward, laser interference biometry was applied (IOL Master; Carl Zeiss Co, Oberkochen, Germany).

According to the META-PM Study Group, myopic maculopathy was classified into 5 categories: category 0, no maculopathy; category 1, tessellated fundus; category 2, diffuse choroidal atrophy; category 3, patchy chorioretinal atrophy; and category 4, macular atrophy (Fig 1).[10,11] Three additional features supplementing these categories were defined as plus lesions, including LCs, myopic choroidal neovascularization (CNV), and Fuchs spot. Diffuse choroidal atrophy as assessed on ophthalmoscopy was an ill-defined yellowish lesion in the posterior fundus; patchy atrophy was a grayish-white, well-defined atrophy; and LCs were fine, irregular, yellowish lines often branching and crisscrossing in the fundus (Fig 1).[13] The detection of LC was made on fundus photographs. There were several supplements for classification of maculopathy in the present study. Diffuse choroidal atrophy additionally was subclassified as peripapillary diffuse choroidal atrophy and macular diffuse choroidal atrophy.[14] Patchy atrophy was subclassified based on its location and extent, within the vascular arcades or beyond the arcades. Macular atrophy was subclassified into CNV-related macular atrophy centered on the fovea and expanding centrifugally and into patchy atrophy-related macular atrophy developing outside of the foveal area and enlarging, or coalescing with other patchy atrophies, into the foveal center. The differentiation was based on a history of myopic CNV in the medical records or based on its morphologic features (Fig 2).[13,15] Myopic CNV included 3 stages: the active stage with proliferation of a fibrovascular membrane including CNV, exudation, and hemorrhage; the scar stage exemplified by a Fuchs spot; and the atrophic stage represented by a CNV-related macular atrophy. Thus, Fuchs spots were not analyzed as independent lesions. Posterior staphylomas were not analyzed because the wide macular type of staphylomas as the predominant type[16] did not fit within the 50° conventional fundus photographs.[17]

Based on the META-PM study,[10,11] PM was defined by myopic macular changes equal to or more serious than diffuse choroidal atrophy (category 2) or if CNV or LCs were present. Eyes with typical morphologic features of PM were classified as having PM even if their refractive error or axial lengths did not meet the criteria of high myopia. Progression of myopic maculopathy was characterized by an increase in the category of myopic maculopathy, development of a plus lesion, enlargement of a patchy atrophy or macular atrophy, increase in the number of lesions, or progression of peripapillary diffuse choroidal atrophy to macular diffuse choroidal atrophy, which was the only criteria for enlargement of diffuse atrophy. Development or enlargement of combined parapapillary γ and δ zones (parapapillary atrophy) also was noted.[18] Because the various photographic technologies and magnification factors differed between the baseline examination and the last visit, we used the qualitative analysis for comparing assessed changes in the development or enlargement of parapapillary atrophy between baseline and the last visit qualitatively in a yes-or-no manner. All fundus photographs obtained at the initial visit and at the last visit were examined independently by 3 specialists (Y.F., N.N., K.O.-M.). In the case of disagreement, a panel decision for final agreement was made. Because of the retrospective study design, the follow-up period was not consistent among the study participants; thus, the rate of progression was expressed as eye-years (calculated as the ratio of the number of events divided by the sum of the eyes' follow-up time) as recommended by Jabs.[19] Because multiple patterns of development and progression of myopic maculopathy occurred during the follow-up of more than 10 years, we used the follow-up time when the first progression event occurred for the calculation of eye-years.

In the statistical analysis, we first described the distribution of the main parameters by calculating their means and standard deviations. The comparisons of groups in age, axial length, refractive error, and visual acuity were performed in a univariate analysis using the Mann−Whitney U test. Frequency and gender distribution were compared using the chi-square test. Multivariate binary regression analysis was performed with the backward stepwise mode with the occurrence of progression of myopic maculopathy as the dependent variable and other parameters such as gender, age at baseline, follow-up duration, axial length at baseline, and axial elongation during the study period as independent variables. We calculated the odds ratios (ORs) and their 95% confidence intervals (CIs). A 1-way analysis of variance with least significant difference multiple comparisons tests was performed to compare age and axial length between the various categories of myopic maculopathy. The F test's score was recorded for the results of the 1-way analysis of variance. A P value of less than 0.05 was taken to be statistically significant. All statistical analyses were performed with the statistical package SPSS version 22.0 (IBM-SPSS, Chicago, IL).

Results

Of the 3236 highly myopic patients (6174 eyes) who had been examined at least once at the High Myopia Clinic of Tokyo Medical and Dental University, 626 patients (1211 eyes) did not return for a follow-up. Of the remaining 2610 patients (80.7%), 609 patients (1175 eyes) had a follow-up of less than 2 years, 546 patients (1039 eyes) had a follow-up of 2 years or more but less than 4 years, 431 patients (815 eyes) had a follow-up of 4 years or more but less than 6 years, 343 patients (642 eyes) had a follow-up of 6 years or more but less than 8 years, and 176 patients (335