The Extent of Angioid Streaks Correlates With Macular Degeneration in Pseudoxanthoma Elasticum

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• PURPOSE: To investigate whether the extent of Bruch's membrane calcification is associated with choroidal neovascularization (CNV) and macular atrophy in patients with pseudoxanthoma elasticum (PXE) by using the extent of angioid streaks as a surrogate marker for the degree of Bruch's membrane calcification.

• DESIGN: Retrospective cross-sectional study.

• METHODS: We investigated 301 patients with PXE (median age, 52 years; range, 9-79 years) in a tertiary referral center. For both eyes, we graded the extent of angioid streaks, that is, their distance from the optic disc, into 5 groups. Imaging was systematically assessed for signs of CNV and macular atrophy. Associations between the extent of angioid streaks and CNV or macular atrophy were investigated using regression analysis.

• RESULTS: CNV was present in 148 patients (49%) and retinal atrophy in 71 patients (24%). The extent of angioid streaks was associated with older age (P for trend $= 1.92 \times 10^{-15}$) and a higher prevalence of CNV and/or macular atrophy (P for trend $= 4.22 \times 10^{-10}$ and P for trend $= 5.17 \times 10^{-6}$, respectively). In addition, the extent of angioid streaks was associated with the presence of CNV when adjusted for age and sex (odds ratio, 1.9; 95% confidence interval, 1.3-2.9) and with more severe macular atrophy (proportional odds ratio, 2.3; 95% confidence interval, 1.5-3.6).

• CONCLUSIONS: In patients with PXE, longer angioid streaks are associated with an increased risk of CNV and macular atrophy, even after adjustment for age. These findings are relevant when counseling PXE patients on their visual prognosis. (Am J Ophthalmol 2020;220:82–90.

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PSEUDOXANTHOMA ELASTICUM (PXE) IS A RARE DISorder in which biallelic mutations of the *ABCC6* gene lead to calcification of elastic fibers in the skin, vasculature, and eyes.[1] Clinically, calcification of Bruch's membrane (BM) leads to peau d'orange, which is hypothesized to be the visible transition zone of calcified BM.[2,3] Peau d'orange is typically seen at the posterior pole in childhood, is thought to spread centrifugally during life, and precedes the formation of angioid streaks in the brittle calcified BM.[3,4] Angioid streaks are defects in BM and present as irregular jagged breaklines.[5] They originate from the optic disc, surround it concentrically, and radiate outward to the periphery, but they do not cross the transition zone of calcified BM.[3] Angioid streaks allow for the ingrowth of fibrovascular tissue, causing choroidal neovascularizations (CNV) with the subsequent risk of hemorrhage, exudation, and scarring. Furthermore, patients with PXE often suffer from macular atrophy, similar to geographic atrophy in age-related macular degenation.[6] Both CNV and macular atrophy contribute to a high prevalence of visual impairment in patients with PXE.[7]

PXE is a slowly progressive disease, and the prevalence of CNV and macular atrophy increases with increasing age.[6,7] However, even in patients with similar age and genotype, the severity of macular degeneration is highly variable.[7–9] To predict the visual prognosis in PXE, it is necessary to gain insight in the determinants of CNV and macular atrophy. Gliem and associates[6] proposed that BM calcification is a risk factor for atrophy of the outer retina and retinal pigment epithelium (RPE), which can be considered as a natural endpoint in PXE. Angioid streaks predispose to the occurrence of CNV, and therefore the location of the angioid streaks (foveal or extrafoveal) is highly relevant for visual function. Moreover, the extent of angioid streaks is limited to the area of BM calcification and thus depends on the degree of BM calcification.

We hypothesize that patients with a larger extent of BM calcification have a higher risk of developing macular degeneration and thereby a worse visual prognosis. The aim of this study is to investigate whether the extent of angioid streaks, as a proxy for the degree of BM calcification, is associated with the occurrence of CNV and macular atrophy in patients with PXE.

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METHODS

• **STUDY DESIGN AND POPULATION:** This monocenter cross-sectional study was performed at the University Medical Center Utrecht in the Netherlands, which houses the Dutch National Expertise Center for PXE. The study adhered to the tenets of the declaration of Helsinki, and the Institutional Ethics Committee approved the study protocol (METC 19/257). All patients had a confirmed diagnosis of PXE, according to the criteria as proposed by Plomp and associates.[10] PXE was diagnosed if at least 2 major diagnostic criteria were present (skin involvement, eye involvement, and genetic confirmation of *ABCC6* mutations).[10] All patients with PXE with an ophthalmologic examination were included in this study, resulting in 301 patients. Genetic data were available in 296 patients: 281 patients had at least 2 *ABCC6* mutations, 11 had 1 mutation, and in 4 patients, no mutations in the *ABCC6* gene were found.

