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Factors associated with the development of chorioretinal atrophy around choroidal neovascularization in pathologic myopia

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Abstract *Purpose:* To examine the influencing factors on the development of chorioretinal atrophy, which is the main cause of long-term visual decrease in myopic choroidal neovascularization (CNV), in a large series of highly myopic patients. *Methods:* Sixty-five patients (81 eyes) with myopic CNV were studied retrospectively. The influence of the patient's age, refractive error, axial length, visual acuity at onset of CNV, size of CNV, and grade of myopic retinopathy on the extent of chorioretinal atrophy more than 3 years after CNV onset was investigated by means of multiple linear regression analysis. *Results:* Seventy-seven of 81 eyes (95.1%) developed chorioretinal atrophy around myopic CNV during the follow-up period. Multiple linear regression revealed that age was the most influencing factor for the development of chorioretinal atrophy in all the subjects. When we divided the subjects into two groups according to their age, however, CNV size was the only factor to influence the development of chorioretinal atrophy in the patients younger than 40 years, whereas age was still the only influencing factor in those older than 40 years. *Conclusions:* The factors influencing the development of chorioretinal atrophy differ according to patient age. Local factors, such as CNV size, determine the tendency to develop chorioretinal atrophy in young patients. Systemic factors, such as patient age, play a greater part in older subjects.

Introduction

High myopia is a major cause of legal blindness in many developed countries [6, 13, 16]. It affects 27–33% of all myopic eyes, corresponding to a prevalence of 0.2% to 0.4% in the general population of the United States [13]. High myopia is especially common in Asia and the Middle East [3]. In Japan, the overall number of cases of myopia is unknown, but pathologic or high myopia affects 6–18% of the myopic popula-

