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Intracranial atherosclerosis in pseudoxanthoma elasticum: A case-control study

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ABSTRACT

Background and aims: Pseudoxanthoma elasticum (PXE) is a genetic disorder characterized by systemic calcification of elastin fibers. Additionally, PXE is associated with an increased risk of stroke. It has been hypothesized that this may be caused by accelerated (intracranial) atherogenesis, as a consequence of specific genetic mutations underlying PXE. Hence, we compared the distribution and burden of intracranial atherosclerosis between PXE patients and healthy controls.

Methods: Fifty PXE patients and 40 age-and-sex-matched healthy controls (without previous ischemic cerebrovascular disease) underwent 3T MRI to visualize atherosclerotic intracranial vessel wall lesions (VWLs). We compared the presence and burden of VWLs (total and for the anterior cerebral, middle cerebral, intracranial internal carotid, posterior cerebral, and basilar arteries separately) between PXE patients and healthy controls using logistic (presence *versus* absence) and negative binomial regression models (VWL count) adjusted for relevant confounders. All regressions included group (PXE patients *vs.* healthy controls) as independent variable.

Results: We found that 34 (68.0%) PXE patients and 28 (70.0%) healthy controls had a VWL (odds ratio for presence 1.06 [95%CI 0.38–2.91]). In addition, the total burden of VWLs was similar between PXE patients (68 VWLs) and healthy controls (73 VWLs, incidence rate ratio for count 0.81 [95%CI 0.55–1.20]). Findings were similar when analyses were stratified for artery.

Conclusions: The distribution and burden of intracranial atherosclerosis were similar between PXE patients and healthy controls. This implies PXE and its underlying mutations do not involve increased (intracranial) atherogenesis and that vascular calcification or other mechanisms explains the increased stroke risk in PXE.

1. Introduction

Pseudoxanthoma elasticum (PXE, OMIM #264800) is a genetic disorder characterized by degradation and calcification of elastin fibers in various connective tissues, including the internal elastic lamina (IEL) of arteries throughout the body [1–3]. In addition, it has been hypothesized that genetic mutations that underlie PXE are involved in atherogenesis [4,5].

Recent investigations have highlighted that PXE patients are at an increased risk for stroke [6]. There has been scientific debate whether this is caused by the involved arterial calcification processes or by increased occurrence of (intracranial) atherosclerosis, as both are important risk factors for stroke [7,8]. Besides an increased carotid intima-media thickness and a decreased ankle-brachial index, both of which are thought to reflect atherosclerosis, data is lacking on actual *in vivo* assessment of atherosclerosis in PXE [9,10]. Further determining

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the putative association between PXE and intracranial atherosclerosis might improve the understanding of atherogenesis and stroke etiology in PXE, which could facilitate the development of targeted preventive strategies aimed at stroke reduction.

Therefore, we assessed the distribution and burden of intracranial atherosclerotic vessel wall lesions (VWL) on 3T MRI in PXE patients and healthy controls.

2. Patients and methods

2.1. Setting and study population

PXE patients were derived from the Dutch National Expertise Center for PXE (DNECP), which is an ongoing prospective PXE cohort situated at the University Medical Center Utrecht (UMCU) in the Netherlands. The DNECP currently comprises over 300 patients with a confirmed PXE diagnosis (99% Caucasian), which is based on the presence of at least two of the following three diagnostic features: 1) pseudoxanthoma's of the skin, 2) peau d'orange and/or angioid streaks of the retina, and/or 3) two pathogenic variants in the *ABCC6* gene (criteria by Plomp and colleagues) [11]. Based on an estimated prevalence of 1:25,000–1:50,000, the DNECP reflects a considerable portion of the total Dutch PXE population (between 50% and 95%) [12–15].