• **OPHTHALMOLOGIC MEASUREMENTS:** We investigated the data acquired on the first visit of the patients at the ophthalmology department. All patients underwent routine ophthalmologic examination, including best-corrected visual acuity (BCVA). Imaging included color fundus photography (FF 450 plus; Carl Zeiss Meditec AG, Jena, Germany), spectral-domain optical coherence tomography (SD-OCT), near-infrared reflectance (NIR) imaging, and fundus autofluorescence (FAF) (all Spectralis HRA-OCT; Heidelberg Engineering, Heidelberg, Germany). Fluorescein angiography and/or indocyanine green angiography was performed on indication. BCVA was used to classify the presence and severity of visual impairment, based on the visual acuity of the better eye, according to the World Health Organization.[11] Before 2018, both Snellen charts and Early Treatment of Diabetic Retinopathy Study charts were used.[12] From 2018 on, only Early Treatment of Diabetic Retinopathy Study charts were used. The BCVA was converted to the logarithm of the minimum angle of resolution.

Per eye, the available imaging was graded on the presence or absence of CNV and macular atrophy in the posterior pole by 3 individuals (S.R., R.v.L., J.O.v.N.). The presence of CNV was based on sub- or intraretinal fluid and/or neovascular or fibrotic tissue on SD-OCT, leakage of neovascular tissue and/or staining of fibrovascular scars on fluorescein or indocyanine green angiography, and hemorrhage, subretinal fibrosis or hyperpigmentation on fundus photography. The presence of macular atrophy was based on the focal loss of the RPE layer on SD-OCT, sharply demarcated areas of hypofluorescence on FAF and hyperreflectivity on NIR, hypopigmentation and visible choroidal vessels on fundus photography, or window defects on FA. If macular atrophy was present, it was classified into "mild atrophy" or "severe atrophy," based on the size of the atrophic area. If the atrophic area was smaller than the equivalent of twice the area of optic disc, it was graded as "mild atrophy," and if it was larger than the equivalent of twice the area of the optic disc, it was graded as "severe atrophy." In case of multiple atrophic areas, we graded the largest atrophic area. An atrophic zone <0.5 diameter of the optic disc surrounding an (in)active CNV, and peripapillary atrophy were considered unrelated to macular atrophy and therefore not classified as macular atrophy. If an atrophic area surrounding an (in)active CNV was larger than 0.5 diameter of the optic disc, only the area >0.5 diameter of the optic disc surrounding the CNV was graded, and the atrophic area directly adjacent to the CNV was excluded from grading.

Furthermore, the presence of pattern dystrophy–like changes was graded on FAF imaging. In 285 patients, FAF imaging was obtained at the same time as the imaging for the grading of the ophthalmologic phenotype. The FAF imaging was assessed for the presence of increased autofluorescence in the posterior pole resembling pattern dystrophy. Eyes with extensive scarring of FAF imaging of inadequate image quality for a reliable assessment were classified as "not assessable."

Angioid streaks were evaluated and graded using five 55-degree NIR images of the posterior pole and mid-periphery. In case of doubt, color fundus photography was also used. Because angioid streaks originate at the optic disc and spread toward the periphery, we constructed a grading system based on the distance from the center of the optic disc to the longest angioid streak. We defined 5 zones, based on the extent of the longest angioid streak: zone 1 corresponds with angioid streaks within a 3 mm radius, zone 2 corresponds with angioid streaks extending up to 6 mm, zone 3 corresponds with angioid streaks extending up to 9 mm, and zone 4 corresponds with angioid streaks that are longer than 9 mm (Figure 1). Eyes of young patients with peau d'orange but without detectable angioid streaks were classified as "zone 0." Eyes with extensive macular pathology in which grading of angioid streaks was not possible were classified as "not assessable."

Of all 301 patients, 4 patients did not have 55-degree NIR imaging, in 7 patients no angioid streaks were visible, and in 9 patients the image quality or severe scarring impaired reliable grading. Thus, grading could be performed in 297 patients, resulting in 288 patients of whom at least 1 eye could be assessed.

