厚生労働科学研究費補助金（難治性疾患政策研究事業）
分担研究報告書

萎縮型加齢黄斑変性に関する研究

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萎縮型加齢黄斑変性（萎縮型 AMD）にみられる網膜外層、網膜色素上皮（RPE)、および脈絡膜毛細血管板の境界明瞭な萎縮病巣は地図状萎縮（GA）と呼ばれる。今回我々は、アジア人における GA の臨床的特徴と進行率を明らかにする目的で、日本人の GA を調査した。その結果、アジア人の GA 患者は男性優位で、白人患者よりも脈絡膜が比較的厚く、pachychoroid の特徴を有する GA 患者が一定の割合で存在していた。アジア人における GA の進行率は、白人集団のそれよりも比較的遅かった。またベースラインの GA 面積と reticular pseudodrusen の有無が GA 進行率の速さと関連していた。今回の研究により、日本人を含むアジア人における GA の臨床的特徴と GA 進行率が初めて明らかにされた。

Ａ．研究目的

加齢黄斑変性(AMD)は我が国の視覚障害の主要原因を占める疾患である。一般的に AMD は新生血管型(滲出型)と萎縮型に分類される。萎縮型 AMD にみられる網膜外層、網膜色素上皮(RPE)、および脈絡膜毛細血管板の境界明瞭な萎縮病巣は以前から「地図状萎縮」(GA) と呼ばれてきた。

これまで日本を含むアジア人における GA の病態に関して多施設で解析した大規模な研究はなかった。そこで今回我々は、アジア人における AMD の臨床的特徴と GA 進行率を明らかにするために、日本人の GA 患者を調査した。

Ｂ．研究方法

GA 面積は眼底自発蛍光（FAF）画像を用いて半自動的に測定した。FAF 画像で 6 ヵ月以上追跡できた群では、GA 進行率を 2 つの方法(1 年当たりの mm^2 と平方根変換(SQRT)法を用いた 1 年当たりの mm）で算出した。単回帰分析および重回帰分析を用いて、GA 進行率と関連するベースライン因子を同定した。

（倫理面への配慮）

今回の研究に関しては患者の個人情報は全て匿名化し、倫理面に十分配慮して行った。

Ｃ．研究結果

平均年齢は 76.8+/-8.8 歳で、109 例

(63.0%)が男性であった。62例(35.8%)が両側GAであった。平均GA面積は3.06+/-4.00 mm^2 (1.44+/-1.00 mm [SQRT])であった。38眼(22.0%)は、pachychoroid GAに分類された。Drusenとreticular pseudodrusenはそれぞれ115眼(66.5%)、73眼(42.2%)検出された。平均中心窩脈絡膜厚は194.7+/-105.5μmであった。追跡群(追跡期間:46.2+/-28.9か月)では、平均GA進行率は1.01+/-1.09 mm^2/年(0.23+/-0.18 mm/年 [SQRT])であった。多変量解析において、ベースラインのGA面積(SQRT;P= 0.002)とreticular pseudodrusenの存在(P < 0.001)が、より速いGA進行率(SQRT)と有意に関連していた。

D. 考察

アジア人におけるGAの臨床的特徴は、白人のそれとは異なる可能性があることが示された。アジア人のGA患者は男性優位で、白人患者よりも脈絡膜が比較的厚い。またドルーゼンを認めないがpachychoroidの特徴を有するGA患者が一定の割合で存在していた。このアジア人におけるGAの進行率は、白人のそれよりも比較的遅かった。ベースラインの大きなGAとreticular pseudodrusenがGA進行率の速さと関連していた。

E. 結論

今回の研究により、日本人を含むアジア人におけるGAの臨床的特徴とGA進行率が初めて明らかにされた。

F. 健康危険情報 : なし

G. 研究発表

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H. 知的財産権の出願・登録状況

1. 特許取得　なし

2. 実用新案登録　なし

3.その他　なし

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Clinical Characteristics and Progression of Geographic Atrophy in a Japanese Population

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Purpose: To elucidate the clinical characteristics and progression rate of geographic atrophy (GA) associated with age-related macular degeneration (AMD) in a Japanese population.

Design: Retrospective, multicenter, observational study.

Participants: A total of 173 eyes from 173 patients from 6 university hospitals in Japan were included. Of 173 study eyes, 101 eyes from 101 patients were included in the follow-up group. All patients were Japanese, aged ≥ 50 years and had definite GA associated with AMD in at least 1 eye.

Methods: The GA area was measured semiautomatically using fundus autofluorescence (FAF) images. In the follow-up group followed for > 6 months with FAF images, the GA progression rate was calculated by 2 methods: mm^2 per year and mm per year using the square-root transformation (SQRT) strategy. Simple and multiple linear regression analyses were used to identify the baseline factors associated with the GA progression rate.

Main Outcome Measures: Clinical characteristics of GA and the GA progression rate.

Results: The mean age was 76.8 ± 8.8 years, and 109 (63.0%) were males. Sixty-two (35.8%) patients had bilateral GA. The mean GA area was 3.06 ± 4.00 mm^2 (1.44 ± 1.00 mm [SQRT]). Thirty-eight eyes (22.0%) were classified as having pachychoroid GA. Drusen and reticular pseudodrusen were detected in 115 (66.5%) and 73 (42.2%) eyes, respectively. The mean subfoveal choroidal thickness was 194.7 ± 105.5 μm. In the follow-up group (follow-up period: 46.2 ± 28.9 months), the mean GA progression rate was 1.01 ± 1.09 mm^2 per year (0.23 ± 0.18 mm/year [SQRT]). In the multivariable analysis, the baseline GA area (SQRT; $P = 0.002$) and the presence of reticular pseudodrusen ($P < 0.001$) were significantly associated with a greater GA progression rate (SQRT).

Conclusions: Certain clinical characteristics of GA in Asian populations may differ from those in White populations. Asian patients with GA showed male dominance and relatively thicker choroid than White patients. There was a group with GA without drusen but with features of pachychoroid. The GA progression rate in this Asian population was relatively lower than that in White populations. Large GA and reticular pseudodrusen were associated with a greater GA progression rate.

Financial Disclosure(s): Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology Retina 2023;7:901-909*

Supplemental material available at www.ophthalmologyretina.org.

