Pseudoexfoliation: An Ocular Finding with Possible Systemic Implications

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ABSTRACT: Pseudoexfoliation syndrome (PES) is a common age-related disorder affecting 60–70 million people worldwide. Patients with PES have abnormal production and deposition of fibrillar material in the anterior chamber of the eye. These exfoliated fibrils, easily detected by ocular slit-lamp examination, have also been found to exist systematically in the skin, heart, lungs, liver and kidneys. Recently, a myriad of studies have associated PES with systemic conditions such as increased vascular risk, risk of dementia and inflammatory state. We review here the most current literature on the systemic implications of PES. Our aim is to encourage further studies on this important clinical entity.

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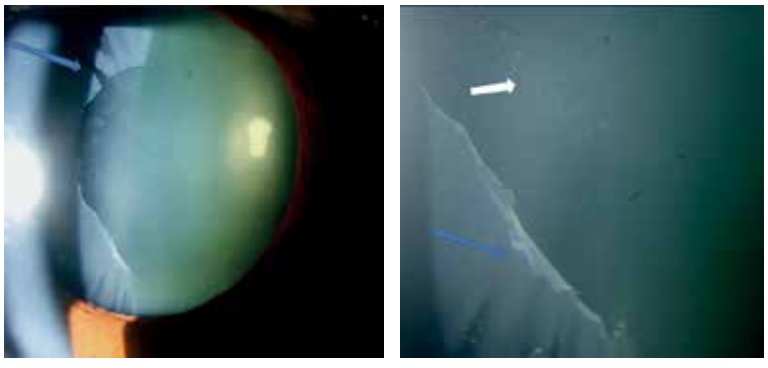
KEY WORDS: pseudoexfoliation syndrome (PES), slit-lamp examination, microfibrils

Pseudoexfoliation syndrome (PES) is an age-related disorder affecting up to 30% of the population over 60 years of age and 60–70 million people worldwide [1]. PES is characterized by the abnormal production and accumulation of fibrillar extracellular material in anterior eye segment structures lined by aqueous humor (lens, iris, cornea, trabecular meshwork, ciliary body and zonules) [Figure 1]. The pathogenesis of PES is considered to be a type of stress-induced elastosis, associated with the excessive production of a mixture of elastic and glycoprotein microfibrils (8–10 nm in diameter) [Table 1]. Genetic studies of multiple populations have found that single nucleotide polymorphisms in the lysyl oxidase-like 1 (*LOXL1*) gene, which may lead to functional change in the LOXL1 protein – a pivotal cross-linking enzyme responsible for elastic fiber formation and stabilization, contributes significantly to PES development [2]. Ocular manifestations of PES include pseudoexfoliation-associated glaucoma (PES-G, a secondary type of glaucoma), cataracts, zonular instability and lens subluxation.

Figure 1. Slit-lamp photos of PES material overflowing the pupillary border (blue arrow), with deposition on the lens anterior surface (white arrow). With permission from [29]



In patients with PES, extraocular deposition of the fibrillar material has been observed in various organs such as blood vessels, skin, liver, gallbladder, kidneys, lungs, heart, cerebral meninges and the inner ear [1]. Recent studies have associated PES with various systemic diseases such as angina, hypertension, myocardial infarction (MI), stroke, peripheral vascular disease, aneurysm, sensory hearing loss, and renal artery stenosis.

Our aim was to review the systemic involvement of PES in order to promote awareness of PES as part of a general disorder that is currently considered to be a specifically ophthalmologic entity.

CARDIOVASCULAR DISEASES

Increased risk for cardiovascular diseases was notably associated with PES by Wang et al. [3] who meta-analyzed 16 studies involving 8533 PES patients and 135,720 controls. Overall combined odds ratio (OR) for any cardiovascular disease was 1.72 in ocular PES patients compared to the control group: 95% confidence interval (95%CI) 1.31–2.26, $P < 0.001$. The ocular PES patients also showed increased risk of coronary heart disease (OR 1.61, 95%CI 1.22–2.14, $P < 0.05$), cerebrovascular disease (OR 1.59, 95%CI 1.12–2.23, $P < 0.05$), and aortic aneurysm (OR 2.48, 95%CI 1.30–4.72, $P < 0.05$).