To investigate the interobserver agreement of the angioid streak grading system, we compared the scoring of 25 random patients (50 eyes) by 2 experienced ophthalmology graders (C.v.B. and S.R.). Interobserver agreement of the angioid streak grading system was quantified by the weighted kappa, which was 0.84 ($P < .001$). This can be interpreted as a strong agreement.[13]

• **DATA ANALYSES:** The correlation between the extent of angioid streaks between the right and left eye was assessed with the Goodman-Kruskal gamma, which is a measure of

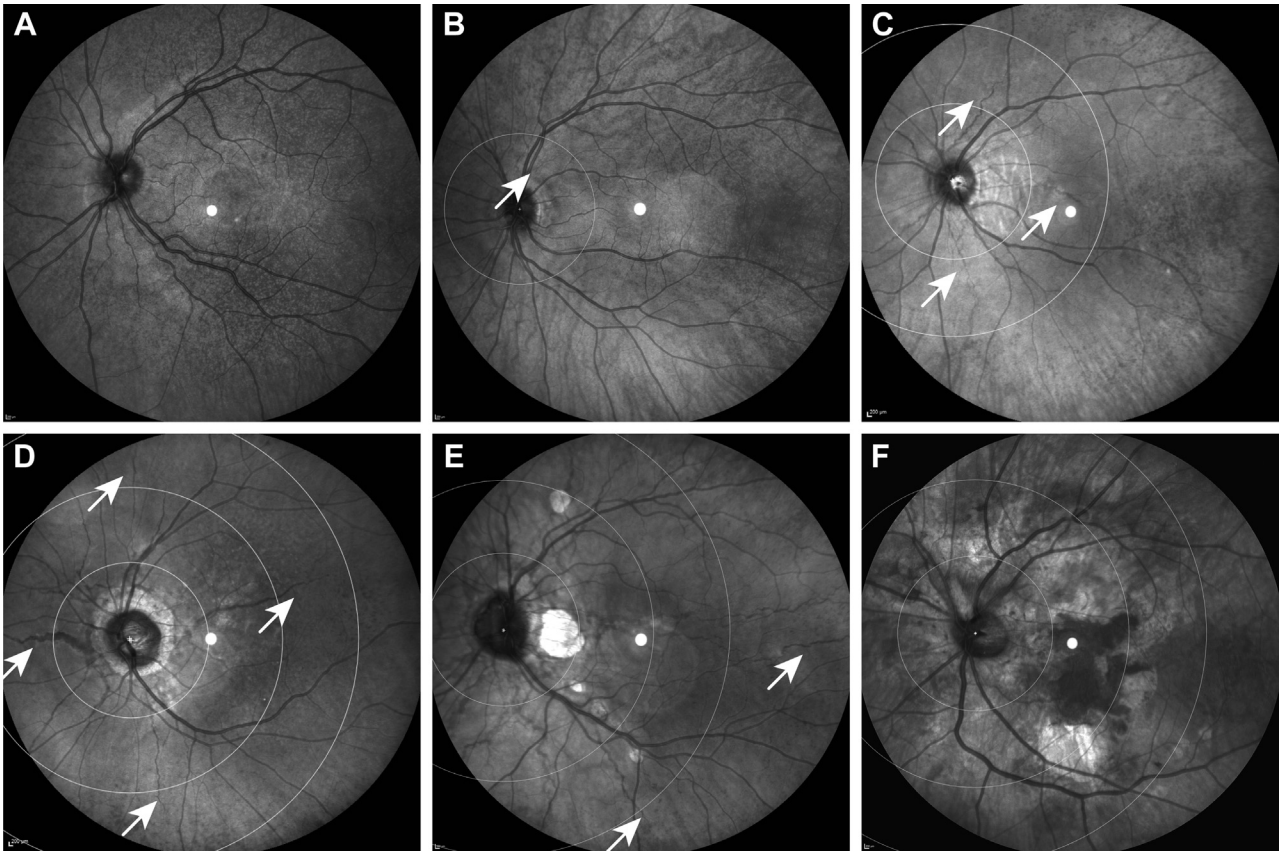

FIGURE 1. Grading of the extent of angioid streaks. Grading of angioid streaks performed with Heidelberg Eye Explorer, based on five 55-degree near-infrared reflectance images of the posterial pole and the midperiphery. The white circles represent circles with a 3 mm, a 6 mm, and a 9 mm radius and are centered on the optic nerve. The white arrows indicate angioid streaks. Angioid streaks were classified into 5 zones. If there were no detectable angioid streaks, the eye was classified as zone 0 (A). Zone 1 corresponds with angioid streaks within 3 mm of the optic disc center (B), zone 2 corresponds with angioid streaks extending up to 3-6 mm from the optic disc center (C), zone 3 corresponds with angioid streaks extending up to 6-9 mm from the optic disc center (D), and zone 4 with angioid streaks that extend further than 9 mm from the optic disc center (E). In eyes with extensive macular pathology, grading of angioid streaks was not possible and graded as "not assessable" (F).

association between categorical variables.[14] For descriptive analysis at patient level, the extent of angioid streaks in the right eye was used. If the imaging of the right eye was not assessable, imaging of the left eye was used. Eyes graded as "not assessable" were excluded from association and regression analyses.