Age-related macular degeneration (AMD) is a leading cause of irreversible visual loss in older people in developed countries.[1,2] Most visual impairments occur in advanced AMD, which is associated with the typical clinical forms of geographic atrophy (GA) and neovascular AMD. Geographic atrophy is defined on color fundus photography (CFP) as a sharply demarcated atrophic lesion of the outer retina resulting from the loss of photoreceptors, retinal pigment epithelium (RPE), and choriocapillaris.[3] The GA area tends to expand with time, and central vision is severely impaired when it starts to involve the fovea.[4]

Ethnic differences have been reported in the prevalence and clinical features of GA.[5] In the United States (US), the prevalence of GA is 0.90% in people aged 70 to 74 years and 1.78% in people aged 75 to 79 years[6]; however, in Asian populations, the prevalence in people aged ≥ 70 years is 0.29%.[7] Although there are relatively equal numbers of neovascular AMD and GA in White populations,[5] GA is significantly less common than

https://doi.org/10.1016/j.oret.2023.06.004
ISSN 2468-6530/23

neovascular AMD as a late-stage complication of AMD in Asian populations.[7] However, it remains unclear whether the GA progression rate and factors that influence its progression are different between White populations and Asian populations.

Recently, there has been the first approved treatment for GA in the US.[8] In Asian countries, although the prevalence of GA is low,[7] the rapidly aging population means that GA is becoming an increasingly urgent and unmet medical need.

However, there is scarce information on the clinical characteristics of GA in Asian populations.[7,9,10] Therefore, it is essential to accumulate clinical data on GA, especially regarding the GA progression rate and factors that modify this progression in Asian populations, to better understand the differences in GA in the different ethnicities to ensure appropriate and effective treatments can be delivered to Asian patients. Better characterization of GA in Asian populations will also ensure that appropriate participants are recruited into treatment trials aiming to assess the efficacy of potential GA treatments in Asian patients. In the current study, we examined Japanese patients with GA to elucidate the clinical characteristics and the GA progression rate associated with AMD in an Asian population.

Methods

Ethics Statement

This research was conducted in accordance with the tenets of the Declaration of Helsinki and approved by the institutional review board and ethics committee of the Kyoto University Graduate School of Medicine. The requirement for written informed consent was waived because of the retrospective design of this study, and only deidentified data were available for analysis.

Participants

This retrospective multicenter study enrolled consecutive patients with GA associated with AMD from 6 university hospitals in Japan (Kyoto University Hospital, Tokyo Women's Medical University Hospital, University of the Ryukyus Hospital, Osaka University Hospital, Yokohama City University Medical Center, and Kansai Medical University Hospital) between January 2009 and December 2021. The inclusion criteria were Japanese ethnicity, age $\geq$ 50 years, and definite GA diagnosis associated with AMD in at least 1 eye. The diagnosis of GA was based on the diagnostic criteria for GA in Japan.[11,12] According to this guideline, GA should have all of the following fundoscopic findings: (1) at least 250 μm in diameter; (2) round/oval/cluster-like or geographic in shape; (3) sharp delineation; (4) hypopigmentation or depigmentation in RPE; and (5) clear visualization of large and medium choroidal vessels. Patients with inherited diseases, high myopia, chronic central serous chorioretinopathy, traumatic injury, retinal epithelial tear, history of laser photocoagulation, and macular neovascularization (MNV) were excluded. Eyes without fundus autofluorescence (FAF) images or with poor image quality were also excluded. In cases where both eyes of a patient were eligible, only the right eye was included.

Patients followed up with FAF images for $>$ 6 months were categorized as the follow-up group and were evaluated to assess the natural course of the disease and GA progression rate. The dates of the first and last FAF assessment were defined as the baseline and final visit, respectively. When MNV developed during the course of the disease, the subsequent period was not included in the follow-up analysis to exclude atrophy secondary to MNV. Smoking status was surveyed on medical charts.

Multimodal Imaging Methods

All patients underwent a comprehensive ophthalmic examination, including best-corrected visual acuity (BCVA), slit-lamp biomicroscopy with a noncontact lens, FAF, CFP (TRC50DX, Topcon; TRCNW6S, Topcon; and TRCNW8F, Topcon), spectral-domain OCT (SD-OCT) (OCT3000, Carl Zeiss; HRA, Heidelberg Engineering; and Avanti, Optovue) or swept-source OCT (SS-OCT) (Atlantis, Topcon; Triton, Topcon), and axial length measurement. Fundus autofluorescence was obtained using a confocal scanning laser ophthalmoscope (HRA; Heidelberg Engineering) with a field of view of 30° $\times$ 30° and centered on the fovea. Spectral-domain OCT and SS-OCT images were obtained with horizontal and vertical line scans through the foveal center, followed by SD-OCT images in the same position using an enhanced depth imaging (EDI) technique.[13]

Image Analysis

Drusen were graded based on CFP and confirmed with SD-OCT and SS-OCT as follows: (1) medium-sized drusen (with a diameter of 63−124 μm)[14]; (2) large drusen (with a diameter of 125−249 μm); (3) confluent drusen (with a diameter of 250−432 μm); (4) drusenoid pigment epithelial detachment (PED; with a diameter of 433−3000 μm)[15]; and (5) large drusenoid PED (with a diameter of $>$ 3000 μm).[16] Reticular pseudodrusen were diagnosed if at least 1 of the following findings were definite: (1) interlacing network of drusen-like deposits, discrete whitish dot-like deposits, or yellow-white globules located outside the vascular arcades on CFP[17]; (2) ill-defined small areas of decreased autofluorescence surrounded by areas of increased autofluorescence on FAF image[18]; (3) diffuse granular materials, or mounds of or conic accumulations above RPE on OCT[19]; or (4) hyporeflective lesions against a mildly hyperreflective background, which can have a hyper (or ISO) reflective core, on infrared reflectance image.[20] Central macular thickness (CMT) was defined as the distance between the internal limiting membrane and Bruch membrane at the center of the fovea. Subfoveal choroidal thickness (SFCT) was defined as the distance between Bruch membrane and the chorioscleral interface at the center of the fovea. Each distance was measured manually on SD-OCT and SS-OCT images of the vertical and horizontal scans through the center of the fovea, using a built-in caliper, and averaged. Subfoveal choroidal thickness was measured using SS or EDI OCT.