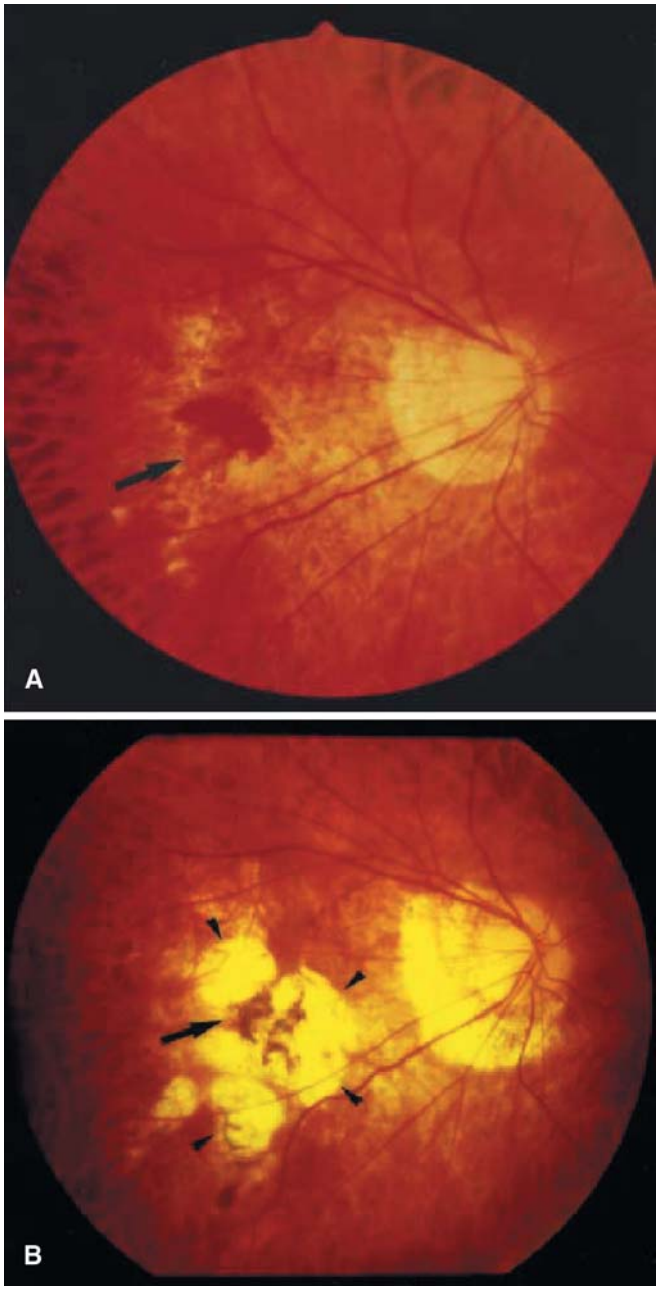

Fig. 1A, B Representative photograph of chorioretinal development around the regressed myopic choroidal neovascularization (CNV). A 49-year-old woman. **A** Right fundus at the initial examination (September 1992) showed a CNV with bleeding temporal to the macula (*arrow*). Visual acuity was 20/30, and the refractive error was –8.5 D. **B** Five years later (December 1997), the CNV had regressed and become flat (arrow). Extensive chorioretinal atrophy (*arrowheads*) had developed around the regressed CNV (*arrow*). Visual acuity had dropped to 20/200

tion, representing approximately 1% of the general population [15].

High myopia is associated with progressive and excessive elongation of the eyeball, which results in various funduscopic changes within the posterior staphyloma [2, 8, 12]. These changes include areas of atrophy of the retinal pigment epithelium and choroid, lacquer cracks in Bruch's membrane, subretinal hemorrhage, and choroidal neovascularization (CNV; so-called Fuchs' spot) [1, 9, 14]. Among the various myopic fundus lesions, macular CNV is the most common vision-threatening complication of high myopia [2, 17, 20, 21].

We previously reported that the long-term visual outcome of myopic CNV is extremely poor [21]. This poor prognosis was mainly due to the development of chorioretinal atrophy around the regressed CNV (Fig. 1). Active treatments such as photodynamic therapy have recently been applied for myopic CNV [11, 18]. It is uncertain, however, whether these active treatments could also prevent the later development of chorioretinal atrophy around the area of CNV. To improve the long-term visual prognosis of myopic CNV, treatments that can also prevent the development of chorioretinal atrophy are necessary.

The mechanism underlying the development of chorioretinal atrophy around myopic CNV is unclear, although this phenomenon seems characteristic of CNV caused by pathologic myopia. As a first step towards clarification of the mechanism for the development of chorioretinal atrophy, we set out to examine influencing factors on the development of chorioretinal atrophy in a large series of highly myopic patients. The results of the present study provide additional information about the factors that are important for the development of chorioretinal atrophy and the characteristics that make some patients more vulnerable to the enlargement of chorioretinal atrophy.

Patients and methods

Patients

Sixty-five consecutive patients (81 eyes) with high myopia and submacular (subfoveal or juxtafoveal) CNV were identified using clinical records from 1988 to 2002 at the high myopia clinic of Tokyo Medical and Dental University and were enrolled in the present study. Informed consent wa obtained from all patients. The study was approved by the ethics committee of the university. Inclusion criteria for this study were (1) refractive error of –8 D or more; (2) fundus changes typical of pathologic myopia: chorioretinal atrophy, lacquer cracks, atrophic patches; (3) presentation within 6 months of the onset of the symptoms, i.e., loss of visual acuity and/or metamorphopsia; (4) fluorescein angiographic documentation of macular CNV; and (5) minimum follow-up of 3 years. Patients who underwent laser photocoagulation or surgical treatment of CNV, and those with less than 3 years follow-up, were excluded from the study. Additional exclusion criteria included a history of visual loss due to myopic chorioretinal atrophy, history of retinal detachment surgery, history of cataract surgery, diabetic retinopathy, or other retinal vascular diseases, age-related maculopathy, dense cataract, glaucoma, and ocular injuries. The initial evaluation included refraction, axial length measurements, best-corrected Snellen visual acuity, detailed fundus drawings us-

ing indirect stereoscopic ophthalmoscopy, fluorescein angiography, and color photographs.

Measurement of chorioretinal atrophy

Color fundus photographs at the final examination as well as fluorescein fundus angiogram at the onset of CNV were scanned using an image scanner (Scanjet IICX/T; Hewlett Packard, Palo Alto, CA), and exported to NIH Image software (version 1.62). The area of the chorioretinal atrophy was carefully outlined. The area of the chorioretinal atrophy that developed around the area of CNV was defined as:

$$\frac{\text{Total number of pixels of chorioretinal atrophy at final examination} - \text{total number of pixels of CNV at initial examination}}{\text{Total number of pixels of optic discarea}}$$

