Myopic Macular Atrophy in the Two-Continent Population-Based Study

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Purpose. To examine the prevalence of Bruch's membrane defects (BMDs) and subretinal proliferations (SRPs) in highly myopic eyes with myopic macular atrophy (myopic macular degeneration [MMD] stage 4) and myopic patchy atrophies (MMD stage 3) in three ethnically different cohorts recruited in a population-based manner.

Methods. The Ural Eye and Medical Study (UEMS) and Beijing Eye Study (BES) included individuals aged 40+ years, and the Ural Very Old Study (UVOS) examined individuals aged 85+ years. Main outcome measures were the prevalence of BMDs and SRPs.

Results. Among 5794 UEMS participants, 19 eyes had MMD stage 4, with 17 (89%) eyes showing a foveal BMD; two eyes could not fully be explored. All 19 eyes showed localized SRPs. Among 21 eyes with MMD stage 3, BMD and SRP prevalence was 9 of 21 (44%) and 7 of 21 (33%), respectively. Among 930 UVOS participants, 17 eyes had MMD stage 4, with 16 (94%) eyes showing foveal BMDs and SRPs; one eye could not be assessed. Among 18 eyes with MMD stage 3, BMD and SRP prevalence was 3 of 18 (17%) and 2 of 18 (11%), respectively. Among 3468 BES participants, 8 eyes had MMD stage 4, with all eyes showing foveal BMDs and SRPs. Among 14 eyes with MMD stage 3, BMD and SRP prevalence was 10 of 14 (71%) and 7 of 21 (33%), respectively.

Conclusions. All eyes with assessable myopic macular atrophy showed foveal BMDs associated with SRPs, while patchy atrophies could be differentiated into those with BMDs and SRPs and those without BMDs and without SRPs. Independent of the MMD stage, the prevalences of BMDs and SRPs were highly significantly associated with each other.

Keywords: myopic macular degeneration, myopic macular atrophy, myopia, high myopia

Myopic macular degeneration (MMD) has been graded into four stages, with stage 3 showing patchy atrophies in the parafoveal region and stage 4 characterized by "macular atrophy" in the foveal center.[1] According to clinical and histologic studies, patchy atrophies and macular atrophies consist of an almost circular defect in the retinal pigment epithelium (RPE) layer, often surrounding a smaller defect in Bruch's membrane (BM) in its center.[2–4] In the middle of patchy atrophies, in association with the absence of BM in those with a central BM defect (BMD), the choriocapillaris and the layer of the middle-sized choroidal vessels are totally absent, while the large choroidal vessel layer can be scarcely present. On the inner side of the patchy atrophies and macular atrophies, in direction to the vitreous cavity, the RPE defect usually surrounds a smaller defect of the photoreceptor layer. In the case of patchy atrophies, by definition located outside of the foveal center, the defect in the photoreceptor layer encloses a smaller defect in the outer plexiform layer and in the inner nuclear layer.[2,4] The patchy atrophies are covered by the retinal nerve fiber layer, which can get so thin that eventually only the inner limiting membrane, as a so-called inner limiting membrane bridge, remains.[5]

The description of the morphology of patchy atrophies and macular atrophies has been based on few recent histomorphometric investigations and relatively few clinical studies so far.[2–15] These studies, however, did not provide information about specific differences in the pathomorphology of patchy atrophies versus macular atrophies, and no information has been available so far about the prevalence of such differences and their potential ethnic associations. The studies refer in particular to the relationship between the occurrence of macular BMDs and the occurrence of subretinal proliferations (SRPs) as a sign of a previous macular

neovascularization. To cite an example, it has remained unclear so far whether myopic macular atrophy and/or patchy atrophies are always associated with BMDs and SRPs, and whether the presence of SRPs in eyes with patchy atrophies has a prognostic importance as a potentially predisposing factor for the progression to stage 4 of MMD with the development of a macular atrophy.[10–12] Assessing a concurrence of BMDs with SRPs would also be of interest when addressing the question whether and under which conditions a direct communication between the choroidal space and the subretinal compartment leads to a choroidal-subretinal neovascularization. We therefore conducted this study to explore the anatomy of myopic macular atrophies and patchy atrophies in population-based studies with different ethnic backgrounds.