In addition, Akdemir et al. [4] found a possible association between PES and coronary artery abnormalities in a cross-sectional study. The authors compared the prevalence of PES in 40 patients with coronary artery ectasia and 40 gender-matched subjects [4]. The patients with coronary artery ectasia had a significantly higher PES rate than did control patients with normal coronaries (52.5% vs. 20%, $P = 0.005$).

Table 1. PES material and genes associated with its pathologic production

Gene expression in PES tissue		Proteins found in PES tissue		
FBN1 (fibrillin-1)	Extracellular matrix metabolism	Elastin	Laminin	Latent transforming growth factor-ß binding proteins
TTIMP1 and TIMP2 (tissue inhibitors of matrix metalloproteinase 1 and 2)		Tropoelastin	Complement factors	Heparan sulfate
TGF-ß1 (transforming growth factor-ß1)		Vitronectin	Apolipoprotein	Chondroitin sulfate
ADORA3 (adenosine receptor A3)	Cellular stress response and regulation	Microfibril-associated glycoprotein	Clusterin	Dermatan sulfate
CLU (clusterin)		fibronectin	Matrix metalloproteinases	Laminin
mGST-1 (microsomal glutathione-S transferase 1)		Amyloid-p	Emilin	Transglutaminase 2

Adapted from [2]
PES = pseudoexfoliation syndrome

Gonen and colleagues [5] examined the relationship between PES and aorta-renal vasculature in a case-control study that included 49 PES patients and 42 control subjects with no atherosclerotic risk factors. Using Doppler ultrasonography and subsequent computed tomography (CT) angiography, the authors demonstrated that renal artery stenosis was more prevalent among PES patients than controls (18.4% vs. 2.4%, $P = 0.017$). There was no significant difference in abdominal aortic aneurysm rates between the PES and control groups (8.2% vs. 0%, $P = 0.061$). Notably, this study was later criticized for neglecting to evaluate serum cholesterol level as a risk factor for atherosclerosis [6].

Demir et al. [7] evaluated cardiac function in 32 PES patients and 25 healthy age- and gender-matched controls with no overt cardiac disease (congestive heart failure, valvular diseases, cardiomyopathy or left ventricular hypertrophy). The authors demonstrated by Doppler ultrasonography that the peak systolic velocities of septal, lateral, anterior, and inferior annuluses were all significantly lower in PES patients (6.8 ± 1.3 vs. 8.1 ± 1.2 cm/sec, $P < 0.001$; 7.8 ± 1.6 vs. 8.9 ± 1.5 cm/sec, $P = 0.01$; 7.5 ± 1.8 vs. 8.6 ± 1.4 cm/sec, $P = 0.02$; and 7.9 ± 1.4 vs. 8.8 ± 1.2 cm/sec, $P = 0.02$, respectively). Additionally, early diastolic velocity at the septal annulus and the ratio of early/late diastolic velocity at the lateral annulus were significantly lower in the PES group (7.3 ± 1.9 vs. 8.5 ± 2.4 cm/sec, $P = 0.03$; and 0.7 ± 0.2 vs. 0.9 ± 0.3 cm/sec, $P = -0.03$, respectively). The low values of all these echocardiographic indices may suggest that myocardial wall abnormalities and subclinical cardiac ischemia are more prominent in PES patients than in controls.

PES, a common age-related disorder affecting 60–70 million people worldwide, includes the excessive production of microfibrils which can be easily detected by ocular slit-lamp exam

Yilmaz and co-authors [8] also studied the cardiac function of PES patients, comparing 22 PES patients with or without glaucoma to 23 age- and gender-matched PES-free control subjects, none of whom had cardiac disease [8]. The authors investigated left ventricular function using Doppler echocardiography and fasting serum B-type natriuretic peptide (BNP). PES patients showed decreased diastolic function as compared to controls, indicated by lower early diastolic velocities at the basal septum and lateral annulus (7.6 ± 2.0 vs. 9.1 ± 1.6 cm/s, $P = 0.01$; and 9.3 ± 3.5 vs. 11.5 ± 3.1 cm/s, $P = 0.04$, respectively). BNP, which is released from cardiomyocytes in response to cell stretching and is elevated in association with both systolic and diastolic myocardial dysfunctions (normal value 0–125 pg/ml), was significantly higher in PES patients than in controls (129.04 ± 99.38 pg/ml vs. 59.64 ± 53.69 pg/ml, $P = 0.005$). BNP levels were also negatively correlated with the mitral annulus average early diastolic velocities ($r = -0.554$, $P = 0.009$). Ejection fraction, body surface area, left atrium size, left ventricular end-diastolic and end-systolic diameters, and posterior wall diameter during diastole were not significantly different in the two groups.

