World Journal of Cardiology

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DOI: 10.4330/wjc.v6.i8.847

World J Cardiol 2014 August 26; 6(8): 847-854
ISSN 1949-8462 (online)

REVIEW

Pseudoexfoliation syndrome and cardiovascular diseases

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Received: December 18, 2013 Revised: April 9, 2014
Accepted: June 10, 2014
Published online: August 26, 2014

Abstract

Pseudoexfoliation (PEX) syndrome is a well-recognized late-onset disease caused by a generalized fibrillopathy. It is linked to a broad spectrum of ocular complications including glaucoma and perioperative problems during cataract surgery. Apart from the long-known intraocular manifestations, PEX deposits have been found in a variety of extraocular locations and they appear to represent a systemic process associated with increased cardiovascular and cerebrovascular morbidity. However, as published results are inconsistent, the clinical significance of the extraocular PEX deposits remains controversial. Identification of PEX deposits in the heart and the vessel wall, epidemiologic studies, as well as, similarities in pathogenetic mechanisms have led to the hypothesis of a possible relation between fibrillar material and cardiovascular disease. Recent studies suggest that PEX syndrome is frequently linked to impaired heart and blood vessels function. Systemic and ocular blood flow changes, altered parasympathetic vascular control and baroreflex sensitivity, increased vascular resistance and decreased blood flow velocity, arterial endothelial dysfunction, high levels of plasma homocysteine and arterial hypertension have all been demonstrated in PEX subjects. Common features in the pathogenesis of both atherosclerosis and PEX, like oxidative stress and inflammation and a possible higher frequency of abdominal aorta aneurysm in PEX patients, could imply that these grey-white deposits and cardiovascular disorders are related or reflect different manifestations of the same process.

Key words: Pseudoexfoliation; Cardiovascular disease; Cerebrovascular disease; Coronary artery disease; Homocysteine

Core tip: Although much remains to be clarified concerning causes, pathogenesis and systemic role of pseudoexfoliation aggregations, there is accumulating epidemiologic, clinical and laboratory evidence that this well-described clinical entity may occur as part of a systemic disorder with cardiovascular implications. The present review aims to summarize current knowledge on cardiovascular complications which have been associated with these suspicious whitish-gray deposits.

Andrikopoulos GK, Alexopoulos DK, Gartaganis SP. Pseudoexfoliation syndrome and cardiovascular diseases. *World J Cardiol* 2014; 6(8): 847-854 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i8/847.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i8.847

INTRODUCTION

Pseudoexfoliation (PEX) syndrome is an age-related disorder characterized by accumulation and deposition of microfibrillar material on multiple ocular and extraocular structures (Figure 1). The definite clinical diagnosis of the syndrome is based on slit lamp observation of the whitish flake-like deposits on anterior segment structures, particularly on the anterior lens surface and the pupillary border of the iris.

PEX syndrome is the most common identifiable

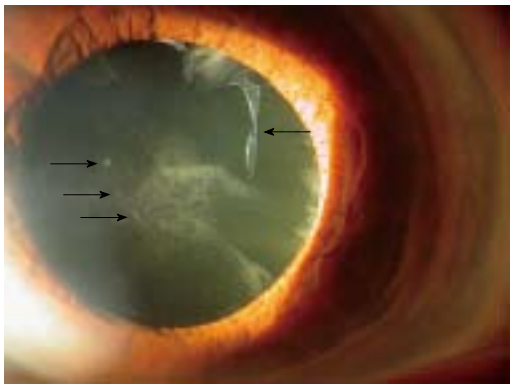

Figure 1 Pseudoexfoliation material on the anterior lens surface.

cause of open angle glaucoma, the so-called PEX glaucoma. It is also associated with cataract progression and intraoperative complications like zonular or posterior capsule rupture, poorly dilating pupil, vitreous loss, fibrinoid reaction, as well as, luxation of intraocular lens implants and corneal endothelial decompensation. In addition to the structures of the anterior segment of the eye, similar deposits have been identified in various visceral organs such as lung, heart, brain, vessels, kidney, gallbladder and meninges with unknown clinical significance.