Methods

The Ural Eye and Medical Study (UEMS) and the Ural Very Old Study (UVOS) were population-based studies conducted in the Russian republic of Bashkortostan, which is located in the southeastern region of the Volga Federal District in Russia.[15,16] The studies were approved by the Ethics Committee of the Academic Council of the Ufa Eye Research Institute, and informed written consent was obtained from all participants. Study regions were an urban region in Ufa as the capital of Bashkortostan and a rural region in the Karmaskalinsky District at a distance of about 65 km from Ufa. The UEMS, with a minimal age of 40+ years as an inclusion criterion, was conducted from 2015 to 2017, and the UVOS, with a minimal age of 85 years as an inclusion criterion, was carried out from 2017 to 2020. Both studies, the UEMS and the UVOS, had an almost identical study design, and the study regions were similar and overlapping. The study population of the UEMS and the UVOS did not differ markedly in the distribution of sex and age from the entire population of Russia, as examined in the national census conducted in 2021.[17]

The Beijing Eye Study (BES) was a population-based investigation conducted in the Greater Beijing region.[11] The Medical Ethics Committee of Beijing Tongren Hospital approved the study protocol according to the Declaration of Helsinki, and all study participants gave their written informed consent. The study was conducted in four communities in the urban district of Haidian in the north of central Beijing and in three villages in the rural area of Yufa of the Daxing District south of Beijing. Inclusion criteria were living in the study regions and an age of 50+ years.

As described in detail previously, the participants of all studies underwent a standardized interview conducted by trained social workers.[15,16,18] The interview contained questions about the socioeconomic background, diet, smoking, alcohol consumption, physical activity, history of major medical diseases, and others. We applied the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER statement guidelines).[19] A series of ophthalmologic examinations included measurement of best-corrected visual acuity, automatic refractometry, slit-lamp–based biomicroscopy of the anterior and posterior ocular segment, and photography and spectral domain optical coherence tomography (OCT) of the optic nerve head and macula, ocular biometry for measurement of axial length, and pneumotonometry. Applying the recommendations made by the meta-analysis for the Pathologic Myopia Study Group, we defined MMD stage 3 as the occurrence of chorioretinal atrophies (or "patchy atrophies") located in

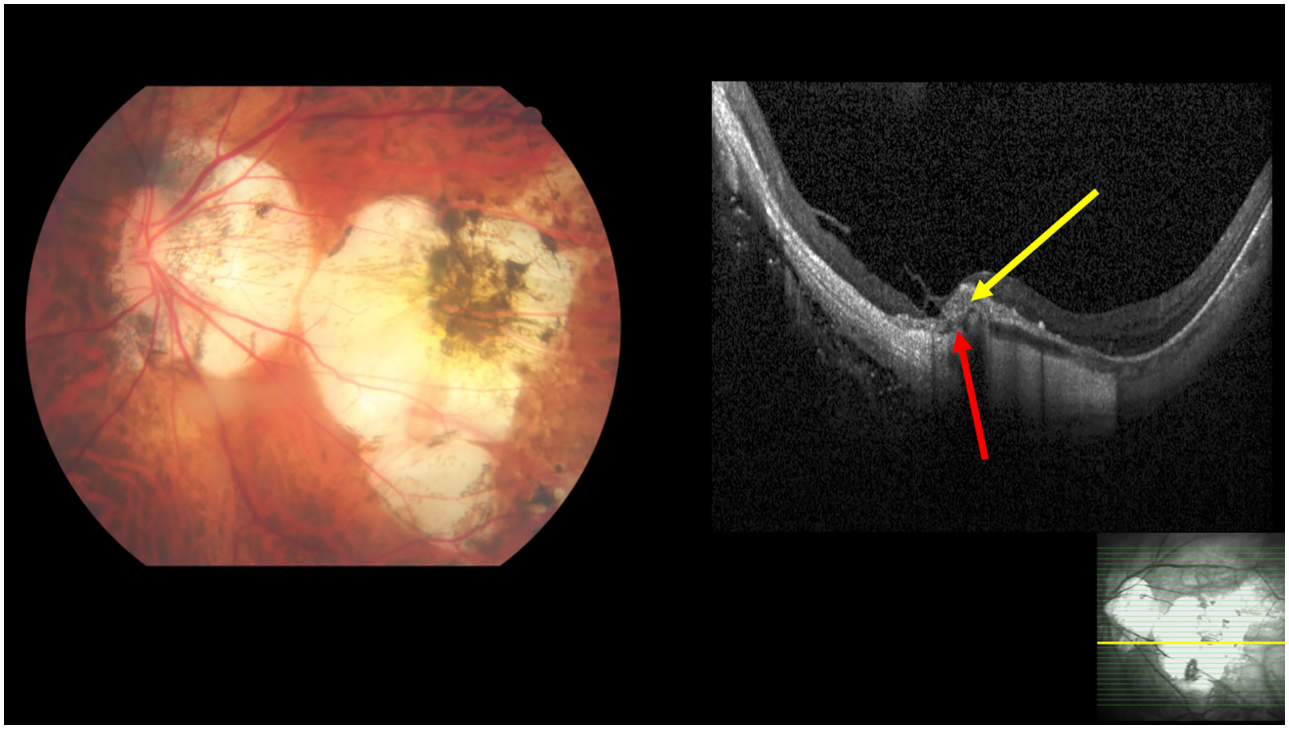

Figure 1. Fundus photograph and optical coherence tomographic image of a highly myopic eye with myopic macular degeneration stage 4, showing a Bruch's membrane defect (*red arrow*) and a subretinal proliferation (*yellow arrow*).