The current case-control study was embedded within the larger Determinants of Ectopic Calcification in Pseudoxanthoma Elasticum and Healthy controls: Evaluation of their Relations (DECIPHER) Study, which was a case-control study aimed at the assessment of cognitive, ophthalmologic and cardiovascular disease in PXE, including intracranial atherosclerosis. To this end, PXE patients from the DNECP were asked to participate and undergo additional measurements, including a magnetic resonance imaging (MRI) scan of the head. These patients were approached at the national PXE patient day as well as through a mailing to the PXE patient association. Thusly, we were able to include 50 PXE patients. From their surroundings, we gathered 40 age-and-sex matched healthy controls (non-first or second degree relatives), whom also underwent extensive clinical and imaging assessments. Inclusion criteria for the current study were age $\geq$18 years, no contra-indication for MRI (i.e. allergy to gadolinium, an estimated glomerular filtration rate (eGFR) $<$30 ml/min/1.73 m^2, claustrophobia, a pacemaker, implantable cardioverter-defibrillator, or a metallic foreign body in the eye), and, additionally, a negative history of cerebrovascular disease for healthy controls. The current study was approved by the medical ethical review committee of the UMCU, and all participants provided written informed consent (additional information on the study protocol and MERC approval is available in English at www.toetsingonline.nl/to/ccmo_search.nsf under number NL58514.041.16).

2.2. MRI based assessment of intracranial atherosclerosis

The MR protocol involved imaging of the brain at 3T (Achieva; Philips Healthcare, Best, the Netherlands) with an 8-channel phased array sensitivity encoding head coil. Acquisitions involved a three-dimensional T1-weighted volumetric isotropic reconstructed turbo spin-echo acquisition, with FOV 200 x 166 $\times$ 45 mm^3, acquired voxel size 0.5 x 0.5 $\times$ 0.5 mm^3, TSE factor + startup echoes 56 + 5, repetition time (TR)/echo time (TE) 1500/40 ms, acquisition time approximately 4:39 min, which also included a post-contrast scan for which 0.1 mL/kg of a gadolinium-containing contrast agent (Gadobutrol; Gadovist 1.0 mmol/mL; Bayer Schering Pharma) was administered approximately 5 min before acquisition.

VWLs were assessed according to a previously described methodology [16]. In short, a VWL was defined as the presence of one or both of the following two criteria: 1) an increase in vessel wall thickness $\geq$50% compared to adjacent sections of the vessel wall (in the case of concentric thickening) or compared to the contralateral vessel wall (in the case of eccentric thickening), and/or 2) focal or diffuse vivid contrast enhancement of the vessel wall. An illustrative example of an atherosclerotic vessel wall lesion is presented in Fig. 1. We assessed VWLs in the following arterial beds: the left and right anterior cerebral artery (ACA, A1 and A2 segments), middle cerebral artery (MCA, M1 and M2 segments), internal carotid artery (ICA, C3 to C7 segments including the bifurcation with the MCA), posterior cerebral artery (PCA, P1 and P2 segments), and the basilar artery (BA, including the bifurcation into the PCAs).

All images were assessed by a medical doctor (CL, 1 year of experience in VWL assessment), who was trained prior to the current study by a last-year radiology resident (AK) with 10 years of experience in intracranial VWL assessment. All assessments were performed blinded to patient characteristics. Interrater reliability between CL and AK was assessed on a randomly chosen subset of 30 scans of the current study (kappa 0.6).

2.3. Assessment of covariates

Low-density lipoprotein (LDL)-cholesterol was calculated using the Friedewald formula [17]. Hypercholesterolemia was defined as a serum LDL cholesterol $\geq$3.0 mmol/L and/or the use of lipid lowering drugs [18]. Blood pressure measurements were performed three times with a nonrandom sphygmomanometer on both arms, using the mean of the measurements from the arm with the highest blood pressures. Hypertension was defined as a systolic blood pressure $>$140 mmHg and/or a diastolic blood pressure $>$90 mmHg and/or use of antihypertensive drugs. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Obesity was defined as a BMI $\geq$30 kg/m [19]. Smoking status was categorized into current smoking, former smoking, or never smoking. Estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration equation [20]. Chronic kidney disease (CKD) was categorized according to the guidelines by the Kidney Disease Improving Global Outcome (KDIGO) [21]. Previous cerebrovascular disease was defined as a positive history of a cerebral ischemic infarction and/or a transient ischemic attack (which were based on the criteria of the American Heart Association) [22]. For PXE patients, the presence of mutations in the *ABCC6* gene was assessed according to previously described methods [23]. In short, *ABCC6* mutations were identified by Sanger sequencing and multiplex ligation-dependent probe amplification, and pathogenicity was estimated based on the ClinVar criteria (https://clinvarminer.genetics.utah.edu/variants-by-gene/ABCC6).