Color fundus photography, FAF, and SD-OCT SS-OCT images of all participants were gathered at a single institute (Kyoto University Hospital). Diagnosis of GA, GA location (central or noncentral), GA pattern (unifocal or multifocal), and measurements of CMT and SFCT were performed at each research institute. Geographic atrophy was classified as conventional or pachychoroid, with the latter being diagnosed when the following criteria were met: (1) clinical and anatomic features of the pachychoroid phenotype were identified, including reduced fundus tessellation on CFP and dilated outer choroidal vessels on OCT; and (2) no drusen were observed.[21] The GA classification was made independently by 2 retinal specialists (Y.S. and N.UA.). In cases of discrepancy, a third retinal specialist (A.Takahashi) was consulted. Geographic atrophy areas were measured on FAF images by a single grader (Y.S.) using the Region Finder software, version 1.10.2.0 (Heidelberg Engineering; Fig 1). To

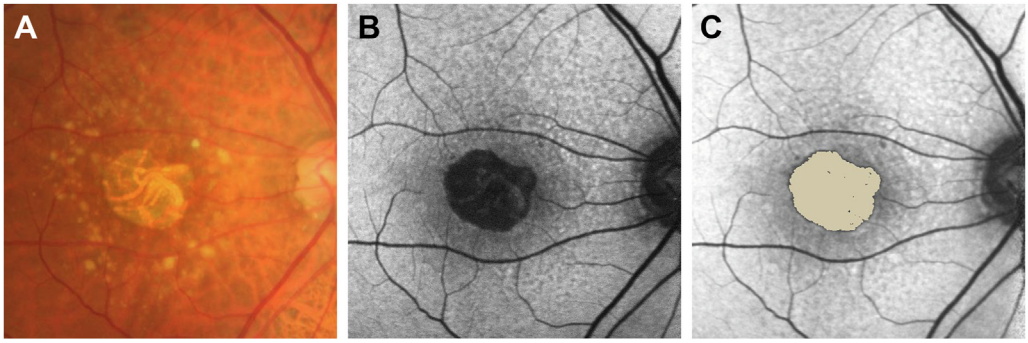

Figure 1. Semiautomatic measurements of the geographic atrophy (GA) area using the Region Finder software. Images from an 81-year-old man with GA associated with age-related macular degeneration. **A**, Color fundus photograph shows unifocal GA with drusen. **B**, Fundus autofluorescence (FAF) image shows GA as a well-defined hypoautofluorescent area. Reticular pseudodrusen are seen in the area surrounded by the yellow line. **C**, The GA area is delineated and measured using the Region Finder software on an FAF image.

ensure reproducibility, a random sample of 57 images (20.8%) was evaluated by a second grader (N.UA.) in a masked fashion, and the intraclass correlation coefficient was calculated.

The GA progression rate was calculated using 2 methods. First, the difference in the GA area between the baseline and final visit was divided by the follow-up period (mm^2 per year). Second, using a square-root transformation (SQRT) strategy,[22] the difference in GA size after transforming the measurements to the square-root scale between the 2 visits was divided by the follow-up period (mm per year).

Statistical Analysis

Statistical analysis was performed using the JMP software (version 16.2, SAS Institute Inc) All values are presented as mean ± standard deviation or number. Best-corrected visual acuity was measured using a Landolt chart and converted into the logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Mann−Whitney *U* tests were used to compare the means between the 2 groups. To compare values between > 2 groups, analysis of variance or Fisher exact test were used. Bonferroni correction was used in the post hoc analysis. Simple and multiple linear regression analyses were used to identify baseline factors associated with the GA progression rate (SQRT). *P* values of < 0.05 were considered statistically significant.

Results

A total of 173 eyes from 173 patients were included in this study, and 101 eyes from 101 patients were included in the follow-up group. Table 1 shows the demographic and ocular characteristics of all the patients. One hundred and nine patients (63.0%) were men. The mean GA area was 3.06 ± 4.00 (median: 1.47 [0.05−24.88]) mm^2. One hundred and fifteen eyes (66.5%) had drusen, and 73 eyes (42.2%) had reticular pseudodrusen. The mean difference between the 2 graders was 0.220 (95% confidence interval [CI]: 0.036−0.405) mm^2, and the ICC for GA area measurements was 0.993.

Table S2 (available at www.ophthalmologyretina.org) shows the characteristics of the patients and the studied eyes stratified by fellow eye status. Three patients lacked information on their fellow eyes due to phthisis. Sixty-two patients (36.5%) had bilateral GA (group 1). This group showed significantly larger GA size ($P < 0.001$), a predominance of the multifocal GA ($P < 0.001$), the thinnest SFCT, and the highest prevalence of reticular pseudodrusen. There were no significant differences in the GA location among the groups.

Table 3 shows the demographic and ocular characteristics of the 101 eyes from 101 patients in the follow-up group. During the follow-up period (mean: 46.2 ± 28.9; median: 39 months), the mean GA area was enlarged from 2.77 ± 3.40 (median: 1.45) to 6.08 ± 6.76 (median: 4.33) mm^2 ($P < 0.001$), and the mean BCVA in logMAR was decreased from 0.34 ± 0.44 to 0.49 ± 0.51 (Snellen equivalent: from 20/45 to 20/63; $P < 0.001$). The mean CMT and SFCT significantly decreased and the GA area in all eyes increased (CMT: from 148.1−117.5 μm; SFCT: from 199.4−180.1 μm), and the mean GA area in all eyes increased (from 2.77−6.08 mm^2; Fig 2). The mean GA progression rate was 1.01 ± 1.09 (median: 0.63) mm^2 per year and 0.23 ± 0.18 (median: 0.16) mm per year. Further, 15 (30.0%) of 50 eyes with noncentral GA at baseline progressed to central GA, and 6 eyes (5.9%) developed MNV.

We compared the GA progression rate (SQRT) between groups divided according to various baseline parameters (Table 4). Sex (female), conventional GA, multifocal pattern, drusen, reticular pseudodrusen, and GA/late AMD in the fellow eye were associated with a significantly higher GA progression rate (SQRT). Table 5 shows the results of the univariable and multivariable analyses assessing the association between GA progression rate (SQRT) and baseline factors. In the multivariable analysis, baseline GA area ($P = 0.002$) and reticular pseudodrusen ($P < 0.001$) were significantly associated with the GA progression rate (SQRT).