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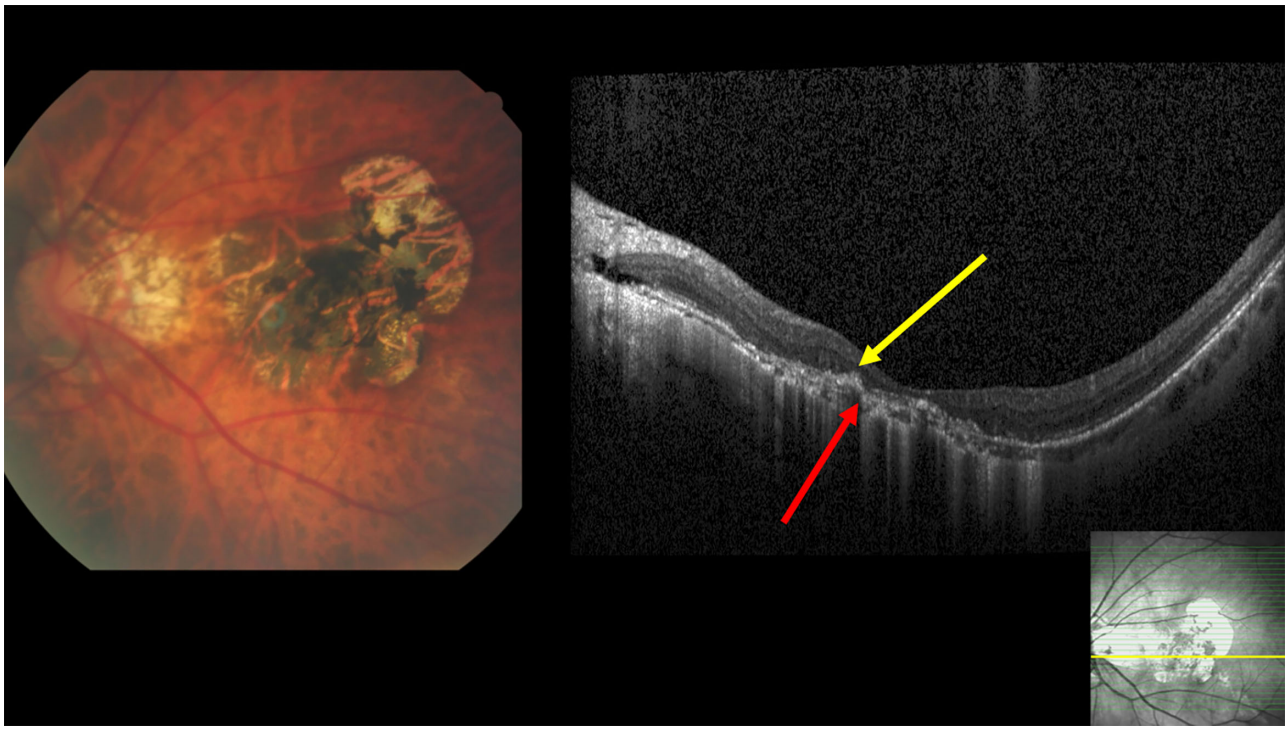

Figure 2. Fundus photograph and optical coherence tomographic image of a highly myopic eye with myopic macular degeneration stage 4, showing a Bruch's membrane defect (*red arrow*) and a subretinal proliferation (*yellow arrow*).