2.4. Statistical analysis

Baseline characteristics were presented per group as mean and standard deviation (SD) for normally distributed continuous variables, median with 25th and 75th percentiles (Q1-Q3) for non-normally distributed continuous variables, or number and percentages for categorical variables. The distribution of continuous variables was assessed visually with quantile-quantile plots and numerically with the Shapiro-Wilk test. Differences in baseline characteristics between groups were assessed with analysis of variance (ANOVA), the Kruskal-Wallis rank sum test, or the chi-square test. To assess differences in the overall distribution of VWL presence and burden across intracranial arteries, we used logistic (presence *versus* absence) and negative binomial (VWL count) generalized linear mixed models, accounting for the fact that participants might have VWLs in multiple arterial beds. To this end, the fit of a model including group (PXE *versus* healthy controls) and arterial bed was compared to a model additionally including an interaction term between group and arterial bed. Next, we compared the presence and burden of VWLs (total and artery-specific) between PXE patients and healthy controls using logistic (presence *versus* absence) and negative binomial regression models (VWL count). All regressions included group (PXE patients *vs.* healthy controls) as independent variable. Model 1 was unadjusted. Model 2 was adjusted for age, sex, hypercholesterolemia,

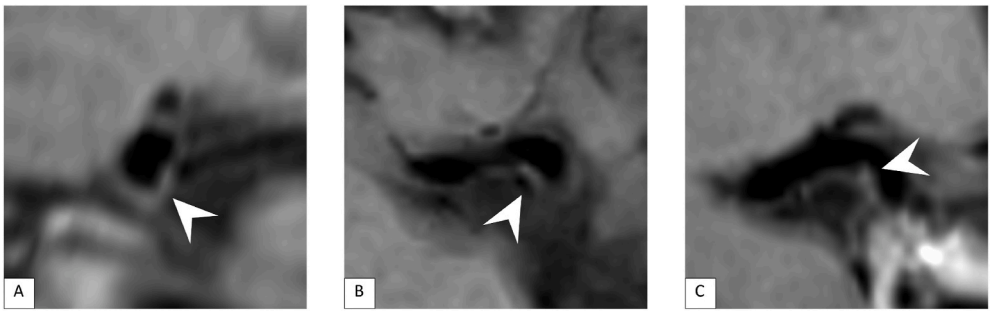

Fig. 1. Example of a vessel wall lesion on 3T MRI.
A 3T T1-weighted vessel wall image in the sagittal (A), axial (B), and coronal (C) plane showing eccentric enhancement of a vessel wall lesion (arrowhead) in the right intracranial internal carotid artery.

hypertension, obesity, smoking, and chronic kidney disease. Then, LDL cholesterol was lower in PXE patients compared to healthy controls. This is due to lipid lowering medication being prescribed early (according to the high risk group of the European Guidelines on Cardiovascular Disease Prevention) [18] at the DNECP, in light of the putative role atherosclerosis plays in the increased occurrence of cardiovascular disease observed in PXE. To deal with this, we repeated the analyses on total VWL presence and count (not including artery-specific analyses due to limited power) in patients with a normal LDL cholesterol (<3.0 mmol/L) and in patients that did not use lipid lowering medication. Lastly, to affirm the robustness of our findings, we repeated the analyses on total VWL presence and count in patients with genetically confirmed PXE.