PES may also be involved in peripheral vascular pathology, as was suggested by Praveen el al. [9] in a case-control study which included 40 PES patients and 120 age-matched controls. The lowest mean ankle-brachial indices were lower in the PES group than in the control (0.88 ± 0.02 vs. 0.98 ± 0.03, $P < 0.001$), suggesting an increased risk of vascular disease in PES patients.

Several mechanisms potentially responsible for the increased cardiovascular risk in PES patients have been suggested. Gokce and colleagues [10] speculated that accumulation of pseudoexfoliative material in vessel walls may damage the arterial structure and increase cardiovascular risk in PES patients. The authors examined the relationship between PES and great vessel dysfunction by examining ultrasonographic imaging of the carotid and renal arteries for evidence of atherosclerotic-like wall changes. In a case-controlled prospective study including 19 PES patients and 18 control subjects, the thickness of the carotid intima media was significantly higher in the PES group (0.73 ± 0.02 vs. 0.59 ± 0.06 mm, $P = 0.003$) [10]. However, the renal artery resistance index did not differ significantly for the two groups.

YKL-40, a potential biomarker for pro-inflammatory processes, is associated with cardiovascular morbidity and may have

a role in causing endothelial cell dysfunction and atherosclerosis [11]. Turkyilmaz at al. [12] investigated the relationship of YKL-40 to PES by comparing 40 PES patients with 40 age- and gender-matched control subjects. Higher levels of YKL-40 were detected in the PES group (102.5 ± 68.1 vs. 65.0 ± 28.0 ng/ml, $P < 0.001$). In addition, several other parameters contributing to atherosclerosis and cardiovascular risk were detected in the PES group: significantly higher levels of high sensitivity C-reactive protein (hsCRP) (0.7 ± 0.6 vs. 0.3 ± 0.2 mg/dl), total cholesterol (200.1 ± 26.8 vs. 145.5 ± 47.0 mg/dl), low density lipoprotein (LDL) (128.3 ± 24.1 vs. 104.2 ± 29.0 mg/dl), triglycerides (134.4 ± 49.5 vs. 107.4 ± 36.3 mg/dl), and systolic (127.5 ± 9.6 vs. 121.8 ± 8.2 mmHg) and diastolic blood pressures (70.1 ± 11.4 vs. 65.2 ± 6.9 mmHg) were recorded for the PES group (for all comparisons $P < 0.01$). Moreover, significantly lower levels of high density lipoprotein (HDL) were detected in the PES group (44.7 ± 14.5 vs. 53.5 ± 14.2 mg/dl, $P = 0.002$).

Several biological markers associated with increased cardiovascular risk were also found to be more prevalent in the PES population. Altintas et al. [13] suggested that anticardiolipin IgG, a prothrombotic factor associated with increased cerebrovascular and cardiovascular risk, was significantly associated with PES. In a cross-sectional prospective study, 17 PES patients, 19 PES patients with glaucoma (PES-G) and 15 primary open-angle glaucoma (POAG) patients were compared to 18 healthy controls matched for age, gender, hypertension and diabetes. Anticardiolipin levels were shown to be significantly higher in the PES and PES-G groups than in the control group (8.53 ± 3.7 and 11.59 ± 5.2 vs. 0.42 ± 0.12 GPL/ml, $P = 0.007$ and $P = 0.047$, respectively). High levels of anticardiolipin IgG (> 15 GPL units/ml) were found in eight of the patients with PES or PES-G, but not in any of the control subjects.

Fibrillary deposits, the main feature of PES, have been detected histologically in various bodily organs

Several other mechanism have been suggested for the increased risk of vascular diseases in PES patients, such as accumulation of fibrillary material in the arterial wall of PES patients leading to impaired endothelial function, and high levels of plasma homocysteine among PES patients resulting in hypercoagulable state. However, this is beyond the scope of this review.

While various studies have linked PES to cardiovascular pathology, others have failed to identify relationships between PES and either mortality or cardiovascular morbidity. Speckauskas et al. [14] reviewed 1065 participants (aged 45–72) in a population-based study in Lithuania and found no significant association between PES and ischemic heart disease, diabetes mellitus or hypertension after controlling for effect of age.