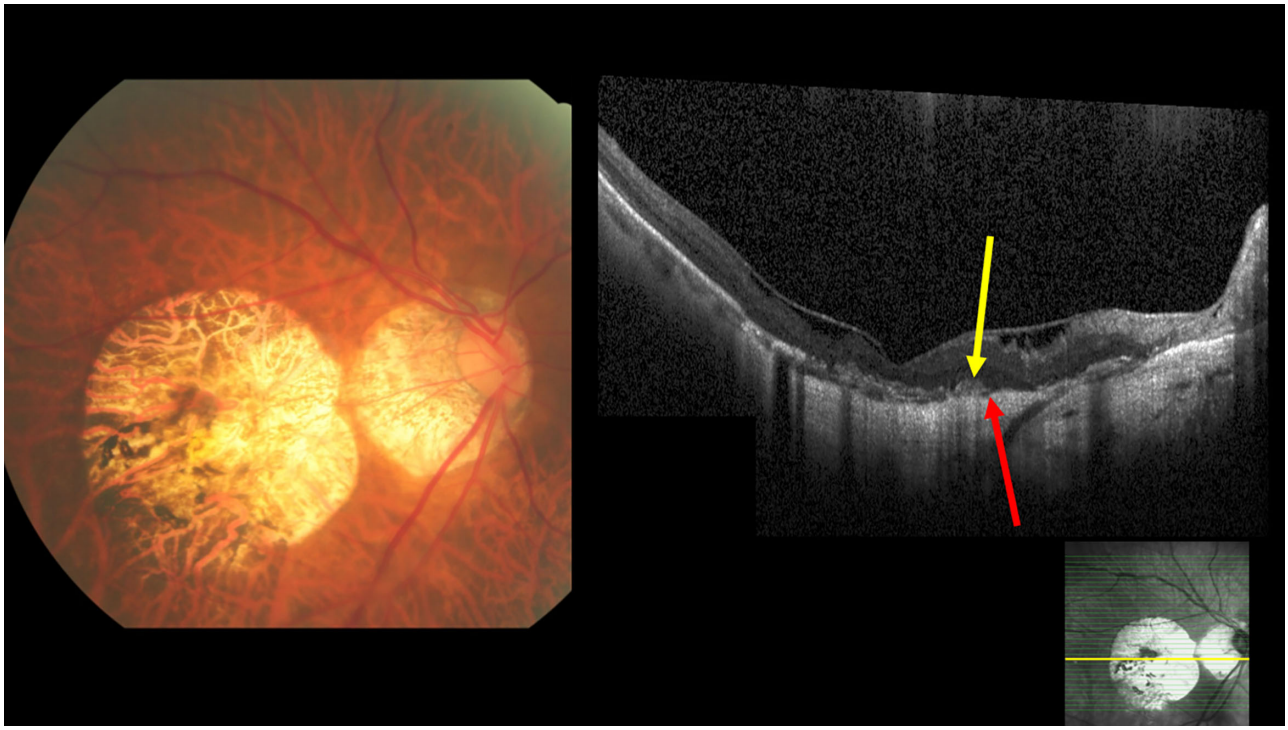

Figure 3. Fundus photograph and optical coherence tomographic image of a highly myopic eye with myopic macular degeneration stage 4, showing a Bruch's membrane defect (*red arrow*) and a subretinal proliferation (*yellow arrow*).

the macular, but extrafoveal, region and as visualized on the color fundus photographs in eyes with an axial length of more than 26.5 mm.[1] Stage 4 of MMD was characterized by a chorioretinal atrophy located in the foveal region.

The fundus images and the OCT images of all study participants with MMD stages 3 and 4 were repeatedly reexamined by experienced clinicians (JBJ, SP-J, RAJ) for the presence of BMDs and SRPs (Figs. 1–5). In the case of

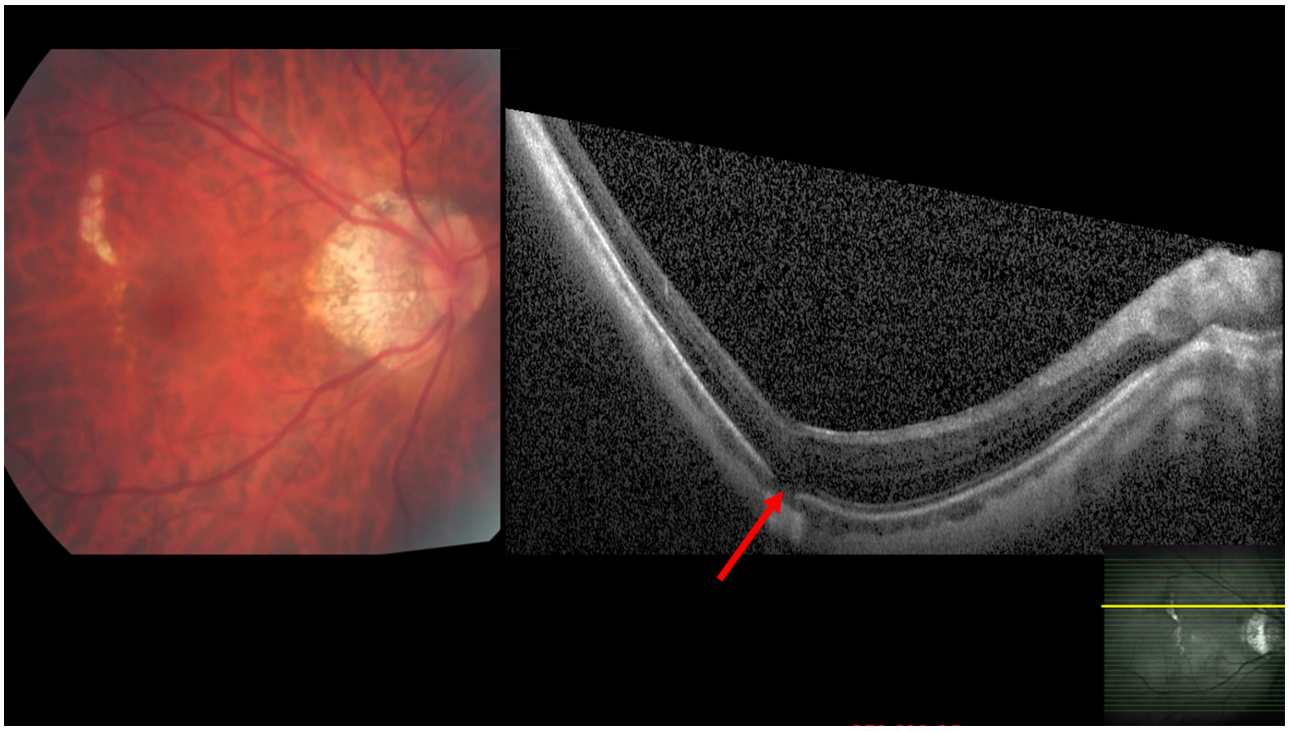

Figure 4. Fundus photograph and optical coherence tomographic image of a highly myopic eye with myopic macular degeneration stage 3, showing a Bruch's membrane defect (*red arrow*) in the region of the patchy atrophy.