Discussion

In this study of 173 Japanese patients with GA, we elucidated the clinical characteristics of GA in an Asian population. Using a follow-up group of 101 eyes, we also evaluated the GA progression rate and factors that influence this rate. Our results revealed that GA in this Asian population was male dominant, had small lesions, a relatively thicker choroid, and a low-GA progression rate. There was a group with GA without drusen but with features of pachychoroid. In addition, large baseline GA area and

Table 1. Demographic and Ocular Characteristics

Characteristic	Value
Patients, n	173
Age (median, range), yrs	76.8 ± 8.8 (78, 53–97)
Sex, males, n, males (%)	109 (63.0)
Smoking status, n, current or former/never/unknown	90/61/22
Axial length, mm(n = 123)	23.4 ± 0.9
BCVA, logMAR (Snellen equivalent)	0.34 ± 0.43 (20/45)
CMT (median, range), μm	144.9 ± 72.1 (151.0, 6.0–617.0)
SFCT (median, range), μm	194.7 ± 105.5 (169.0, 36.5–622.0)
GA area (median, range), mm^2	3.06 ± 4.00 (1.47, 0.05–24.88)
GA area (SQRT) (median, range), mm	1.44 ± 1.00 (1.21, 0.23–4.99)
GA type, n, conventional GA/pachychoroid GA	135/38
GA location, n, central/noncentral	90/83
GA pattern, n, unifocal/multifocal	103/70
Drusen, n, present/absent	115/58
Drusen size, n, medium-sized drusen/large drusen/confluent drusen/drusenoid PED/large drusenoid PED	17/44/41/12/1
Reticular pseudodrusen, n, present/absent	73/100

BCVA = best-corrected visual acuity; CMT = central macular thickness; GA = geographic atrophy; logMAR = logarithm of the minimum angle of resolution; n = number of patients; PED = pigment epithelial detachment; SFCT = subfoveal choroidal thickness; SQRT = square-root transformation. All values are presented as mean ± standard deviation or number.

reticular pseudodrusen were associated with faster GA progression.

Some characteristics of GA in Asian populations have been suggested to differ from those in White populations.[7] Previous studies on White patients showed no sex differences in the prevalence of GA.[5] In our study, however, patients with GA were predominantly men (63%). This tendency is consistent with a meta-analysis on GA in Asian populations, which showed a prevalence of 1.62 per 1000 in men and 0.87 per 1000 in women.[7] The GA size

Table 3. Demographic and Ocular Characteristics at Baseline and the Final Visit in the Follow-up Group

Characteristic	Baseline Visit	Final Visit	*P* Value
Patients, n	101		
Follow-up period (median, range), mos	46.2 ± 28.9 (39, 6–123)		
Age, yrs (median, range), yrs	76.6 ± 8.7 (87, 53–94)		
Sex, n, males (%)	63 (62.4)		
Smoking status, n, current or former/never/unknown	50/40/11		
Axial length, mm; n = 80	23.5 ± 0.9		
BCVA, logMAR (Snellen equivalent)	0.34 ± 0.44 (20/45)	0.49 ± 0.51 (20/63)	< 0.001
CMT (median, range), μm	148.1 ± 79.9 (152.0, 6.0–617.0)	117.5 ± 71.7 (119.0, 6.0–285.0)	< 0.001
SFCT (median, range), μm	199.4 ± 111.9 (170.0, 36.5–622.0)	180.1 ± 102.4 (157.0, 15.5–571.0)	< 0.001
CMT thinning (median, range), μm/yr	11.6 ± 24.9 (4.9, −12.5–162.4)		
SFCT thinning (median, range), μm/yr	4.7 ± 15.4 (4.0, −62.0–58.2)		
GA area (median, range), mm^2	2.77 ± 3.40 (1.45, 0.05–16.16)	6.08 ± 6.76 (4.33, 0.15–37.10)	< 0.001
GA area (SQRT) (median, range), mm	1.37 ± 0.95 (1.20, 0.23–4.02)	2.12 ± 1.26 (2.08, 0.38–6.09)	< 0.001
GA progression rate (median, range), mm^2/yr	1.01 ± 1.09 (0.63, 0.02–4.59)		
GA progression rate (SQRT) (median, range), mm/yr	0.23 ± 0.18 (0.16, 0.04–2.70)		
GA type, n, conventional GA/pachychoroid GA	79/22		
GA location, n, central/noncentral	51/50	66/35	
GA pattern, n, unifocal/multifocal	63/38	59/42	
Drusen, n, present/absent	67/34		
Drusen size, n, medium-sized drusen/large drusen/confluent drusen/drusenoid PED/large drusenoid PED	14/27/20/5/1		
Reticular pseudodrusen, n, present/absent	43/58		
MNV development†, n		6	
Fellow eye status, n, GA/neovascular AMD/intermediate AMD/no AMD; n = 100*	31/37/15/17	37/39/9/15	

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CMT = central macular thickness; GA = geographic atrophy; logMAR = logarithm of the minimum angle of resolution; MNV = macular neovascularization; n = number of patients; PED = pigment epithelial detachment; SFCT = subfoveal choroidal thickness; SQRT = square-root transformation. All values are presented as mean ± standard deviation or number.
*In 1 patient, information on the fellow eye was lacking due to phthisis.
†The subsequent period was not included in the follow-up analysis when MNV developed during the course of the disease.