We accounted for missing values (maximum proportion of missing values was 7%) using the Markov Chain Monte Carlo method with predictive mean modeling for continuous variables and polytomous logistic regression for categorical variables (25 imputations and 200 iterations). Statistical analyses were performed using R 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria). For all analyses, the level of significance was set to p-value <0.05.

3. Results

3.1. Baseline characteristics

In total, 50 PXE patients (median age 58.7 years [Q1-Q3 51.0–66.2]) and 40 healthy controls (median age 59.5 years [Q1-Q3 54.3–66.2]) were included in this case-control study. Of PXE patients, 48 (96%) had a biallelic pathogenic mutation of the *ABCC-6* gene (2 had a pathogenic mutation combined with a mutation of unknown pathogenicity), 50

Table 1
Baseline characteristics of study population.

Characteristics	PXE patients (n = 50)	Healthy controls (n = 40)	p-value
Continuous variables			
Age (years)	58.7 (51.0–66.2)	59.5 (54.3–66.2)	.41
LDL cholesterol (mmol/L)	2.8 (0.9)	3.6 (0.8)	<.01
HDL cholesterol (mmol/L)	1.5 (0.4)	1.6 (0.4)	.10
Triglycerides (mmol/L)	1.3 (0.9–1.7)	1.2 (1.0–2.0)	.586
Total cholesterol (mmol/L)	5.0 (1.1)	5.9 (1.0)	<.01
Systolic blood pressure (mmHg)	134.0 (124.2–147.8)	132.5 (123.0–140.2)	.50
Diastolic blood pressure (mmHg)	76.0 (71.0–80.8)	78.5 (74.5–84.0)	.13
BMI (kg/m^2)	25.7 (23.5–27.7)	26.2 (23.2–28.0)	.55
eGFR (ml/min/1.73m^2)	90.0 (82.5–90.0)	87.5 (78.0–90.0)	.15
Categorical variables			
Diagnostic PXE criteria according to Plomp [11]			
Biallelic pathogenic mutation of *ABCC6* gene	48 (96%)		
Peau d'orange and/or angoid streaks of retina	50 (100%)		
Pseudoxanthomas of skin	43 (86%)		
Sex (women)	27 (54.0%)	20 (50.0%)	.87
Hypercholesterolemia	38 (76.0%)	34 (85.0%)	.43
Use of lipid lowering medication	26 (52.0%)	5 (12.5%)	<.01
Hypertension	24 (48.0%)	17 (42.5%)	.76
Use of blood pressure lowering medication	13 (26.0%)	7 (17.5%)	.48
Obesity (≥30 kg/m^2)	8 (16.0%)	4 (10.0%)	.60
Smoking status			.23
Current smoker	6 (12.0%)	4 (10.0%)	
Former smoker	19 (38.0%)	9 (22.5%)	
Never smoker	25 (50.0%)	27 (67.5%)	
Chronic kidney disease (ml/min/1.73m^2)			.08
≥90	30 (60.0%)	18 (45.0%)	
60-89	20 (40.0%)	19 (47.5%)	
<60	0 (0.0%)	3 (7.5%)	
Previous cerebrovascular disease	8 (16.0%)	0 (0.0%)	.02

Data are presented as mean (standard deviation), median (25th percentile-75th percentile), or number (percentages).
p-values are for differences between groups as assessed by ANOVA for normally distributed continuous variables, the Kruskal-Wallis rank sum test for non-normally distributed continuous variables, or the chi-square test for categorical variables.
PXE, pseudoxanthoma elasticum; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; BMI, body mass index; CKD, chronic kidney disease.

Table 2
The distribution of intracranial atherosclerosis in PXE patients compared to healthy controls.