PEX syndrome's prevalence demonstrates considerable geographic, ethnic and racial variation. Low PEX syndrome rates (< 6% in patients older than 70 years) have been reported in Greenland Eskimos, India, the eastern part of the United States, Germany, Britain, Australia, Japan, Austria, Denmark and Switzerland. In contrast, high PEX syndrome frequencies (> 15%) have been reported in Iceland, Finland, Russia, Tunisia, Saudi Arabia, Sweden, Norway, Turkey and Greece[1-3].

Although specific synthesis and pathogenesis of PEX material are still unknown, the concept of an elastotic process has recently been established. Molecular and biochemical data support the pathogenetic concept of PEX as a type of stress-induced elastic microfibrillopathy. PEX etiopathogenesis involves both genetic and non-genetic factors. Single-nucleotide polymorphisms (SNPs) in the coding region of the lysyl-oxidase-like 1 *(LOXL1)* gene, which is responsible for cross-linking of elastin, have been identified as strong genetic risk factors for PEX syndrome and PEX glaucoma[4]. Moreover, non-genetic factors including ultraviolet light exposure, dietary factors, infectious agents and trauma, as well as, oxidative stress, hypoxia and inflammation have been suggested to act as co-modulating external factors[5]. Pro-fibrotic cytokines (Interleukin-6), growth factors (GFs) and particularly transforming growth factor-β1 (TGF-β1), impaired cellular protection system with increased cellular and oxidative stress, a change in the local balance between Matrix Metalloproteinases and Tissue Inhibitor of Metalloproteinases appear to be involved in the disorder of the fibrotic matrix with accumulation of extracellular material. Ischemia/hypoxia, cross-linking mechanisms and aggregation of misfolded stressed proteins, as well as, low-grade chronic inflammatory processes have also been implicated[6-9]. PEX material seems to represent a highly cross-linked glycoprotein-proteoglycan complex which is mainly consisted of elastic microfibrillar components, such as fibrillin-1 and latent transforming growth factor binding proteins, as well as, chaperone molecules, such as clusterin, and cross-linking enzymes, such as LOXL1[10].

A variety of epithelial, endothelial and mesenchymal cells may be associated with impaired synthesis of the extracellular fibrillar material in intra- and extraocular sites. Intraocular material seems to be produced mainly in the pre-equatorial lens epithelium, the nonpigmented ciliary epithelium and the iris pigment epithelium, and secondarily in the corneal endothelium, the trabecular endothelium and by almost all cell types of the iris stroma[11]. Extraocular PEX material has been detected by electron microscope in connective tissue of visceral organs and in close proximity to fibroblasts, smooth and striated muscle cells, as well as, heart muscle cells[12,13]. These types of cells are probably involved in its production throughout the body. The fibrillar material shows ultrastructural and immunohistochemical similarities in both intra- and extraocular sites.

Although there is no clear-cut evidence that these deposits would cause degeneration of the extraocular tissues, they have been associated with cardiovascular and cerebrovascular morbidity. However, the clinical significance of the PEX-related systemic disorders remains controversial, as published results are inconsistent.

Studies implying a relationship between PEX syndrome and cardiovascular disease are mentioned below, along with others not supporting such a relationship.

HEART DISEASES

In Australia, the Blue Mountains Eye Study proposed that a history of angina, hypertension or a combined history of angina, acute myocardial infarction and stroke are significantly associated with the presence of PEX syndrome after multivariate adjustment including age, sex, glaucoma and vascular risk factors. This was attributed to the effect of elastosis in the vessel wall[14]. Citirik *et al*[15] found a significantly higher prevalence of PEX in 50 patients with coronary artery disease (CAD) proven by angiography than in healthy controls, and a higher prevalence of CAD in PEX individuals**.** PEX has been positively associated with presence of CAD among a large cohort of patients scheduled for cataract surgery[16,17]. More recently, French *et al*[18] reported significant associations of PEX and PEX glaucoma with a variety of cardiovascular disorders, including various stages of ischemic heart disease, cardiomyopathy and aortic aneurysm. Moreover, subclinical myocardial ischemia, by tissue Doppler echocardiography, has been found in PEX patients[19].