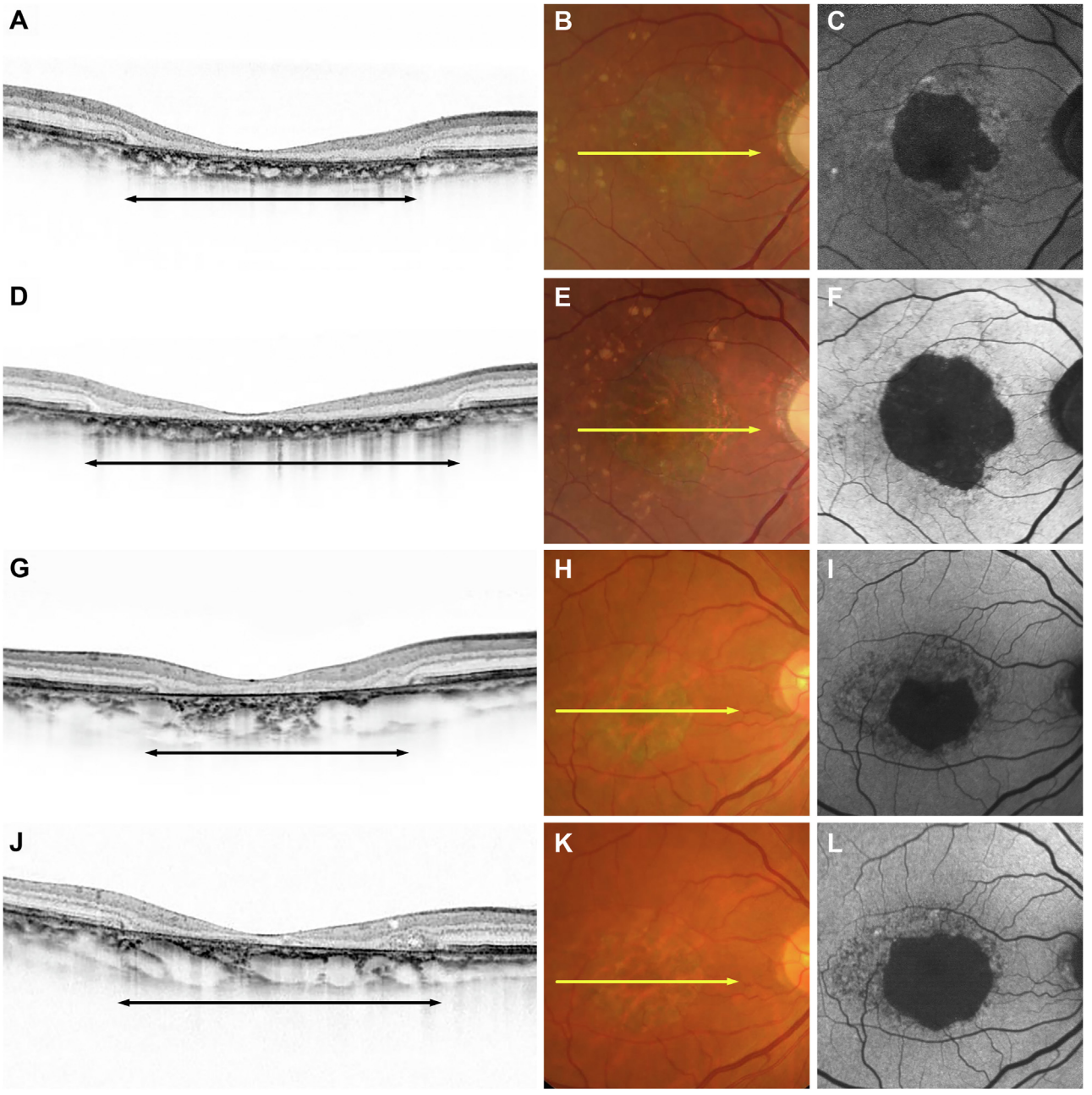

Figure 2. Multimodal imaging of conventional geographic atrophy (GA) of an 83-year-old man with 75 months' follow-up (**A**–**F**) and pachychoroid GA of a 61-year-old woman with 66 months' follow-up (**G**–**L**). The GA area enlarged from baseline (**A**–**C, G**–**I**) to the final visit (**D**–**F, J**–**L**). **A, D, G, L,** Horizontal scan images of spectral-domain OCT (SD-OCT) show complete retinal pigment epithelium and outer retinal atrophy. **B, E, H, K,** Color fundus photographs. Yellow arrows indicate the scan lines of SD-OCT images of panels **A, D, G** and **J, C, F, I, L,** Fundus autofluorescence images.

(3.06 ± 4.00 mm^2) in our patients was smaller than that reported in previous observational cohort studies on White populations (4.62–6.00 mm^2).[23,24] All our patients in the follow-up group showed progression of GA with time. The duration from the initial development of GA to the diagnosis could partially account for the differences in GA size.

Reticular pseudodrusen were observed in 42.2% of our patients, which is comparable to previous reports in Japanese (38.3%–50.0%)[12,25] and White (36%–37.8%) patients.[26,27] Because it is sometimes difficult to determine reticular pseudodrusen in the late stage, its prevalence might have been underestimated in this study. In addition, the mean SFCT in our patients (194.7 μm) was larger than that in White populations (151–173.0 μm).[28–30] A previous Korean study on GA also showed a relatively greater SFCT (188.3 μm).[9] In Asian populations, MNV (polypoidal choroidal vasculopathy and pachychoroid neovascularization) is frequently associated with a thick choroid.[31] There might be ethnic differences in the choroidal thickness in GA as well as in MNV.

Table 4. Comparison of GA Progression Rate (SQRT) between 2 Groups of Follow-Up Patients Divided by Various Parameters

Parameters	GA Progression Rate (SQRT) (mm per yr)		P Value
	Group 1 (n)	*Group 2 (n)*	
Sex (group 1: male, group 2: female)	0.20 ± 0.15 (63)	0.30 ± 0.19 (38)	0.008
Smoking status (group 1: current or former, group 2: never)	0.21 ± 0.15 (50)	0.28 ± 0.20 (40)	0.205
GA type (group 1: conventional GA, group 2: pachychoroid GA)	0.27 ± 0.18 (79)	0.11 ± 0.07 (22)	< 0.001
GA location (group 1: central, group 2: noncentral)	0.22 ± 0.16 (51)	0.25 ± 0.19 (50)	0.968
GA pattern (group 1: unifocal, group 2: multifocal)	0.18 ± 0.15 (63)	0.33 ± 0.17 (38)	< 0.001
Drusen (group 1: present, group 2: absent)	0.26 ± 0.17 (67)	0.17 ± 0.17 (34)	0.003
Reticular pseudodrusen (group 1: present, group 2: absent)	0.34 ± 0.17 (43)	0.15 ± 0.13 (58)	< 0.001
GA in fellow eye (group 1: present, group 2: absent)	0.33 ± 0.18 (31)	0.18 ± 0.15 (69)	< 0.001
Late AMD in fellow eye (group 1: present, group 2: absent)	0.27 ± 0.18 (68)	0.15 ± 0.12 (32)	0.001

AMD = age-related macular degeneration; GA = geographic atrophy; n = number of patients; SQRT = square-root transformation.

Table S6 (available at www.ophthalmologyretina.org) shows the GA progression rate in the current study compared with that in previous reports. The mean GA progression rate of our patients (1.01 ± 1.09 mm^2 per year) was relatively smaller than that of previous White (1.27−1.43 mm^2 per year)[23,24] and Korean reports (1.47 mm^2 per year).[9] Previous reports showed that the GA progression rate significantly depended on the baseline GA area.[2,32] Therefore, it is difficult to compare GA progression rates (mm^2 per year) among studies with different baseline GA areas, which was smaller in our follow-up group (2.77 ± 3.40 mm^2) than that of previous reports (4.62−6.00 mm^2).[23,24] To reduce the effect of baseline GA area, the SQRT strategy is recommended to measure the GA progression rate.[2] When applying this strategy, the GA progression rate in our patients (0.23 ± 0.18 mm per year [SQRT]) was more comparable to, but remained slightly lower than that in White patients (0.29 mm per year [SQRT]).[23] Few of the previous reports on Japanese GA have used the SQRT strategy; therefore, this study provides important information on the GA progression rate (SQRT) in a Japanese population.