	PXE patients (n = 50)	Healthy controls (n = 40)
Presence of a vessel wall lesion		
Anterior cerebral arteries	4 (11.8)	5 (17.9%)
Middle cerebral arteries	9 (26.5%)	6 (21.4%)
Intracranial internal carotid arteries	23 (67.6%)	18 (64.3%)
Posterior cerebral arteries	8 (23.5%)	9 (32.1%)
Basilar artery	12 (35.3%)	14 (50.0%)
Total	34 (100.0%)	28 (100.0%)
Total amount of vessel wall lesions		
Anterior cerebral arteries	4 (5.9%)	7 (9.6%)
Middle cerebral arteries	9 (13.2%)	9 (12.3%)
Intracranial internal carotid arteries	33 (48.5%)	26 (35.6%)
Posterior cerebral arteries	10 (14.7%)	13 (17.8%)
Basilar artery	12 (17.6%)	18 (24.7%)
Total	68 (100.0%)	73 (100.0%)

Data are presented as the number of participants with a VWL (VWL presence) and the total VWL count per artery, with percentage relative to the total amount per group. Proportions of VWL presence do not add up to 100% as participants can have a VWL in multiple arterial beds. Overall, we found no difference in VWL distribution across arteries between PXE patients and healthy controls (VWL presence $p = 0.75$, VWL count $p = 0.65$).
PXE, pseudoxanthoma elasticum; VWL, vessel wall lesion.

(100%) had eye manifestations, and 43 (86%) had skin manifestations. Eight (16.0%) PXE patients had a history of cerebrovascular disease. PXE patients more frequently used lipid lowering medication (52.0% *versus* 12.5%, $p < 0.01$) and had lower LDL cholesterol levels (2.8 ± 0.9 *versus* 3.6 ± 0.8, $p < 0.01$) compared to healthy controls. Levels of HDL-cholesterol and triglycerides did not differ between groups. Other characteristics of the study population are displayed in Table 1.

3.2. Intracranial atherosclerosis in PXE patients compared to healthy controls

We found 68 VWLs in 30 (68%) PXE patients and 73 VWLs in 28 (70.0%) healthy controls. Overall, the distribution of VWLs across intracranial arteries was similar for PXE patients and healthy controls (PXE *versus* controls: VWL presence $p = 0.75$, VWL count $p = 0.65$; Table 2). Relative to the total amount of VWLs per group, VWLs occurred predominantly in the ICAs (33 VWLs [48.5%] in PXE patients, 6 VWLs [35.6%] in healthy controls) and least frequently in the ACAs (4 VWLs [5.9%] in PXE patients, 7 VWLs [9.6%] in healthy controls).

Fig. 2 displays the results of the regression models comparing PXE patients to healthy controls, revealing there were no differences in total or artery-specific VWL presence (odds ratio for total presence 0.95 [95% CI 0.33–2.71]) or VWL burden (incidence rate ratio for total count 0.85 [95%CI 0.56–1.29]). Similar results were observed when analyzing only participants with normal LDL cholesterol levels (<3.0 mmol/L) or participants that did not use lipid lowering medication (Table 3). Excluding