The possibility of an association between PEX and asymptomatic myocardial diastolic dysfunction (an important cause of heart failure), as assessed by two-dimensional echocardiography and pulsed Doppler echocardiography, has been suggested[20]. In addition, a higher prevalence of heart failure has been described in PEX

individuals[21].

Although there is convincing evidence that PEX syndrome is related to cardiovascular disorders, no significant relationship between PEX and CAD, aortic aneurysm or peripheral artery disease was reported by Emiroglu *et al*[22]. In the same line, arterial hypertension, ischemic heart disease, cerebrovascular disease and prevalence of diabetes mellitus did not differ between patients with or without PEX[23-27]. Of note, a higher prevalence of arrhythmia has been found in PEX individuals[23]. Also, a study by Tarkkanen *et al*[28] failed to show any significant difference in the frequency of hypertension or ischemic heart disease between patients with primary open-angle glaucoma (POAG) and PEX glaucoma, while the latter had a lower frequency of diabetes mellitus. Moreover, in the Thessaloniki Eye Study, no association was found between PEX and the history of specific or any systemic disease (self-reported history of hypertension, diabetes, cardiovascular disease, migraine, heart attack, coronary artery bypass, vascular surgery)[29]. Avsar *et al*[30] found no significant differences in time domain heart rate variability parameters (a measure of cardiac autonomic function) between patients with PEX syndrome and control subjects. Furthermore, several studies failed to demonstrate an association between PEX deposits and increased cardiovascular, cerebrovascular or total mortality[31-35].

VASCULAR AND CIRCULATION DISTURBANCES

Major manifestations of cardiovascular diseases such as a decreased blood flow and ischemia have frequently been documented in PEX syndrome. Deposition of PEX material within the vasculature with subsequent increases in vascular resistance and decreases in blood flow, vascular dysregulation and altered parasympathetic vascular control may be implicated in the pathogenesis of cardiovascular disorders in PEX subjects. Moreover, local ischemia and atherosclerosis have been correlated with elastosis in different tissues[36,37].

Increased aortic stiffness in PEX patients, which may be at least partially responsible for the increased incidence of CAD in this patient group has been described[38]. In addition, using the ultrasound wall tracking system Visontai *et al*[39] reported a lower distensibility and higher rigidity in the common carotid artery, as well as, altered parasympathetic vascular control connected to increased plasma homocysteine level in PEX/PEX glaucoma than the control group. Similar results were drawn by other studies showing lower myocardial peak systolic tissue Doppler imaging velocities and increased carotid intima-media thickness in patients with PEX syndrome when compared to controls. On the contrary, PEX and carotid plaque measurements were weakly correlated[40]. An impairment of parasympathetic cardiovascular regulation, baroreflex sensitivity and pulse wave velocity has also been described in PEX patients[41]. Arterial stiffening is an indicator of increased cardiovascular disease risk and, likewise, decreased baroreflex sensitivity has been described in hypertension, heart failure, myocardial infarction and metabolic syndrome. Lower cutaneous capillary blood flow and altered response to cold and warmth, without any change of plasma endothelin-1 concentration was also demonstrated[42]. Furthermore, Köz *et al*[43] found high levels of coronary risk markers such as lipoprotein (a), apolipoprotein A, homocysteine, as well as, impaired brachial artery dilation and increased carotid intima-media thickness in PEX patients. In a study by Praveen *et al*[25] PEX subjects had a significantly lower ankle brachial index as compared to controls, suggestive of PEX as a possible risk factor for peripheral vascular disease.