To ensure reproducibility, the number of pixels was independently measured five times for each eye, and the mean value was used for analysis. In some eyes in which the margin of chorioretinal atrophy was difficult to define by color fundus photographs alone, stereoscopic observations by ophthalmoscopy or using a +90 D lens and fluorescein fundus angiography were also evaluated. Also, several photographs acquired at different time points after onset were used to determine the newly-developed area of chorioretinal atrophy and the area of expansion of the surrounding myopic fundus lesion. In addition, to detect even very small areas of chorioretinal atrophy around the area of CNV, the presence or absence of chorioretinal atrophy was determined using a combination of color fundus photographs, fluorescein fundus angiography, and stereoscopic observation using a +90 D lens. CNV was considered subfoveal if any portion of a new vessel system was under the center of the fovea. Other cases were termed juxtafoveal.

Statistical analysis

The influence of the patient's age at the onset of CNV, refractive error, axial length, the visual acuity at onset, the size of the area of CNV, and the grades of myopic retinopathy on the size of chorioretinal atrophy measured by the above method was investigated by means of Spearman's correlation analysis and multiple linear regression analysis. Because of the skewed nature of the enlargement of chorioretinal atrophy distribution, natural logarithms of the latter were used with multiple linear regression. A backward-elimination procedure was used to identify the best mathematical model to predict the enlargement of the area of chorioretinal atrophy. In the procedure, a P value of 0.05 was used to eliminate potential variables from the model.

The refractive error and the axial length in the eye were highly significantly correlated (Spearman correlation coefficient r=–0.631, P<0.001). Hence, only axial length was analyzed as an influencing factor on the development of chorioretinal atrophy. The degree of background myopic retinopathy was categorized in each patient according to Avila et al. [1]. The myopic fundus changes (M) were graded retrospectively on a scale of increasing severity from 0 to 5: grade M_0, normal-appearing posterior pole; M_1, choroidal pallor and tessellation; M_2, choroidal pallor and tessellation, with posterior pole staphyloma; M_3, choroidal pallor and tessellation, with posterior staphyloma and lacquer cracks; M_4, choroidal pallor and tessellation, with posterior pole staphyloma, lacquer cracks, and focal areas of deep choroidal atrophy; M_5, posterior pole showing large geographic areas of deep choroidal atrophy ("bare sclera"). In the present study, the eyes that showed myopic fundus changes of grades M_0, M_1, and M_2 were categorized as mild retinopathy, and eyes with grades M_3, M_4, and M_5 were considered as having severe retinopathy. The correlation between the development of chorioretinal atrophy and the grades of myopic retinopathy (mild vs severe) were analyzed. For the purpose of analysis, Snellen visual acuity data were transformed into equivalent logarithms of the minimum angle of resolution (logMAR values). Also, various factors between younger (<40 years old) and older patients (>40 years old) were compared using a t test or chi-square test.

Statistical analyses were performed using SAS version 8 software (SAS Institute, Cary, NC). A P value of less than 0.05 (two-sided) was considered statistically significant.

Results

The characteristics of the 65 patients (81 eyes) are summarized in Table 1. The duration of follow-up ranged from 38 to 178 months (mean 80.1±39.3 months). Visual acuity at the initial and final examination in all subjects is shown in Fig. 2. Chorioretinal atrophy developed in 77 of 81 eyes (95.1%) at the final examination. In these 77 eyes, the size of chorioretinal atrophy that developed around the myopic CNV at the final examination ranged from 0.1 to 12.8 disc areas (mean 2.71±2.80 disc areas).

The results of Spearman correlation analyses are shown in Table 2. Chorioretinal atrophy development was statistically significantly related to patient age, size of area of CNV, and initial visual acuity. Table 3 shows the correlations between patient age and other factors. The size of the area of CNV and the initial visual acuity correlated with age. Because of our previous finding that the visual prognosis of myopic CNV differed according to patient age [20], we then divided the patients into two