Continuous variables are presented as mean ± standard deviation, or as median with interquartile range, depending on the distribution. Categorical variables are presented as numbers (%). The association between the extent of angioid streaks and other variables was analyzed using linear, logistic, or ordinal regression analysis, when appropriate. The extent of angioid streaks was entered as a continuous variable to test for trend. A P value of $<.05$ was considered statistically significant.

We used regression analysis to investigate the association between the extent of angioid streaks and the presence of CNV and the severity of macular atrophy. To test the association with the presence of CNV, we used logistic regression analysis. To test the association with the severity of atrophy, we used ordinal regression analysis. The models are presented as crude models and age- and sex-adjusted models. The extent of angioid streaks was modeled as a continuous determinant. In all analyses, the right eye was used first, and the left eye was used as confirmation.

R version 3.4.1 was used for data analysis. Additional packages "mess" (version 2019.4-25) and "ordinal" (version 0.5.6) were used to measure Goodman-Kruskal gamma and ordinal regression, respectively.

RESULTS

IN TOTAL, 301 PATIENTS WITH PXE WERE INCLUDED. THE PAtient characteristics are presented in Table 1 for both the

TABLE 1. Patient Characteristics

		Extent of Angioid Streaks[a,b]						
	Total	Zone 0, No Angioid Streaks	Zone 1, <3 mm	Zone 2, 3-6 mm	Zone 3, 6-9 mm	Zone 4, >9 mm	*P*	*P* for Trend
Number	301	7	3	78	81	119		
Age	52 (41; 60)	11 (11; 13)	25 (24; 34)	45 (28; 57)	54 (48; 60)	52 (47; 61)	8.36×10^{-9}	1.92×10^{-15}
Sex								
Female	189 (63%)	5 (71%)	2 (67%)	61 (78%)	49 (61%)	64 (54%)	0.01	2.17×10^{-3}
Ophthalmologic manifestations								
Visual acuity[c]	0.08 (−0.02; 0.70)	−0.02 (−0.04; 0.01)	−0.08 (−0.12; −0.08)	0.01 (−0.08; 0.10)	0.08 (0.00; 0.40)	0.20 (0.00; 1.26)	6.97×10^{-6}	2.56×10^{-7}
Visual impairment	86 (29%)	0	0	7 (9%)	19 (24%)	48 (40%)	1.01×10^{-5}	6.69×10^{-7}
Signs of (in)active CNV	148 (49%)	0	0	14 (18%)	47 (58%)	75 (63%)	2.00×10^{-10}	4.22×10^{-10}
Severity of atrophy								
None	229 (76%)	7 (100%)	3 (100%)	72 (92%)	64 (80%)	79 (66%)	9.68×10^{-4}	5.17×10^{-6}
Mild	35 (12%)	0	0	6 (8%)	10 (12%)	17 (14%)		
Severe	36 (12%)	0	0	0	7 (9%)	23 (19%)		
Pattern dystrophy–like changes[d]	116 (44%)	0	0	15 (19%)	37 (50%)	62 (63%)	1.41×10^{-8}	2.34×10^{-9}

CNV = choroidal neovascularization.

Data are presented as number (%) or median (interquartile range). All eye-specific details are shown for the right eye, unless this imaging could not be assessed; then the left eye was used.

[a]Stratified details for the extent of angioid streaks are presented for 288 patients with pseudoxanthoma elasticum. Four patients did not have 55-degree infrared imaging, and in 9 patients, the quality of the imaging or severe scarring or atrophy impaired reliable grading.

[b]The extent of the angioid streaks was measured as the extent of the longest angioid streak from the center of the optic disc on 55-degree near-infrared imaging.

[c]Visual acuity is the best corrected visual acuity presented as the logarithm of the minimum angle of resolution.

[d]Pattern dystrophy–like changes were assessed in 285 patients with available fundus autofluorescence imaging. In total, 28 right eyes and 28 left eyes had severe scarring of low image quality and were excluded. This resulted in data from 264 patients that are presented in this table.