CENTRAL NERVOUS SYSTEM

Dementia and cognitive impairment are believed to be associated with PES. Cumurcu et al. [15] reported 67 PES patients and 67 control subjects matched for age, gender, and educational background. A higher frequency of Alzheimer's-related dementia was observed in patients with PES (67.2% vs. 26.9%, $P = 0.0001$). However, in contrast to the findings of these previous reports, Ekstrom et al. [16] retrospectively reviewed the medical records of a population-based cohort (n=1123) and did not find any association between PES and newly diagnosed Alzheimer's disease (AD) patients (hazard ratio 0.98, 95%CI 0.69–1.74). The commonality between PES and AD may be amyloid-associated proteins, as the amyloid-β peptide (Aβ) can be found in the aqueous humor of a high proportion of PES patients.

SENSORINEURAL HEARING LOSS

The tectorial and basilar membranes of the inner ear and anterior segment of the eye share a common embryological origin, as both derive from neural ectoderm. It has been suggested that pseudoexfoliation material can be found in the organ of Corti, which is located in the cochlea [17]. Pseudoexfoliation depositions in the inner ear can disrupt mechanoreceptor function and cause sensorineural hearing loss (SNHL). Singham et al. [18] examined the association between PES and hearing loss. In a case-control study, 68 PES and PES-G patients were compared with 55 control subjects matched for age and gender. Below average hearing threshold was significantly higher in the PES/PES-G group than in the control ($P = 0.01$, OR 3.00, 95%CI 1.25–7.19). Overall, 85 subjects were diagnosed with SNHL, among whom 51 (60%) were PES/PES-G patients and the remaining 34 (40%) were controls. Similarly, Samarai and collaborators [19] found that SNHL is significantly more common in PES patients than in their age- and gender-matched controls ($P = 0.001$).

INSULIN RESISTANCE AND OBESITY

Omentin is an adipocytokine synthesized in visceral adipose tissue that functions as a receptor for bacterial arabinogalactans and lactoferrin. Omentin has been found to increase insulin signal transduction and to enhance insulin-stimulated glucose transport. Low levels of omentin are associated with obesity and insulin resistance and omentin is therefore regarded as a predictor for metabolic risk. Bucak et al. [20] suggested, by showing generally low levels of omentin in PES patients, that they might be at increased risk for obesity and insulin resistance [20]. In a case-controlled study, serum omentin levels were lower in 24 PES patients than in 20 healthy controls matched for age, gender and body mass index (BMI) (801.5 ± 317.1 vs. 1150.1 ± 584.1 ng/ml, $P = 0.016$).

RENAL FUNCTION

No significant association between PES and chronic kidney disease (CKD) or renal dysfunction has been established. In a study of 86 PES patients, 91 POAG patients and 94 non-glau-

coma control subjects, Zakrzewski et al. [21] compared serum creatinine level and estimated glomerular filtration rate (eGFR) at presentation with the numbers obtained at 3 months. After adjusting for diabetes mellitus and age, the researchers found no significant difference between groups.

Gonen et al. [22] examined 49 PES patients and 42 control subjects matched for age, gender and blood pressure. No significant differences were observed in mean creatinine, urea, blood urea nitrogen, microalbumin and creatinine clearance levels. There was also no significant difference in renal volume resistive index or pulsativity index, non-specific parameters for renal parenchymal dysfunction obtained by Doppler ultrasound.

IMMUNE SYSTEM

Sorkhabi at al. [23] compared serum hsCRP (an acute-phase protein and a marker for endothelial dysfunction) and tumor necrosis factor-alpha (TNFα, a cytokine involved in the acute-phase reaction) levels of 30 PES patients and 30 age- and gender-matched control subjects after controlling for conditions that may affect inflammatory biomarkers (history of trauma, inflammatory or infectious disorders, migraines, Raynaud's phenomenon, diabetes, ischemic heart disease, hypertension, hypercholesterolemia, renal and hepatic dysfunction, cerebral vascular accident, immune deficiency, and treatment with corticosteroids, non-steroidal anti-inflammatory drugs, antihypertensives, cholesterol-lowering drugs, aspirin, nitrates, hormone replacement or antioxidants). Significantly higher levels of hsCRP and TNFα were demonstrated in PES patients than in controls (3.95 ± 0.88 vs. 2.51 ± 0.79 mg/L, $P = 0.001$; and 3.32 ± 0.99 vs. 0.43 ± 0.15 pg/ml, $P = 0.002$, respectively). The higher hsCRP levels support a previously mentioned link between endothelial dysfunction and increased risk for cardiovascular events in PES patients. Yüksel et al. [24], however, found no significant difference in hsCRP levels between the groups when they prospectively investigated 31 PES patients, 26 PES-G patients and 25 control subjects matched for age, gender, BMI, heart rate and blood pressure.