Table 1 Patients' characteristics

Gender	
Male	8/65 (12.3%)
Female	57/65 (87.7%)
Age, years [mean (SD)]	48.5 (15.9)
Refractive error, D [mean (SD)]	–13.8 (3.4)
Axial length, mm [mean (SD)]	28.7 (1.8)
Initial Snellen visual acuity	
>20/40	27/81 (33.3%)
20/40–20/200	37/81 (45.7%)
<20/200	17/81 (21.0%)
Baseline logMAR [mean(SD)]	0.68 (0.5)
Size of CNV, disc diameters [mean(SD)]	0.80 (0.50)
Location of CNV	
Juxtafoveal	11/81 (13.6%)
Subfoveal	70/81 (87.5%)
Grade of myopic retinopathy	
M_0	0/81 (0%)
M_1	2/81 (0.2%)
M_2	7/81 (0.9%)
M_3	37/81 (45.6%)
M_4	35/81 (43.2%)
M_5	0/81 (0%)

groups according to patient age at onset of CNV (<40 years and ≥40 years). Twenty-two patients (29 eyes) were less than 40 years old at onset of CNV, and 43 patients (52 eyes) were 40 or older at onset of CNV. Analysis by means of the *t* test revealed that the older subjects had significantly larger area of CNV and worse visual acuity at onset (Table 4) than their younger counterparts.

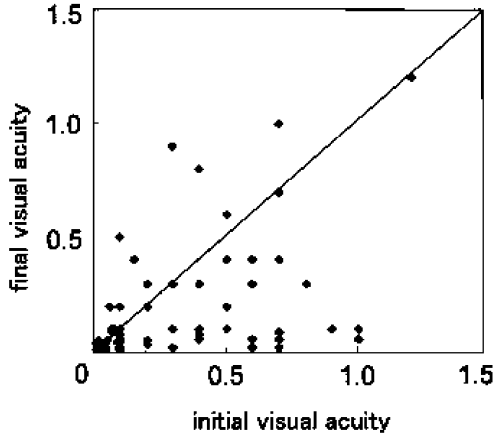

Fig. 2 Initial and final visual acuities in all subjects. *Dots on the line* indicate unchanged visual acuity, *dots above the line* indicate improvement, and *dots below the line* indicate worsening

Table 2 Results of Spearman correlation analyses

Variable	Correlation coefficient	*P* value
Age	0.614	0.001
Size of CNV	0.271	0.014
Initial visual acuity	0.257	0.021
Grade of myopic retinopathy*	0.035	0.755
Axial length	–0.088	0.435

Table 3 Correlations between patient age and other factors

Variable	Correlation coefficient	*P* value
Size of CNV	0.242	0.029
Initial visual acuity	0.319	0.004
Grade of myopic retinopathy*	0.048	0.671
Axial length	–0.095	0.398

The multiple linear regression of all the data showed that the patient's age at onset was the only factor that significantly correlated with an enlargement of chorioretinal atrophy. All independent variables except patient age were eliminated by the backward-elimination procedure. The final model demonstrated a highly significant relationship between enlargement of chorioretinal atrophy and patient's age at onset of CNV (β=0.063, F=41.8, P=0.001). In the patients under 40 years old at onset of myopic CNV, the size of the area of CNV was the only factor that correlated significantly with an enlargement of chorioretinal atrophy. Patient's age at onset was not significantly correlated with an enlargement of chorioretinal atrophy in this group. The final model demonstrated a highly significant relationship between enlargement of chorioretinal atrophy and size of area of CNV (β=2.175, F=5.7, P=0.025). Secondly, in the patients over 40 years old at onset of CNV, linear regression showed that patient age was the only factor that significantly correlated with an enlargement of chorioretinal atrophy, similar to the finding for both groups combined. The final model demonstrated a highly significant relationship between enlargement of chorioretinal atrophy and patient's age (β=0.046, F=11.7, P=0.001).

Discussion

Choroidal neovascularization is the most common vision-threatening complication of high myopia. In our previous study, we followed up 27 eyes with myopic CNV for more than 10 years after onset of CNV and found that visual acuity dropped to less than 20/200 and visual prognosis was poor [21]. That study also clarified that the poor prognosis of myopic CNV in the long term was mainly due to the development and an enlargement of chorioretinal atrophy, which gradually occurs around the regressed CNV [21].