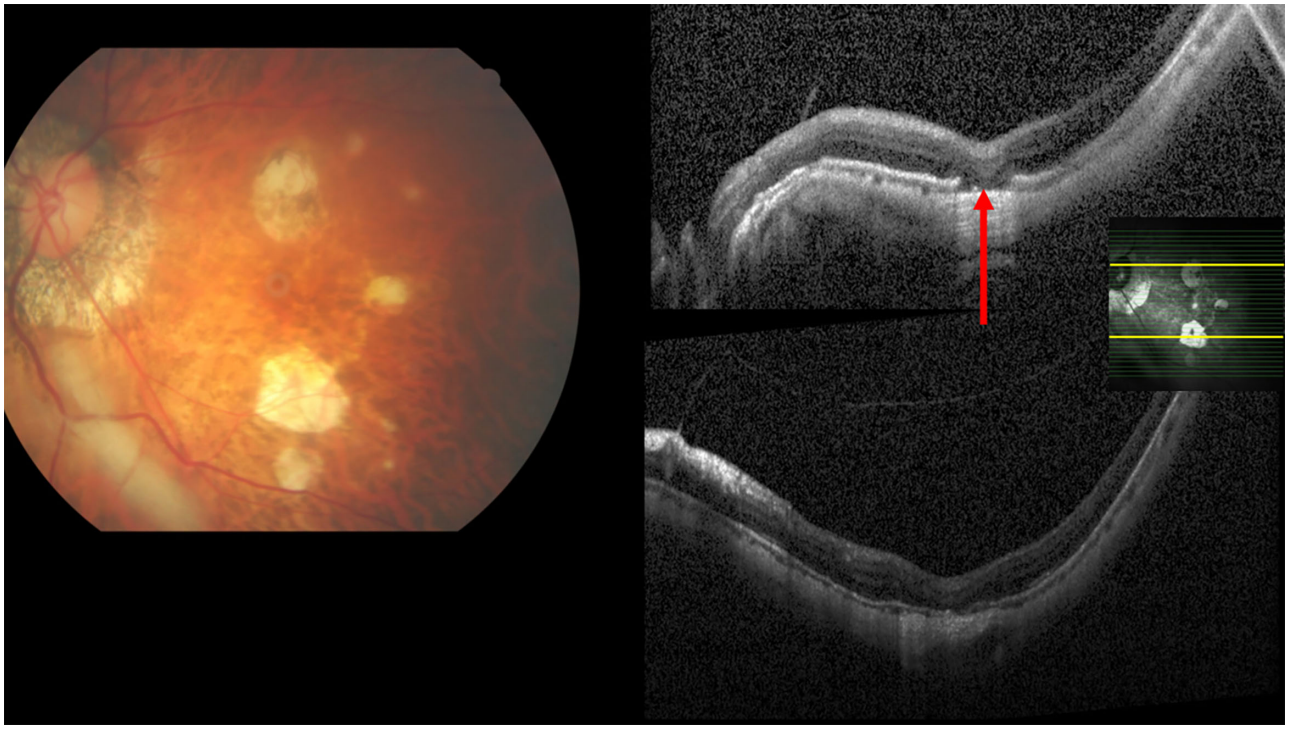

Figure 5. Fundus photograph and optical coherence tomographic image of a highly myopic eye with myopic macular degeneration stage 3, showing a Bruch's membrane defect (*red arrow*) in the region of the patchy atrophy.

disagreement between the reviewers, a final diagnosis was made and agreed upon by all three reviewers together. BMDs were defined as clear interruptions of the OCT line representing BM, and SRPs were defined as a localized thickening of the RPE as visualized upon OCT, which usually spatially corresponded to a localized hyperpigmentation on the conventional fundus images.

We performed the statistical analysis using a statistical software package (SPSS for Windows, version 27.0; SPSS, Chicago, IL. USA). We described the parameters by their

means ± standard deviations or by their means and 95% confidence intervals (CIs). The significance of differences in the prevalence of BMDs and SRPs between groups was tested using the χ^2 test. We calculated the odds ratios (ORs) and their 95% CIs. All *P* values were two-sided and considered statistically significant when the values were less than 0.05.