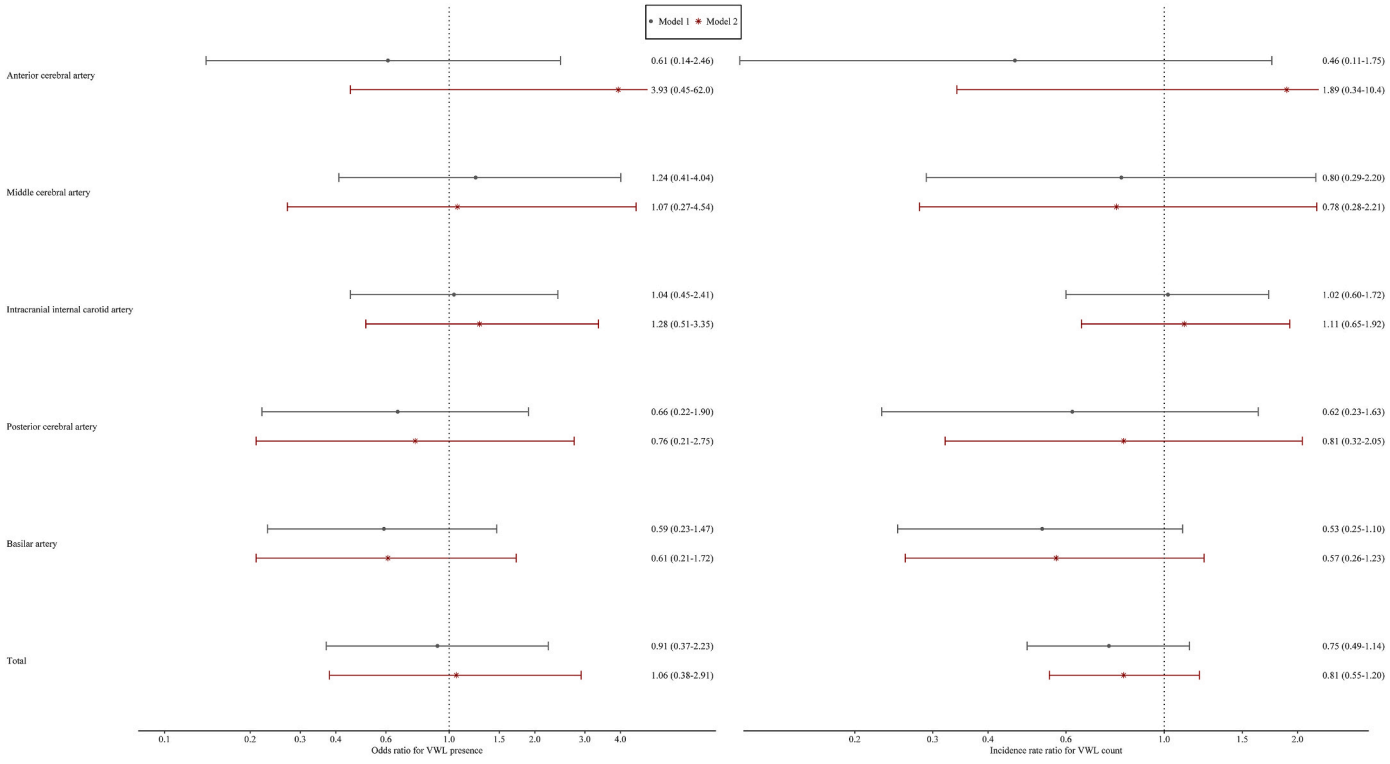

Fig. 2. The burden of intracranial atherosclerosis in PXE patients compared to healthy controls.
Data are (for PXE patients compared to healthy controls) odds ratios associated with VWL presence (*vs.* absence) and incidence rate ratios associated with VWL count, both in total and artery-specific, with corresponding 95% confidence intervals. Model 1 is unadjusted. Model 2 is adjusted for age, sex, hypercholesterolemia, hypertension, obesity, smoking, and chronic kidney disease. PXE, pseudoxanthoma elasticum; VWL, vessel wall lesion.

Table 3
The burden of intracranial atherosclerosis in PXE patients compared to healthy controls for specific subpopulations.

	All participants (as reference)	Participants with an LDL cholesterol <3.0 mmol/L (30 PXE patients *versus* 9 healthy controls)	Participants that do not use lipid lowering medication (35 PXE patients *versus* 24 healthy controls)
Odds ratio			
Model 1	0.91 (0.37–2.23)	0.96 (0.16–5.01)	1.02 (0.31–3.47)
Model 2	1.06 (0.38–2.91)	0.80 (0.10–5.73)	1.10 (0.29–4.47)
Incidence rate ratio			
Model 1	0.75 (0.49–1.14)	0.54 (0.25–1.15)	0.81 (0.48–1.36)
Model 2	081 (0.55–1.20)	0.74 (0.35–1.58)	0.88 (0.53–1.44)

Data are (for PXE patients compared to healthy controls) odds ratios associated VWL presence and incidence rate ratios associated with VWL count, both in total and artery-specific with 95% confidence intervals. Model 1 is unadjusted. Model 2 is adjusted for age, sex, hypercholesterolemia, hypertension, obesity, smoking, and chronic kidney disease.
LDL, low-density lipoprotein; PXE, pseudoxanthoma elasticum.

patients without genetically confirmed PXE (n = 2) did not materially change results (data not shown).