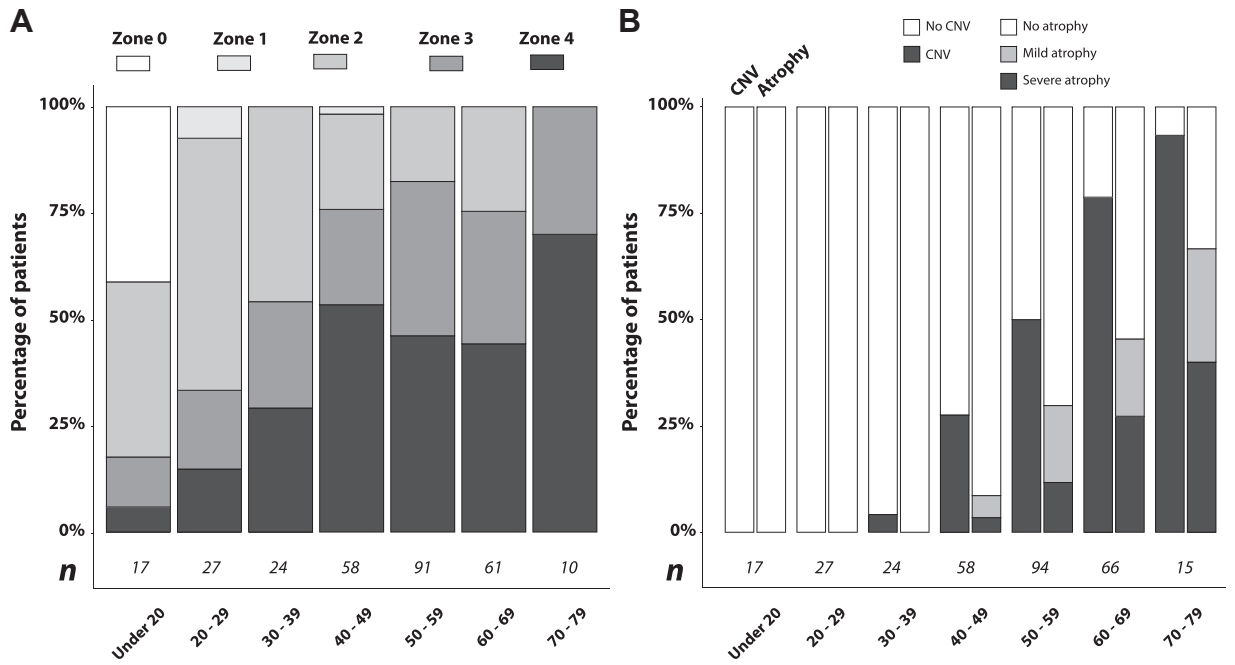

FIGURE 2. Relationship between age and extent of angioid streaks and macular phenotype. The extent of angioid streaks (A) and presence of choroidal neovascularization and macular atrophy (B) in the right eye, presented for age in years. The numbers at the bottom represent the number of patients within each group. The zones (A) represent the extent of the longest angioid streak. Zone 0 corresponds with no angioid streaks, zone 1 with angioid streaks extending up to 3 mm, zone 2 with angioid streaks extending between 3 and 6 mm, zone 3 with angioid streaks extending between 6 and 9 mm, and zone 4 with angioid streaks extending further than 9 mm from the optic disc center. CNV = choroidal neovascularization.

TABLE 2. Inter-Eye Correlation of the Extent of Angioid Streaks

		Zone of Right Eye					
Zone of left eye		0	1	2	3	4	NA
	n	7	3	90	73	112	12
0	7	7	0	0	0	0	0
1	3	0	1	2	0	0	0
2	78	0	2	71	4	1	0
3	78	0	0	16	52	10	0
4	115	0	0	1	14	97	3
NA	16	0	0	0	3	4	9

The extent of angioid streaks was measured in 297 patients with pseudoxanthoma elasticum, because 4 patients did not have 55-degree infrared imaging. If no angioid streaks were detected, the eye was classified as zone 0. Zone 1 corresponds with angioid streaks within 3 mm from the optic disc center, zone 2 corresponds with angioid streaks extending up to 3-6 mm from the optic disc center, zone 3 corresponds with angioid streaks extending up to 6-9 mm from the optic disc center, and zone 4 with angioid streaks that extend further than 9 mm from the optic disc center. In eyes with extensive scarring and atrophy, grading of angioid streaks was not possible and graded as "not assessable" (NA).

total group and subgroups of the extent of angioid streaks. The median age was 52 years (range, 9-79; interquartile range, 41-60) and the majority was female (63%). The length of the angioid streaks increased with age (Figure 2, A). Also, the prevalence of CNV and the severity of atrophy increased with age (Figure 2, B).