Results

Out of 7328 eligible individuals, the UEMS included 5899 (80.5%) participants (2580 [43.7%] men; 3319 [56.3%] women), among them 1185 (20.1%) Russians, 1061 (18.0%) Bashkirs, 2439 (41.3%) Tatars, 587 (10.0%) Chuvash, 21 (0.4%) Mari, and 606 (10.3%) individuals without self-reported ancestry. Mean age was 58.8 ± 10.6 years (range, 40–94 years), and mean axial length was 23.30 ± 1.10 mm (median, 23.21 mm; range, 19.02–32.87 mm). Fundus images were available for 5794 (98.2%) individuals. MMD stage 3 was detected in 13 (0.23%) right eyes and 8 (0.14%) left eyes, and MMD stage 4 was found in 10 (0.17%) right eyes and 9 (0.16%) left eyes.

All 21 eyes with MMD stage 3 had by definition an intact BM and intact RPE layer in the foveal region. In the region of the patchy atrophies, characterized by a defect in the RPE layer, 9 (44%) of the 21 eyes showed a BMD, and 7 (33%) eyes showed SRPs. Among the 19 eyes with MMD stage 4, 17 eyes showed a foveal BMD while in 2 eyes, the presence of BMD could not clearly be detected or ruled out. All 19 eyes showed SRPs corresponding to a subretinal hyperpigmentation (Table).

The UVOS consisted of 1526 (81.1%) of 1882 eligible inhabitants aged 85+ years. Assessable fundus images were available for 930 (60.9%) individuals (mean age, 88.6 ± 2.7 years). The mean axial length was 23.1 ± 1.1 mm. Among the UVOS cohort, 18 eyes (1.1%) had MMD stage 3, and 17 eyes (1.0%) had MMD stage 4. Among the 18 eyes with MMD stage 3, three (16.7%) eyes showed a BMD and two (11.1%) eyes showed signs of SRPs in the region of the patchy atrophy. Among the 17 eyes with MMD stage 4, 16 (94.1%) eyes showed a foveal BMD and SRPs, while in 1 eye, it was not possible to clearly assess the presence or absence of a foveal BMD or of SRPs (Table).

The BES included 3468 individuals (1963 women; 56.6%) out of a total eligible population of 4403 individuals (response rate, 78.8%). The rural group consisted of 1633 participants (47.1%), and the urban group included 1835 individuals (52.9%). The mean age was 64.6 ± 9.8 years (range, 50–93 years), and the mean axial length was 23.2 ± 1.0 mm (range, 18.96–28.87 mm). Assessable fundus images were available for 6891 eyes (99.4%). MMD stage 3 was found in 14 eyes (0.2%) and MMD stage 4 in 8 eyes (0.1%). Among the 14 eyes with MMD stage 3, 10 (72%) eyes showed a BMD, and 7 (50%) eyes showed SRPs in the region of the patchy atrophies (Figs. 4, 5). Among the 8 eyes with MMD stage 4, all eyes showed a foveal BMD and all showed localized SRPs corresponding to a subretinal hyperpigmentation (Table, Figs. 1–3).

Among the eyes with MMD stage 3 or 4, the prevalence of BMDs ($P = 0.16$) and SRPs ($P = 0.45$) did not differ significantly between the three study cohorts. In all three study cohorts, the prevalence of BMDs (22 [41.5%] of 53 assessable eyes with MMD stage 3 vs. 41 [100%] of 41 assessable eyes with MMD stage 4) and the prevalence of SRPs (16 [30.2%] of 53 assessable eyes with MMD stage 3 vs. 43 [100%] of 43 assessable eyes with MMD stage 4) was lower ($P < 0.001$) in the eyes with MMD stage 3 than in the eyes with MMD stage 4. The same statistical result was obtained if only one eye per individual was included.

Including only eyes with MMD stage 3 or 4 and only one eye per individual, the prevalence of BMDs in the UEMS, UVOS, and BES ($P = 0.70$, $P = 0.08$, and $P = 0.20$, respectively) and the prevalence of SRPs ($P = 0.95$, $P = 0.59$, and $P = 0.80$, respectively) were statistically independent of axial length. As a corollary, the prevalence of MMD stage 3 versus the prevalence of MMD stage 4 was not significantly associated with axial length in all three study cohorts ($P = 0.39$, $P = 0.71$, and $P = 0.48$, respectively). In a similar manner, including only eyes with patchy atrophies (i.e., MMD stage 3) and only one eye per individual, the prevalence of BMDs in the UEMS, UVOS, and BES ($P = 0.90$, $P = 0.24$, and $P = 0.13$, respectively) and the prevalence of SRPs ($P = 0.51$, $P = 0.59$, and $P = 0.61$, respectively) were statistically independent of axial length.