Recent evidence suggests that PES is associated with an increase in cardiovascular morbidity, dementia, sensorineural hearing loss, insulin resistance and increased immune related response

Alpha 1-antitrypsin (AAT) is another acute-phase protein that reportedly plays a role in some ocular diseases with systemic implications (uveitis and Behcet's disease). In one study, Cumurcu and collaborators [25] enrolled 44 PES patients and 40 age- and gender-matched control subjects. Patients with diabetes mellitus, inflammatory gastrointestinal disorder, autoimmune diseases or infection were excluded from the study. These authors found venous blood AAT levels to be higher in PES patients than in the controls (1.545 ± 0.228 vs. 1.256 ± 0.173 g/L, $P = 0.0001$), suggesting that AAT might play a role in the pathogenesis of PES.

MORTALITY AND LIFESPAN

What is overall PES-related mortality? Svensson and Ekstrom [26] conducted a population-based study on the topic in the municipality of Tierp, Sweden [26]. The cohort included 1524 people, representing more than 21,000 person-years at risk. The researchers calculated standardized mortality ratios among PES and PES-free patients. No association was found between PES and mortality (HR 1.00, 95%CI 0.88–1.14) after a mean follow-up of 14 years.

Similar results were observed by Slettedal et al. [27], who conducted an epidemiological survey in Sør-Trøndelag County, Sweden in 1985–1986. Among 1888 individuals surveyed, 319 (16.9%) had PES. In 2014, 99% of participants were already deceased. After age and gender adjustment, no significant difference in the life spans of PES-positive and PES-negative patients was identified (relative risk 1.01, 95%CI 0.89–1.13, $P = 0.932$) [27].

DISCUSSION

PES is a common age-related disorder characterized by the excessive production and accumulation of fibrillary material in the anterior eye segment. It is easily detected by slit-lamp examination. From an ophthalmologic point of view, PES is considered to be a major risk factor for glaucoma and cataract surgery complications.

Extraocular deposits of PES material can be found in various visceral organs and appear to represent a systemic process associated with increased morbidity [Table 2]. The sequence in which PES depositions appear in different organs is not known, and the eye is not necessarily the primary organ for PES deposits. It is therefore difficult to determine whether PES is an ocular disease with systemic implications or a systemic disease with ocular manifestation.

One may regard PES as an altered protein accumulation that is part of the aging process and not as a systemic fibrillinopathic disorder. This view is supported by the fact that PES and PES-G are observed mainly in the elderly population (older than 60). Early-onset PES is rarely documented in the medical literature. PES-associated co-morbidities in young patients can help shed light upon the systemic nature of this disorder. Amini et al. [28] described a 36 year old male diagnosed with coronary artery disease while in his twenties. The patient underwent laser trabeculoplasty for glaucoma control and, 3 years later, was diagnosed with PES by slit-lamp examination. The authors speculated that surgical trauma acted as a trigger for PES [28]. Though feasibly incidental, one can appreciate the occurrence of coronary artery disease concurrently with PES in this young individual.