Patients with PXE with longer angioid streaks were older and more often male, had worse BCVA, more often CNV, more severe macular atrophy, and had more often pattern dystrophy–like changes (Table 1). Details of inter-eye correlation of the extent of angioid streaks can be found in Table 2. According to the Goodman-Kruskal gamma test,

TABLE 3. Association Between the Extent of Angioid Streaks and Macular Degeneration

	Crude Model, Estimate [95% CI]	Age Adjusted, Estimate [95% CI]	Age and Sex Adjusted, Estimate [95% CI]
Signs of (in)active CNV[a]			
Right eye	2.2 [1.7; 3.0]	2.0 [1.4; 3.0]	1.9 [1.3; 2.9]
Left eye	2.4 [1.8; 3.2]	2.0 [1.4; 2.9]	1.9 [1.4; 2.8]
Severity of atrophy[b]			
Right eye	2.5 [1.7; 3.8]	2.3 [1.5; 3.7]	2.3 [1.5; 3.6]
Left eye	2.3 [1.7; 3.4]	2.0 [1.4; 3.0]	2.0 [1.4; 3.0]
Pattern dystrophy like changes[a]			
Right eye[c]	2.6 [1.9; 3.7]	2.9 [1.9; 4.7]	2.9 [1.9; 4.7]
Left eye[c]	2.4 [1.8; 3.4]	2.4 [1.6; 3.8]	2.4 [1.6; 3.7]

CI = confidence interval; CNV = choroidal neovascularization.

If the extent of angioid streaks was graded as not assessable, the eye was excluded from analysis. For right eye analysis, 281 were included. For left eye analysis, 285 eyes were included in analysis.

[a]Models represent logistic regression models with the zone of angioid streaks as a continuous determinant. The estimate represents the odds ratio.

[b]Models represent ordinal regression models with the zone of angioid streaks as a continuous determinant. The estimate represents the proportional odds ratio.

[c]If the eye had severe scarring of the fundus autofluorescence of low quality, the eye was excluded from analyses. For both the right and the left eye, 252 eyes were included in the analyses.

there was a positive correlation between the extent of angioid streaks of both eyes ($\gamma = 0.97$, 95% confidence interval (CI), 0.95; 0.99), which can be considered as a very strong correlation.[15]

In crude analysis, CNV occurred more often in eyes with longer angioid streaks (odds ratio [OR], 2.2; 95% CI, 1.7; 3.0) (Table 3). This effect persisted when adjusted for age and sex (OR, 1.9; 95% CI, 1.3; 2.9). In this multivariable analysis, age was an important determinant of CNV (OR, 1.1; 95% CI, 1.1; 1.2). Interestingly, men had an increased risk of CNV in this multivariable analysis (OR, 2.0; 95% CI, 1.1; 3.7). Confirmation in the left eye yielded similar results for all analyses (Table 3).

Longer angioid streaks were also associated with more severe macular atrophy, even when adjusted for age and sex (proportional OR, 2.3; 95% CI, 1.5; 3.6; Table 3). Thus, there is a 2.3-times increased odds of having more severe atrophy if the extent of angioid streaks increases with 1 zone. In multivariable analysis, adjusted for age and sex, only age was an important determinant (proportional OR, 1.1; 95% CI, 1.1; 1.2), and male sex was not (proportional OR, 1.4; 95% CI, 0.7; 2.6). Again, confirmation in the left eye yielded similar results.

Furthermore, pattern dystrophy–like changes on FAF imaging presented more often in eye with longer angioid streaks (crude OR, 2.6; 95% CI, 1.9; 3.7; Table 3). This effect remained after adjusting for age and sex (OR, 2.9; 95% CI, 1.9; 4.7). In this multivariable analysis, age was associated with the presence of pattern dystrophy–like changes on FAF (OR, 1.2; 95% CI, 1.1; 1.2) but male sex was not (OR, 1.0; 95% CI, 0.5; 2.0).

DISCUSSION

IN THIS STUDY, WE DEVELOPED A MEASURE FOR THE EXTENT of angioid streaks as a surrogate marker for the degree of BM calcification that can be used in nearly all patients with PXE. The length of angioid streaks is symmetrical between both eyes, and angioid streaks appear to extend further with increasing age. Longer angioid streaks are associated with a higher risk of CNV and macular atrophy, also when adjusted for age and sex.