A combination of fluorescein fundus angiography and color fundus photography was used to detect even very small areas of chorioretinal atrophy around the CNV. Thus, we were able to detect the development of chorioretinal atrophy in 77 of 81 eyes (95.1%) in the present

Table 4 Comparison of the two age groups

Variable	Younger group (age <40 years; 29 eyes)	Older group (age≧40 years; 52 eyes)	*P* value
Age years [mean (SD)]	30.7 (4.4)	58.4 (10.3)	–
Size of CNV, disc diameters [mean (SD)]	0.63 (0.35)	0.90 (0.55)	0.016[b]
Initial visual acuity	0.41 (0.38)	0.83 (0.56)	0.001[b]
Proportion of eyes with severe myopic retinopathy[a]	25/29 (86.2%)	47/52 (90.3%)	0.566[c]
Axial length, mm [mean (SD)]	28.85 (1.55)	28.64 (1.95)	0.613[b]

study. In the attempt to determine the underlying mechanism of the development of chorioretinal atrophy, and to establish in which patients chorioretinal atrophy tends to enlarge more, we analyzed influencing factors for the development of chorioretinal atrophy around myopic CNV in a large series of highly myopic patients. Spearman correlation analysis in total subjects showed that patient age, CNV size, and initial visual acuity correlated with an enlargement of chorioretinal atrophy. Because of the high correlation of CNV size and initial visual acuity with increasing age, however, multiple linear regression analysis showed that patient age was the only factor correlating with an enlargement of chorioretinal atrophy in total subjects. This result suggests that in aged individuals the chorioretinal atrophy tends to enlarge more than in younger subjects. This supports our previous finding that the visual prognosis of myopic CNV at 3 years after onset is better in younger subjects [20].

The reason why chorioretinal atrophy tends to enlarge more in older subjects is unclear. Although much remains unknown about the mechanism of chorioretinal atrophy development around myopic CNV, it is considered that the retinal pigment epithelium (RPE) dysfunction in highly myopic eyes might be involved in the development of chorioretinal atrophy. In the process of chorioretinal atrophy development around the regressed CNV, we sometimes find that first a window defect due to RPE atrophy appears around the CNV, as seen on fluorescein fundus angiography, and then the area of window defect develops into a typical chorioretinal atrophy (not shown). RPE function is affected in myopic eyes [7, 10, 19]. Aging is also another important influence on RPE function [4, 5]. Considering these factors, older patients with high myopia can be expected to have more widespread RPE dysfunction than younger patients with high myopia. This might partly explain a correlation of an enlargement of chorioretinal atrophy with increasing age.

We then divided subjects into two groups according to their age at onset of CNV. In young subjects (<40 years old), the size of the area of CNV was the only factor influencing the development of chorioretinal atrophy. Age was not an important factor for the enlargement of chorioretinal atrophy in this group. The reason why CNV size should influence the development of chorioretinal atrophy is unknown. More extensive CNV is sometimes accompanied by a wide area of retinal edema and retinal bleeding around the area of CNV, and the retinal toxicity of these factors might be involved in the later development of chorioretinal atrophy. On the other hand, patient age was still the only influential factor in the older age group. Although older subjects had a significantly larger area of CNV than younger subjects (Table 4), the CNV size was not an influential factor for the development of chorioretinal atrophy by linear regression analysis, partly because CNV size correlated with patient age.

This finding suggests that patient age was overall the most influential factor for the development of chorioretinal atrophy around myopic CNV. The determining factors, however, differ according to patient age. Local factors, such as CNV size, determine the tendency to develop chorioretinal atrophy in young patients, but systemic factors like patient age are more influential in older subjects. On the other hand, the degree of myopia (like the axial length of the eyeball) and the grade of myopic retinopathy around the area of CNV were not important factors in either group. This information might be beneficial in selecting patients for active treatments. For example, in young patients with large CNV, active treatments such as photodynamic therapy might be useful to maintain or improve vision in the long term, because local factors affecting CNV also regulate the later development of chorioretinal atrophy in this group. On the other hand, local treatments of CNV might not provide much therapeutic benefit in older patients, because background systemic factors (like patient age) rather than local factors affecting CNV are more important in the development of chorioretinal atrophy in this group. Also, these data might provide additional information about the mechanism of the development of chorioretinal atrophy. Because the present study revealed that CNV size and patient age were important factors in the development of chorioretinal atrophy, the retinal toxicity caused by retinal bleeding and edema and the RPE dysfunction caused by increasing age might be important for the development of chorioretinal atrophy. This needs further investigation, however.

In summary, we analyzed factors influencing the development of chorioretinal atrophy around myopic CNV using Spearman correlation analysis and multiple linear regression. The results indicate that patient age is the factor that most influences the development of chorioretinal atrophy in all subjects. The influential factors differed according to patient age. This information could be beneficial for long-term management of patients with myopic CNV.

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