4. Discussion

To improve the understanding of atherogenesis and stroke etiology in PXE, we compared the burden of intracranial atherosclerosis between PXE patients and healthy controls. Contrary to our expectations, the distribution and burden of intracranial atherosclerosis were similar between PXE patients and healthy controls, indicating other mechanisms play a role in the increased stroke risk observed in PXE.

The genetic mutations that underlie PXE lead to systemic calcification of elastin fibers, including the IEL of arteries throughout the body [1–3]. As recent investigations highlighted intracranial IEL calcifications are associated with stroke in the general population, it is likely IEL calcification also contributes to the increased stroke risk observed in PXE [24]. Mechanisms by which IEL calcification could cause stroke include intracranial and aortic calcification induced arterial stiffness. Stiffness of the intracranial carotid artery might increase pulsatile energy that travels into the cerebral microcirculation leading to lacunar infarcts and hemorrhagic stroke [25]. Indeed, other investigations at the DNECP revealed intracranial pulsatility is increased in PXE [26]. Also, aortic stiffness might contribute to increased occurrence of cardiogenic stroke through an increased load on the left heart leading to impaired left ventricular function [27,28], which has also been observed in PXE [29]. Lastly, another mechanism that might contribute to the increased stroke risk in PXE is the recent finding of increased occurrence of internal carotid artery hypoplasia in PXE [30].

Strengths of the current study include the relatively large group of PXE patients that underwent vessel wall imaging, as PXE is a rare disease (estimated prevalence between 1 in 25,000 to 1 in 50,000) [15]. There are also several limitations to consider. PXE patients had lower LDL cholesterol and more often used lipid lowering medication (antilipid medication is prescribed relatively early at our center for PXE patients in view of their increased cardiovascular risk profile), which could have protected PXE patients from atherosclerosis formation [31]. However, we observed similar results when including only participants with normal LDL cholesterol levels and when including only participants that did not use lipid lowering medication, implying our findings were irrespective of LDL cholesterol or antilipid medication use. Moreover, we assessed VWLs on 3T MR images, while 7T is preferred due to better vessel wall visibility [32]. However, imaging at 3T is more widely available, which aids replication of our study and implementation of the technique in other centers.

In addition, it is important to note atherosclerosis in extracranial arteries might still be increased in PXE. For example, we previously found the burden of calcification in the intracranial carotid, arm and leg arteries to be increased in PXE (as assessed by CT) [33]. However, arterial calcifications seem to be mostly non-atherosclerotic in PXE [1,34]. Therefore, we encourage future studies to include more direct visualizations of the atherosclerotic process (e.g. using MRI based VWL assessment or NaF^{18} positron emission tomography-CT) to further elucidate the systemic burden of atherosclerosis in PXE. Lastly, ethnicity plays a role in atherogenesis but this information was not available in healthy controls.

Our findings suggest that mechanisms other than intracranial atherosclerosis contribute to the increased stroke risk observed in PXE. Investigations into the effects of arterial calcification and carotid artery hypoplasia on cerebral vascular function in PXE could further improve the understanding of stroke etiology, which could aid the development of targeted preventive strategies aimed at stroke reduction.

CRediT authorship contribution statement

Carlo Lucci: Conceptualization, Methodology, Investigation, Writing – review & editing. **Tim C. van den Beukel:** Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Jonas W. Bartstra:** Conceptualization, Investigation, Writing – review & editing. **Jaco Zwanenburg:** Writing – review & editing. **Anja van der Kolk:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision. **Richard Takx:** Writing – review & editing. **Jeroen Hendrikse:** Writing – review & editing. **Mirjam I. Geerlings:** Writing – review & editing. **Daniel Bos:** Writing – review & editing. **Wilko Spiering:** Conceptualization, Investigation, Writing – review & editing, Supervision. **Pim A. de Jong:** Conceptualization, Methodology, Investigation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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