We hypothesize that the extent of angioid streaks increases with age and represents the natural course of calcification in patients with PXE. It is known that peau d'orange precedes angioid streaks, which fits with our data. The youngest patients did not have angioid streaks yet. We also found that aging, and thus a longer disease duration, is associated with longer angioid streaks. Even though our data are cross-sectional, we assume that angioid streaks are not a static phenomenon and that there is a slow growth of angioid streaks toward the retinal periphery during life. Mansour and associates[16] already described growth of angioid streaks in 2 patients, but it is unknown whether these patients had PXE. Hypothetically, the growth of angioid streaks with increasing age depends on 2 factors. First, it is assumed that a calcified BM may develop angioid streaks.[3] Second, it is assumed that mechanical stress, like eye movements or pressure on the globe, causes the brittle BM to break and form angioid streaks.[2,17,18] Therefore, mechanical stress may induce growth of angioid streaks throughout life. Besides a slow growth with age, angioid streaks may also progress more rapidly, for example due to

trauma causing pressure or acute retinopathy.[18,19] In this cross-sectional study, it is not possible to determine the underlying mechanism of the progression of angioid streaks. Acute retinopathy in PXE is rather rare with a presumed incidence of 5%, and most patients are advised to minimize the risk of suffering from an ocular trauma (avoiding contact sports for example). Therefore, we assume that rapid progression of angioid streaks due to trauma or associated with acute retinopathy alone cannot explain the age-specific prevalence seen in our cohort.

Interestingly, the growth of the angioid streaks after the fifth decade appears to slow down (Figure 2, A). It is plausible that the centrifugal spread of BM calcification stops around that age, which impedes angioid streaks to grow longer. However, the calcified BM is still brittle and prone to break from mechanical stress, and theoretically this may lead to a growth of angioid streaks in the form of branching. However, longitudinal data are required to support this theory, and the clinical relevance of this is unclear. It is possible that the extent of angioid streaks distinguishes well in younger patients but that patients over 50 years require a different approach to visualize the severity of disease. In these patients, often the first signs of macular degeneration are already visible, which probably provide more information on the visual prognosis. Thus, in patients over 50 years, the combined information on the presence of CNV, atrophy, and pattern dystrophy–like changes should be taken into account when counseling patients.

We found that longer angioid streaks are associated with a higher risk of CNV. Angioid streaks are full-thickness defects of BM that allow the ingrowth of neovascular tissue; thus it is plausible that longer and wider angioid streaks increase the risk of CNV.[5,20] A previous study found that patients with longer angioid streaks had a higher prevalence of CNV.[21] However, this study did not correct for age, and not all patients had PXE. In our study, we only assessed the presence of CNV in the posterior pole, and not along the angioid streaks toward the retinal periphery. In theory, this might have led to an underestimation of the prevalence, but in clinical practice, we only observe CNV in the posterior pole.

It is also plausible that longer angioid streaks, and thus a larger area of BM calcification, means that the BM calcification in the posterior pole is more dense and severe as well, and thereby increases the risk of CNV. More dense calcification in BM will impair oxygen diffusion from the choroid to the outer retina.[22] Together with the higher oxygen demand in the macular area, this leads to hypoxia and expression of vascular endothelial growth factors by the RPE.[23] The higher vascular endothelial growth factor level might initiate the growth of a CNV through an angioid streak. We found that longer angioid streaks increase the risk of CNV, which supports the hypothesis that the BM calcification is more dense. To further investigate if more dense BM calcification indeed increases the risk of CNV in PXE, an endpoint for the severity of BM calcification is required, in contrast to the measurement that was used in this study, which is based on angioid streaks and may thereby interfere with the risk of CNV.

We found that men with PXE are more at risk for CNV than women with PXE. This contradicts previous studies investigating the association of sex with CNV in other diseases. The majority of studies investigating late age related macular degeneration (AMD) did not find an effect of sex on CNV, but some studies mentioned a slightly higher prevalence of neovascular AMD in women.[24,25] If male patients with PXE had more BM calcification, they would also be more at risk for macular atrophy, but we did not observe this. Possibly, other unknown factors, for example cardiovascular risk factors such as smoking, are confounders in the association between sex and CNV. However, it is also plausible that female patients with PXE with a milder ophthalmologic phenotype are overrepresented in the younger population, and thereby introduce a selection bias.