We also investigated the baseline factors associated with the GA progression rate. Previous studies have shown that multifocal GA,[2,33] reticular pseudodrusen,[34,35] and bilateral GA[36] are prognostic factors for a higher GA progression rate (SQRT). As mentioned above, it was suggested that the GA progression rate (SQRT) is independent of the baseline GA area.[2] However, our multivariable analysis results showed a correlation between baseline GA area (SQRT) and GA progression rate (SQRT). Previous studies reported associations of reticular pseudodrusen with faster GA progression.[35,37] Recently, the Age-Related Eye Disease Study 2 showed that the difference in GA progression rates was approximately 35% depending on the presence or absence of reticular pseudodrusen.[35] Similarly, the GA progression rates (SQRT) in our patients with and without reticular pseudodrusen were 0.34 and 0.15 mm per year, respectively; thus, we confirmed that reticular pseudodrusen is an important prognostic factor for fast GA progression in the Asian populations.

Takahashi et al[21] defined the pachychoroid GA in relatively younger Asian populations, which is characterized by a thick choroid, choroidal vascular hyperpermeability, smaller lesions, no drusen, and a slow progression. In the current study, 38 eyes (22.0%) were classified as pachychoroid GA. Recently, the EYE-RISK consortium reported a cluster analysis of 196 European individuals with GA to determine whether GA subgroups exist that can be defined by their genotype and phenotype.[38] In their analysis, European GA in subgroup 2 (11.2%), which had low-genetic risk scores,

Table 5. Association between GA Progression Rate (SQRT) and Baseline Factors

Baseline Factors	Univariable Analysis	Multivariable Analysis					
	P Value	*β*	*SE*	*Lower 95% CI*	*Upper 95% CI*	*β*	P *Value*
Sex, female	0.005	6.4×10^{-3}	1.5×10^{-2}	-2.3×10^{-2}	3.6×10^{-2}	0.037	0.666
GA area [SQRT]	< 0.001	5.1×10^{-2}	1.6×10^{-2}	1.9×10^{-2}	8.3×10^{-2}	0.282	0.002
GA type, conventional GA	< 0.001	5.8×10^{-3}	1.9×10^{-2}	-3.2×10^{-2}	4.4×10^{-2}	0.028	0.761
GA pattern, multifocal	< 0.001	7.2×10^{-3}	1.8×10^{-2}	-2.8×10^{-2}	4.2×10^{-2}	0.041	0.684
Reticular pseudodrusen	< 0.001	5.7×10^{-2}	1.8×10^{-2}	3.5×10^{-2}	1.1×10^{-1}	0.407	< 0.001
GA in fellow eye	< 0.001	1.9×10^{-2}	1.7×10^{-2}	-1.5×10^{-2}	5.3×10^{-2}	0.103	0.266
Drusen	0.024						
Smoking status, current or former	0.066						

β = regression coefficient; β = standardized regression coefficient; CI = confidence interval; GA = geographic atrophy; SE = standard error; SQRT = square-root transformation.

foveal atrophy, and few drusen, was similar to pachychoroid GA in terms of genetic and fundus features, suggesting that pachychoroid GA may be present both in Asian and White populations. The proportion of this type of GA may vary between Asian populations and White populations. The features of pachychoroid GA may partially account for some differences between our patients and White patients.

The current study had several limitations. First, this was a retrospective study, and some data were unavailable, such as smoking status or axial length. Second, the study population was limited to Japanese patients and was small compared with previous reports on White populations. Geographic atrophy is rare in the Japanese population, which makes it difficult to include a large number of patients.[39] Third, the prevalence of reticular pseudodrusen may be underestimated because the diagnosis is sometimes difficult in the late stage or cases of large GA. Fourth, the current study contained no genetic information. A large cohort study suggested that some genetic factors are associated with fast GA progression.[40] Further studies are necessary to elucidate the clinical and genetic characteristics of GA in Asian populations.

In conclusion, to our knowledge, the current study, which had the largest number of patients with GA from an Asian population and the longest mean follow-up period, elucidated the clinical characteristics and the GA progression rate in an Asian population. Our results indicate that some characteristics of Asian patients with GA differ from those of White populations. Researchers need to consider the differences in phenotype of GA in different ethnicities because these differences may have implications when researching GA and considering interventions to slow progression of GA.

Acknowledgments

The authors thank Drs Masahiro Miyake and Yuki Mori of Kyoto University Graduate School of Medicine, Kyoto, Japan, for their statistical support.

Footnotes and Disclosures

Originally received: April 5, 2023.
Final revision: June 1, 2023.
Accepted: June 5, 2023.
Available online: June 9, 2023. Manuscript no. ORET-D-23-00126R2.

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Presented at the Association for Research in Vision and Ophthalmology Annual Meeting April 23–27, 2023, in New Orleans, Louisiana.

Disclosures:

All authors have completed and submitted the ICMJE disclosures form.

The authors have made the following disclosures:

N.U.A.: Financial support – Chugai Pharmaceutical; Lecturer – Santen Pharmaceutical, Novartis Pharma, Chugai Pharmaceutical, Bayer Yakuhin.

A.T.: Lecturer – Santen Pharmaceutical, Novartis Pharma, Bayer Yakuhin, MSD.

Y.M.: Financial support – Senju Pharmaceutical.

C.H.: Lecturer – Santen Pharmaceutical, Novartis Pharma, Chugai Pharmaceutical, Bayer Yakuhin.

R.M.: Lecturer – Kyowa Kirin.

H.K.: Financial support – Novartis Pharma, Alcon Japan, Bayer Yakuhin, HOYA, Senju Pharmaceutical, Santen Pharmaceutical, AMO Japan, Otsuka Pharmaceutical, Star Japan, Pfizer, KOWA Pharmaceutical, Nikon; Consultant – Novartis Pharma, Bayer Yakuhin, Chugai Pharmaceutical, Roche, Allergan, Boehringer Ingelheim; Lecturer – Novartis Pharma, Alcon Japan, Bayer Yakuhin, Senju Pharmaceutical, Santen Pharmaceutical, Kowa Pharmaceutical, HOYA, AMO Japan, Otsuka Pharmaceutical, Pfizer, Bausch &Lomb, JFC, Canon, Nidek, Topcon, AbbVie GK, TOMEY, Sumitomo Pharma, Chugai Pharmaceutical, Roche, Sanofi.

R.K.: Financial support – Topcon; Consultant – Office future, Nanolux; Lecturer – Senju Pharmaceutical, Novartis Pharma, Bayer Yakuhin, Kowa Pharmaceutical, Santen Pharmaceutical, Alcon Japan, Bausch &Lomb, Nanolux, Tamron, WHILL.

Y.Y.: Financial support – Alcon Japan, Sanbio; Consultant – Roche, Boehringer Ingelheim; Lecturer – Chugai Pharmaceutical, Novartis Pharma, Bayer Yakuhin, Santen Pharmaceutical, Novartis India Ltd., Boehringer Ingelheim, Senju Pharmaceutical, Roche; Stocks – DeepEyeVision Ltd.