Combining all three study cohorts and including only eyes with MMD stage 3, 12 (55%) of 22 eyes with BMDs showed SRPs, and 12 (75%) of 16 eyes with SRPs showed a

Table. Prevalence of Macular BMDs and SRPs, Stratified by the Stage of Myopic Macular Degeneration in Three Population-Based Studies

Study	Myopic Macular Degeneration Stage 3	Myopic Macular Degeneration Stage 4
Ural Eye and Medical Study	21 eyes: - 9 (44%) eyes with BMDs - 7 (33%) eyes with SRPs	19 eyes: - 17 (89%) eyes with BMDs (2 [11%] eyes not fully assessable) - 19 (100%) eyes with SRPs
Ural Very Old study	18 eyes: - 3 (17%) eyes with BMDs - 2 (11%) eyes with SRPs	17 eyes: - 16 (94%) eyes with BMDs (1 [6%] eye not assessable) - 16 (94%) eyes with SRPs (1 [6%] eye not assessable)
Beijing Eye Study	14 eyes: - 10 (72%) eyes with BMDs - 7 (50%) eyes with SRPs	8 eyes: - 8 (100%) eyes with BMDs - 8 (100%) eyes with SRPs
All studies combined	- 12 (55%) of 22 eyes with BMDs showed SRPs - 12 (75%) of 16 eyes with SRPs showed a BMD	- All eyes with assessable images with BMDs showed SRPs - All eyes with assessable images with SRPs showed BMDs

BMD (Table). The prevalence of SRPs was significantly ($P < 0.001$) associated with the prevalence of BMDs. The OR of having a BMD in eyes with SRPs in the group of eyes with MMD stage 3 was 17.4 (95% CI, 3.31–91.6). Taking all eyes with MMD stages 3 and 4 together, the OR of having SRPs in eyes with a BMD was 78.3 (95% CI, 16.1–382).

Discussion

In this study including three cohorts recruited in a population-based manner in different continents and including individuals with a relatively large age range, 43 of 44 highly myopic eyes with macular atrophy of MMD stage 4 showed SRPs and 41 of 44 eyes showed BMDs, while in the eyes without detected BMDs or without detected SRPs, the images could not fully be examined due to an insufficient image quality. In contrast to these observations made in eyes with MMD stage 4, only 16 (30%) of 53 eyes with MMD stage 3 exhibited SRPs and 22 (42%) of the 53 eyes showed BMDs (Table). A higher prevalence of SRPs correlated with a higher prevalence of BMDs, with an OR of 17.4 within the group of eyes with MMD stage 3 and an OR of 78.3 for the total study population. The prevalence of BMDs and of SRPs within each subgroup did not differ significantly between the three study populations. The finding that myopic macular atrophy (i.e., MMD stage 4) was associated with BMDs and with SRPs in all eyes with fully assessable images suggests that BMDs in association with myopic macular neovascularization, eventually leading to SRPs, may play an essential part in the pathogenesis of myopic macular atrophy. In contrast, the relatively low prevalence of SRPs and BMDs in extrafoveal myopic patchy atrophies may make one infer that the development of patchy atrophies can occur without an early choroidal neovascularization and that patchy atrophies may be subdivided into those without BMDs (and without concurrent SRPs) and into patchy atrophies with BMDs and with concurrent SRPs.

The observations made in our three study cohorts can be put in relation to findings obtained in previous investigations with a hospital-based recruitment of their study populations.[20] Based on long-term follow-up observations, Fang and colleagues[21] suggested that myopic macular atrophy could be subclassified into macular atrophy related to myopic macular neovascularization and into macular atrophy related to patchy atrophies. Macular atrophy due to myopic macular neovascularization was described to develop in the foveola in association with a myopic neovascularization and then to extend centrifugally. Macular atrophy due to patchy atrophies was considered to develop extrafoveally and then to extend, by enlarging and/or coalescing with other patchy atrophies, into the foveola.[21] A major feature differentiating between both types was the history of myopic neovascularization, with the marked majority of macular atrophy due to an atrophic stage of myopic neovascularization, while only in a small fraction of eyes was myopic macular atrophy considered related to a secondary intrafoveal enlargement of originally extrafoveally located patchy atrophies. Correspondingly, in a hospital-based 18-year follow-up study on a highly myopic population, best-corrected visual acuity loss to less than 20/200 was caused in most eyes by the development of myopic neovascularization with induction or enlargement of macular atrophy.[21] These findings obtained in a cohort recruited in a national third referral center for myopia agree with the observations made in our population-based studies in which all eyes with myopic macular atrophy on assessable images showed SRPs as a surrogate of previous myopic macular neovascularizations. The observations also concur with findings made by Ohno-Matsui et al.[22] and Cheung et al.[23] that macular atrophy developed, or was present, in most eyes around a scarred macular neovascularization.