Visual impairment is common in patients with PXE, and the visual acuity of the first eye often deteriorates around the fifth decade.[7,26–28] Because most but not all patients with PXE develop CNV or macular atrophy, the visual prognosis varies and is difficult to predict for an individual.[7] For patients with PXE, the foresight of losing vision impacts their quality of life, emotional well-being, and decisions in life planning.[29] Therefore, it is important to gain insight in determinants of macular degeneration for proper counseling of patients with PXE.

Up to now, the presence of angioid streaks in the fovea or macula indicates whether a patient with PXE is at risk for losing vision, because of the development of CNV. Predictors of macular atrophy have not yet been found in patients with PXE, although increased FAF is associated with macular atrophy.[6] Our findings show that patients with PXE with longer angioid streaks have a higher risk of macular degeneration and implicate that the degree of BM calcification is an important determinant for the final visual prognosis. This is important for counseling patients with PXE, especially younger patients under 40 years who have not yet developed CNV and do not show increased FAF. For example, we can assume that a patient with PXE with angioid streaks longer than the posterior pole will have a higher risk of macular degeneration and a worse visual prognosis than a patient with PXE with angioid streaks confined to the posterior pole. However, when counseling patients, it is important to realize that this study focuses on the loss of visual acuity. Other aspects of retinal function, such as impaired dark adaptation, contrast sensitivity, and the extent and location of paracentral scotomata, also affect the visual function of patients with PXE.[30]

Not only are these findings relevant for counseling patients, they may also give insight in the pathogenesis of atrophy of the outer retina and RPE. Even though not all patients develop RPE atrophy, our findings suggest that a higher degree of BM calcification increases the risk of RPE atrophy. This is supported by our findings that longer

angioid streaks increase the risk of pattern dystrophy–like changes. It is plausible that more BM calcification decreases the permeability of BM for diffusion of nutrients and waste products between the RPE and the choroid. Subsequently, this may lead to RPE dysfunction, which is visible as increased autofluorescence on FAF and often precedes RPE atrophy in patients with PXE.[6] Recently, it was found that pattern dystrophy–like changes are common in patients with PXE over 50 years, which strengthens the hypothesis that BM calcification progresses throughout life.[31] For a better understanding of the role of BM calcification in RPE dysfunction, which may eventually progress to RPE atrophy, an in vivo biomarker for BM calcification is required. Recently, an OCT-based quantification for BM calcification in patients with PXE was proposed.[32] However, further research and external validation is warranted before this is suitable as a biomarker in normal subjects.

A strength of this study is the size of the study population, which is relatively large for a rare disease. We adjusted the effect of the extent of angioid streaks on macular degeneration for age and sex, leading to a better estimation of the true effect. Furthermore, the use of the left eye as a confirmation serves as an internal validation.

Some limitations have to be acknowledged. The extent of angioid streaks is a new surrogate marker for the extent of BM calcification and is not validated yet. Also, the classification of the extent of angioid streaks in zones instead of a continuous measure causes a loss of information, because there is a high variability of the extent of angioid streaks within the different zones. The extent of angioid streaks was not adjusted for the patients' axial length, which might affect the precision of this measure. Furthermore, we did not account for the extent of branching of angioid streaks, which might be another indicator of the severity of angioid streaks. However, it is the first possible measure that can be used in nearly all patients with PXE. Gliem and associates[33,34] quantified the eccentric border of peau d'orange, which likely matches with the extent of BM calcification. This measurement can be performed best on 30-degree NIR imaging, which means that older patients with more eccentric peau d'orange are more difficult to measure. Also, in older patients, peau d'orange often is less visible, if the retina is not already affected by scarring or atrophy. Despite being a rough measure, the extent of angioid streaks can be measured in nearly all patients with PXE and is thereby a useful surrogate marker, also in end stage disease. Lastly, the cross-sectional design of this study allows for descriptions on group level, but it limits detailed insight into an individuals' course of disease. A longitudinal design is required to describe the progression of BM calcification and the natural course of macular degeneration within individuals. Because PXE progresses slowly, we estimate that such a longitudinal study would require a long follow-up time of roughly a decade, depending on the size and ages of the study sample.

CONCLUSION

IN PATIENTS WITH PXE, LONGER ANGIOID STREAKS ARE associated with an increased risk of CNV and macular atrophy, even after adjustment for age. This information is relevant when counseling patients with PXE on their visual prognosis. These findings attribute to a better understanding of the role of BM changes in the complex causal pathway of RPE atrophy.

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