Table 2. Summary of association of PXF and systemic manifestation

	Author	Year	Study	Association	Result
Cardiovascular	Wang et al.	2014	Meta-analysis of 16 different studies	PES and increased risk of vascular diseases CHD, CVD and aortic aneurysm	+
	Akdemir et al.	2014	Cross-sectional	PES and coronary artery ectasia	+
	Gonen et al.	2013	Prospective, case-control	PES and proximal renal artery stenosis	+
	Demir et al.	2011	Cross-sectional	PES and early signs of myocardial ischemia in asymptomatic patients	+
	Yilmaz et al.	2014	Prospective, cross-sectional	PES and myocardial dysfunction PES and increased BNP levels	+ +
	Praveen et al.	2011	Case-control	PES and low ABI values	+
	Speckauskas et al.	2012	Cross-sectional, population-based	PES and ischemic heart disease, diabetes mellitus or hypertension	-
	Gokce et al.	2015	Prospective case-control	PES and increased CIMT and RARI	+ CIMT, - RARI
	Türkylimaz at al.	2013	Case-control	PES and YKL-40 pro-inflammatory protein	+
	Altintas et al.	2012	Prospective, cross-sectional	PES and fasting anticardiolipin (aCL IgG) and lupus (LA) antibodies level	+ aCL IgG - LA
CNS	Cumurcu et al.	2013	Case-control	PES and Alzheimer's dementia	+
	Ekstrom et al.	2014	Retrospective population survey	PES and newly diagnosed Alzheimer's dementia	-
Hearing loss	Singham et al.	2014	Case-control	PES and below average hearing threshold PES and hearing loss	+ +
	Samarai et al.	2012	Case-control	PES and sensorineural hearing loss	+
Metabolic	Bucak et al.	2014	Case-control	PES and lower omentin levels	+
Renal	Zakrzewski et al.	2012	Cross-sectional	PES and POAG with chronic kidney disease	-
	Gonen et al.	2014	Prospective, cross-sectional, case-control	PES influence on renal function	-
Immunologic	Sorkhabi et al.	2013	Prospective, cross-sectional	PES and hsCRP levels PES and TNFα levels	+ +
	Yüksel et al.	2010	Prospective, cross-sectional	PES and PES-G with elevated hsCRP levels	-
	Cumurcu et al.	2008	Case-control	PES and α-1 antitrypsin	+
Mortality	Svensson et al.	2015	Cohort	PES and increased mortality rate	-
	Slettedal et al.	2015	Epidemiologic survey	PES and life-span	-

PES = pseudoexfoliation-associated glaucoma, CIMT = carotid intima media thickness, RARI = renal artery resistive index, CHD = coronary heart disease, CVD = cardiovascular disease, BNP = B-type natriuretic peptide, ABI = acquired brain injury, POAG = primary open-angle glaucoma, hsCRP = high sensitivity C-reactive protein, PES-G = pseudoexfoliation-associated glaucoma

In this review, we observed a significant association between PES and hypertension and associations between PES and cardiovascular morbidities (coronary artery disease, subclinical myocardial ischemia, peripheral dysfunction and renal artery stenosis). We also reviewed various mechanisms that may explain the cardiovascular risk: accumulation of PES material in blood vessel walls, endothelial dysfunction, increased insulin resistance, elevated levels of homocysteine, anticardiolipin and other pro-inflammatory proteins that may be involved in the pathogenesis of cardiovascular events.

Although there are numerous reports on the association between PES and cardiovascular co-morbidity, PES patients did not have significantly increased mortality or life spans when compared to controls.

We also reviewed the significant association between PES and Alzheimer's dementia as well as sensorineural hearing loss. From an immunologic point of view, PES was found to be associated with increased levels of α1-antitrypsin and TNFα. Conflicting observations were made with regard to the involvement of HsCRP in PES.

An improved understanding of PES and its association with systemic morbidity may have important public health and clinical implications. We suggest that slit-lamp identification of PES may help indicate when an individual is at increased cardiovascular and cerebrovascular risk. These at-risk patients should then be referred to their family physicians for further evaluation of blood pressure control, a cardiac follow-up including echocardiography, routine abdominal ultrasound and regular blood glucose measurements. It may be advisable to counsel patients with PES on the potentially systemic consequences of this syndrome. Other authors have suggested that newly diagnosed PES patients be screened for left ventricular function by echocardiography [8] and for renal artery stenosis by invasive catheter angiography or another acceptable non-invasive method [5].

Finally, we would like to suggest that further studies of PES include at least four study groups: PES patients, PES-G patients, POAG patients, and healthy controls. While collecting data, we encountered many studies comparing either PES-only or PES-G-only patients to healthy control subjects. Adding an intermediate POAG group will elucidate whether a certain morbidity is

a PES-related or glaucoma-induced effect. One should also bear in mind that causal relationships between parameters cannot be inferred from cross-sectional studies or case-control studies; therefore, a longitudinal study should be conducted in order to provide stronger evidence and improve our understanding of direct relationships between PES and other co-morbidities. The main purpose of this review was to increase awareness of the PES clinical entity among non-ophthalmologist physicians. Hopefully, it will also encourage further investigation into the nature of PES pathology.

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