T.I.: Financial support – Nidek, Topcon, Santen Pharmaceutical, Alcon Japan, Novartis Pharma, Senju Pharmaceutical, HOYA, AMO Japan, Pfizer, Otsuka Pharmaceutical; Consultant – Bayer Yakuhin, Novartis Pharma, Chugai Pharmaceutical, Boehringer Ingelheim Japan; Patent – Topcon; Lecturer – Bayer Yakuhin, Novartis Pharma, Alcon Japan, Santen Pharmaceutical, Senju Pharmaceutical, Topcon, Chugai Pharmaceutical, Canon, Nidek, Otsuka Pharmaceutical, Nikon.

K.T.: Financial support – Santen Pharmaceutical, Bayer Yakuhin, Novartis Pharma, Chugai Pharmaceutical; Consultant – Senju Pharmaceutical, Kyowa kirin; Lecturer – Santen Pharmaceutical, Bayer Yakuhin, Novartis Pharma, Senju Pharmaceutical, Chugai Pharmaceutical, Alcon Japan.

T.S.: Consultant – Bayer Yakuhin, Roche, Novartis, Boehringer Ingelheim, Kubota Pharm, Senju; Financial support – Novartis Pharma, Bayer Yakuhin, Senju Pharmaceutical, Santen Pharmaceutical, Alcon Japan, Chugai Pharmaceutical, Bausch & Lomb; Lecturer – Novartis Pharma, Bayer Yakuhin, Senju Pharmaceutical, Santen Pharmaceutical, Alcon Japan, Chugai Pharmaceutical, Bausch & Lomb.

A.T.: Financial support – Canon, Findex, Santen Pharmaceutical, Kowa Pharmaceutical, Pfizer, AMO Japan, Senju Pharmaceutical, Wakamoto Pharmaceutical, Alcon Japan, Novartis Pharma, Otsuka Pharmaceutical, Bayer Yakuhin, Nitten Pharmaceutical; Consultant – Senju Pharmaceutical, Bayer Yakuhin, Novartis Pharma, HOYA, Ellex, Allegan Japan, Eisai, Daiich-Sankyo, Chugai Pharmaceutical, MSD; Lecturer – Bayer Yakuhin, Senju Pharmaceutical, Novartis Pharma, Santen Pharmaceutical, Alcon

Pharma, Alcon Japan, AbbVie GK, AMO Japan, Kowa Pharmaceutical, Canon, Otsuka Pharmaceutical, Wakamoto Pharmaceutical.

The other authors have no proprietary or commercial interest in any of the materials discussed in this article.

Supported by Health and Labor Sciences Research Grants for Research on Rare and Intractable Diseases (grant no.: 20FC1029). The funding organization had no role in the design or conduct of this research.

HUMAN SUBJECTS: Human subjects data were used in this study. This research was conducted in accordance with the tenets of the Declaration of Helsinki and approved by the institutional review board and ethics committee of Kyoto University Graduate School of Medicine. The requirement for written informed consent was waived because of the retrospective design of this study and only deidentified data were available for analysis.

No animal subjects were included in this study.

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Obtained funding: Sakamoto

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **CFP** = color fundus photography; **CMT** = central macular thickness; **EDI** = enhanced depth imaging; **FAF** = fundus autofluorescence; **GA** = geographic atrophy; **logMAR** = logarithm of the minimum angle of resolution; **MNV** = macular neovascularization; **PED** = pigment epithelial detachment; **SFCT** = subfoveal choroidal thickness; **RPE** = retinal pigment epithelium; **SD-OCT** = spectral−domain OCT; **SS-OCT** = swept−source OCT; **SQRT** = square-root transformation; **US** = United States.

Keywords:
Age-related macular degeneration, Geographic atrophy, Japanese, Reticular pseudodrusen, Square-root transformation.

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萎縮型加齢黄斑変性の型別比較

佐藤有紀子[1]、上田 奈央子[1]、古泉 英貴[2]、原 千佳子[3]、井上 麻衣子[4]、
柳 靖雄[4]、飯田 知弘[5]、高橋 寛二[6]、坂本 泰二[7]、辻川 明孝[1]

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[6]関西医科大学医学部眼科学、[7]鹿児島大学医歯学域医学系眼科学

1

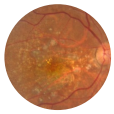
Conflict Of Interest

筆頭演者　佐藤 有紀子　公表基準に該当なし

共同演者　辻川 明孝 【F】: Canon, Findex, Santen Pharmaceutical
飯田 知弘 【F】: Nidek, Topcon、【P】
坂本 泰二 【F】: Novartis Pharma、【P】
高橋 寛二 【F】: Novartis Pharma

2

背景



・萎縮型加齢黄斑変性(age-related macular degeneration: AMD)は
滲出型AMDと共に後期AMDに含まれる

・地図状萎縮（geographic atrophy: GA）は経時的に拡大し、
中心窩に及ぶと視力低下に至る

Sunness JS *et al. Ophthalmology*, 1999

・日本人においてpachychoroidの特徴をもつpachychoroid GAの存在が示唆されている

Takahashi A *et al. Ophthalmol Retina*, 2018

・白人のGAにおいても、異なるphenotypeの存在が示唆されている

Biarnés M *et al. Ophthalmol Retina*, 2020

・米国でGAの治療薬が承認され、治療効果が期待されている

Liao DS *et al. Ophthalmology*, 2020

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背景

日本人のGAのうち20%がpachychoroid GAに分類される

日本人のGAは白人のGAと異なる特徴を有する

・男性優位
・脈絡膜は厚い
・GA面積は小さい
・GAの拡大速度は遅い

Sato Y *et al. Ophthalmol Retina*, 2023

Conventional GA群とpachychoroid GA群のそれぞれの特徴については明らかではない

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目的

日本人のGA をpachychoroid GAとconventional GAに分類し
それぞれの臨床的特徴を明らかにする

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方法

デザイン　後ろ向き多施設観察研究（京都大、東京女子医科大、横浜市立大、大阪大、関西医科大、琉球大）

対象　2009年1月–2021年12月に調査施設を受診した
萎縮型AMDの診断基準[1]を満たす50歳以上の日本人
HRAで撮影した眼底自発蛍光画像 (fundus autofluorescence; FAF) を有する者