The results of the studies conducted by Ohno-Matsui et al. and the findings of our investigation suggest that the development of myopic macular atrophy is strongly connected with myopic neovascularization. While the formation of SRPs is the sequel of subretinal (choroidal) neovascularizations, it has remained unclear how the coexistent BMDs fit into the scheme. One may discuss that either the BMDs developed first, allowing a choroidal vessel to grow into the subretinal space, or that the subretinal neovascularization with the induction of an SRP secondarily led to a BMD. Since the neovascular vessel has to get access to the subretinal space, the first version of a primary BMD and a secondary choroidal vessel ingrowth may be more likely. The finding obtained in our study that all eyes with macular atrophies (and with assessable images) had BMDs also suggests that a foveal BMD is basically involved in the pathogenesis of myopic macular atrophy.

Interestingly, the patchy atrophies in the extrafoveal region could be differentiated into those with BMDs (and concomitant SRPs in almost all eyes) and into patchy atrophies with an intact BM and, concomitantly, without SRPs. In the latter type of patchy atrophies, a defect in the RPE layer was the predominant morphologic feature. One may discuss that in these eyes, the axial elongation-induced enlargement of the inner surface of the eye led to a strain in the RPE layer—namely, the RPE basal membrane—with a primary enlargement of the RPE opening of the optic nerve head canal, leading to the myopic beta zone. If the release in the strain on the RPE basal membrane by the enlargement of the RPE opening was not sufficient, secondary expansion holes in the RPE basal membrane (and RPE cell layer) may have developed in the extrafoveal region. Interestingly, such RPE expansion holes did not develop in the foveal region, at least not without a concomitant foveal BMD, since otherwise, some eyes with myopic macular atrophy would have shown a foveal RPE defect with the underlying BM being intact.

In the case of (extrafoveal) patchy atrophies with underlying BMDs, one may discuss whether it was primarily a BMD, which caused a secondary RPE basal membrane defect, since the fundament of the RPE basal membrane (i.e., the BM with its defect) would have locally markedly expanded, leading to a tear and opening in the overlying RPE layer. Alternatively, one may discuss that a primary RPE defect led via metabolic or other changes to a local weakening of BM, with the sequel of a BMD. Longitudinal studies may address whether patchy atrophies with intact underlying BM may eventually develop BMDs, as a hint for the second hypothesis, or whether they remain stable, as a hint for the first hypothesis.

Interestingly, BMDs, independent of their location in the foveal region or extrafoveal region, had a high risk (OR, 78.3) of having previously developed a myopic neovascularization with the sequel of an SRP. It fits with the model of the retina/choroid barrier, with BM preventing an ingrowth of a choroidal vessel into the space beneath the RPE or beneath the retina. Since patchy atrophies without BMDs did not show a high OR of SRPs, one may discuss whether the

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retina/choroid barrier is located in the level of the RPE or, what may be more likely, located in BM, since the absence of RPE in the presence of an intact BM (patchy atrophies without BMD) was not associated with a markedly increased prevalence of SRPs. These observations and thoughts may also be of interest when addressing the pathogenesis of macular choroidal neovascularization in eyes with exudative age-related macular degeneration. Future studies may examine whether the presence of BMDs and of SRPs in patchy atrophies in eyes with MMD stage 3 are prognostically important to indicate an increased for the development of myopic macular atrophy. Future investigations may also assess whether eyes with MMD stage 3 and patchy atrophies without BMDs and without SRPs are associated with a relatively small myopic beta zone and vice versa, suggesting that a large myopic beta zone, through a relative relaxation of the axial elongation-induced increase in the RPE basal membrane strain, may be protective against the development of patchy atrophies without BMDs. Interestingly, and perhaps as analogy, highly myopic eyes with a large gamma zone (i.e., an enlargement of the BM opening of the optic nerve head canal) have a lower prevalence of patchy atrophies.[24]

Limitations of our study have to be discussed. First, since population-based studies formed the basis of our investigation, the quality of the fundus images and OCT images was not excellent in all eyes examined. This opens the possibility that BMDs and SRPs remained undetected, so that the absence of proof might not have been the proof of absence. An underdiagnosis might have resulted. Despite this limitation, however, all eyes with assessable images and macular atrophy showed BMDs and SRPs. Second, the number of patients with MMD stage 3 or 4 was relatively small. It may be taken into account, however, that a general weakness of any population-based study is the relatively low number of individuals affected by a special disease, combined with the advantage of a low risk of a referral-related bias. Third, the study and conclusions have been based on data assessed in a cross-sectional manner, while longitudinal data obtained in a follow-up study were not available. The study can therefore report only on associations but not on causal relationships. Strengths of our study were the population-based recruitment of the study participants and the combination of different population-based studies from two continents, with the studies having a similar study design and same examiners.

In conclusion, all eyes with myopic macular atrophy showed on assessable images, independent of the ethnic background, foveal BMDs associated with SRPs, while patchy atrophies could be differentiated into eyes with BMDs and concurrent SRPs, as well as into eyes without BMDs and without SRPs. The results suggest that SRPs as a sequel of myopic choroidal neovascularizations may develop in association with BMDs and that patchy atrophies may occur due to a primary BMD with a secondary RPE defect or to an expansion defect in the RPE layer without concomitant underlying BMD.

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