Exclusion criteria　FAFの画質が不良で解析不可な症例

画像検査機器　眼底カラー写真、SD/SS-OCT、FAF

※両眼が満たす場合は、右眼のみを選択した

※半年以上の間隔を空けてFAFを撮影した症例をフォローアップ群として
初回（baseline）と最終回（final）で経過を検討した

SD: spectral-domain, SS: swept-source

1. 高橋寛二ら, 日眼会誌, 2015

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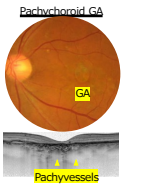
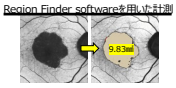
画像の計測と評価

GAの分類
・Type：pachychoroid GA/conventional GA
（1) pachychoroidを示唆する所見を認める
2) 黄斑部にconventional drusenを伴わない）
・Location：central/non-central
・Pattern　：unifocal/multifocal

GAの面積の計測
FAF画像の低蛍光領域を
Region Finder software(Heidelberg) を用いて半自動計測した

GAの拡大速度[SQRT*]
mm/year: 面積を平方根変換[1]し算出した





*SQRT = square-root transformation

1. Yehoshua Z *et al. Ophthalmology*, 2011

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結果1　全対象患者の型別特徴 (173人173眼)

Characteristics	Pachychoroid GA	Conventional GA	*P*-value
患者, n	**38** 22.0%	**135** 78.0%	
年齢, 歳	70.3	78.7	<0.001
性別, %, 男性	89.5	55.6	<0.001
喫煙歴, %, current or former	89.7	47.4	<0.001
視力, log MAR	0.15	0.40	0.002
中心窩下網膜厚, μm	143.6	145.3	0.613*
中心窩下脈絡膜厚, μm	312.4	161.6	<0.001**
GA面積, mm^2	0.59	3.76	<0.001
GAのlocation, %, central	42.1	54.8	0.199
GAのtype, %, unifocal	94.7	49.6	<0.001
Reticular pseudodrusen, %, あり	0	54.1	<0.001

GA = geographic atrophy; logMAR = logarithm of the minimum angle of resolution; n = number of patients.
Mann-Whitney *U* tests were used to compare the means between the two groups. To compare values between more than two groups, analysis of variance or Fisher's exact test were used.
* : age-adjusted, ** : age and sex-adjusted.

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結果2　フォローアップ群の型別特徴 (101人101眼)

Characteristics	Pachychoroid GA		Conventional GA		*P*-value***	
	Baseline	Final	Baseline	Final	Baseline	Final
患者, n	**22**		**79**			
経過観察期間, month	57.0		43.2		0.078	
年齢, 歳	71.2	76.1	78.1	81.7	0.002	0.002
性別, %, 男性	90.1		54.4		0.002	
視力, log MAR	0.19	0.26	0.39	0.55	0.086	0.026
中心窩下網膜厚の減少量 μm/year	6.5		4.1		0.093**	
GA面積, mm^2	0.65	1.91	3.36	7.24	<0.001	<0.001
GAの拡大速度, mm^2/year	0.23±0.25		1.22±1.13		<0.001	
GAの拡大速度 [SQRT], mm/year	0.11±0.07		0.27±0.18		<0.001	
経過中の黄斑部新生血管, n*	1		5		1.000	

GA = geographic atrophy; MNV = macular neovascularization; n = number of patients; SFCT = subfoveal choroidal thickness; SQRT = square-root transformation.
Mann-Whitney *U* tests were used to compare the means between the two groups. To compare values between more than two groups, analysis of variance or Fisher's exact test were used.
*The subsequent period was not included in the follow-up analysis when macular neovascularization developed during the course of the disease. **: age and sex-adjusted, ***Pachychoroid GA vs conventional GA.

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結果の要約

本調査のpachychoroid GA群はconventional GA群と比較して下記の結果であった

・男性優位の傾向が強い　(male: 89.5 vs. 55.6%, *P*<0.001)

・年齢が若い　(70.3 vs. 78.7 years, *P*<0.001)

・中心窩下脈絡膜厚が大きい　(312.4 vs. 161.6 μm, *P*<0.001)

・GA面積が小さい　(0.59 vs. 3.76㎟, *P*<0.001)

・GAの拡大速度が遅い　(SQRT: 0.11 vs. 0.27 ㎜/year, *P*<0.001)

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考察

・Pachychoroid GA：高橋らが2018年に提唱した概念
表現型、遺伝型においてdrusen-relatedなconventional GAとは異なる特徴をもつ。

表現型：年齢が若い、脈絡膜が厚い、GA面積が小さい、GAの拡大速度が遅い
遺伝型：ARMS2 A69S　リスクアレルの頻度が低い　Takahashi A *et al. Ophthalmol Retin*, 2018

・本調査のpachychoroid GAはconventional GAと比較してより男性優位で、年齢が若く、脈絡膜が厚く、GA面積が小さく、GA拡大速度が遅かった。
これらは既報とほぼ同様であった。

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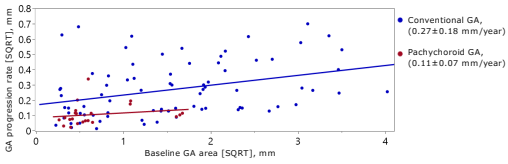
考察



・baselineの年齢と面積を調整後も、GAのsubtypeの違いは拡大速度と有意な相関を認めた
(重回帰分析, *P*=0.03, 回帰係数=4.7×10^{-2})

Pachychoroid GAとconventional GAは経過を含め臨床的に異なる特徴をもつと考えられる

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考察

Characteristics	本研究 conventional GA (>2.5mm², <17.5mm²)	欧米治験[1, 2] GA症例 control群
患者, n	35	81–100 (白人: 97.3-100%)
観察期間, month	42.8	12
年齢, years	76.5	78.2–78.4
性別, %, 男性	57.1	29.2–39.5
Baseline GA面積, mm²	6.43±3.42	3.4–8.2
GA拡大速度 [SQRT] , mm/year	0.33±0.17	0.29–0.40

本研究のconventional GA群は白人のGAと類似した特徴をもつ

日本人のGAが白人のGAと異なる特徴を持つのは、pachychoroid GAが含まれることが影響していると考えられる

1. Liao DS *et al. Ophthalmology*, 2020
2. Jaffe GJ *et al. Ophthalmology*, 2021

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結論

- Pachychoroid GAとconventional GAは臨床的に異なる特徴をもつ
- 日本人のconventional GA群は白人のGAと類似した特徴をもつ
- 日本人のGAが白人と異なる特徴を持つのは、pachychoroid GAが含まれることが影響していると考えられる
- 治療薬の適応を検討するにあたり、これらのsubtypeは考慮する必要がある

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