Ocular vascular and blood flow abnormalities

Dayanir *et al*[44] concluded that PEX decreases ophthalmic artery blood flow velocities and increases vascular resistance. Similar conclusions were drawn by another study where PEX patients had decreased blood flow velocities in the central retinal and the short posterior cilliary arteries and increased vascular resistance in the ophthalmic and central retinal arteries[45]. Reduced blood flow in choroid, optic nerve head and peripapillary retina of the PEX affected eye has also been found[46,47]. Moreover, Galassi *et al*[48] using color Doppler imaging found a decrease in ocular perfusion pressure and deterioration of retrobulbar haemodynamics in PEX glaucoma patients as compared to primary open-angle glaucoma patients and healthy controls. Several studies have demonstrated anterior-chamber hypoxia and iris vasculopathy (narrowing, occlusion, neovascularization) in PEX patients[49-52]. PEX as a potential risk factor for central retinal vein occlusion has also been proposed[53,54]. In support of the above, Cursiefen *et al*[55] found that PEX was significantly more common in eyes enucleated secondary to central retinal vein occlusion as compared to age-matched eyes enucleated for an intraocular tumor; however, morphological evidence of a PEX associated vasculopathy of the central retinal vessels explaining this association was not shown. Endothelin-1, a potent vasoconstrictor which could contribute to the obliterative vasculopathy seems to be increased in the aqueous humor of PEX eyes[56].

Cerebral vascular and blood flow abnormalities

A high frequency of PEX syndrome has been reported in patients with transient ischemic attacks[57-59]. A significantly higher prevalence of magnetic resonance images-defined white matter hyperintensities (ischemic changes) in patients with a clinical diagnosis of PEX with or without glaucoma *vs* control subjects, has also been documented[60]. Studies have indicated that the blood flow velocities of the middle cerebral artery were decreased in patients with PEX and PEX glaucoma[61,62] and there was a decrease in regional brain perfusion in PEX patients[63].

In addition, chronic cerebral diseases such as senile dementia, cerebral atrophy and chronic cerebral ischemia were more common in patients with PEX glaucoma than in those with POAG. The same study showed that patients with PEX glaucoma had higher probability of de-

veloping acute cerebrovascular disease than patients with POAG[51]. Alzheimer's disease has also been correlated to PEX syndrome in several, though not all studies[64-67].

Systemic arterial endothelial dysfunction

Arterial endothelial dysfunction is an independent predictor of future cardiovascular events. Vascular endothelium has a major role in the control of blood flow by releasing factors which may act either to contract the vascular smooth muscle, such as endothelin-1, or to relax it, such as nitric oxide. Atalar *et al*[68] found an impaired endothelial function in the brachial artery of patients with PEX syndrome, as assessed by vascular response to reactive hyperemia and sublingual nitroglycerin using high-resolution ultrasound. Endothelial dysfunction was attributed to the pseudoexfoliative fibrillar accumulation in the vessel wall. In the same line, endothelial dysfunction of the brachial artery was described in PEX subjects[69].

A major theory of atherosclerosis is that lesions result from an excessive fibroproliferative response to various forms of insult to the endothelium and smooth muscle of the vascular wall[70]. Endothelial exfoliation has been defined as thin, friable, mobile and translucent tissue, loosely adherent to the vascular wall[71] that may play a functional role in thrombus formation[72].

Nevertheless, other studies failed to demonstrate a correlation between PEX and endothelial damage, as biomarkers levels of endothelial injury (von Willebrand antigen, E-selectin, P-selectin and high sensitivity C-reactive protein) did not differ in blood plasma of patients with PEX *vs* controls[73,74].

Elevated homocysteine

Homocysteine is an independent risk factor for cardiovascular disease. It is associated with vascular injury and, thus, increased risk for stroke, CAD and venous thrombosis. Possible mechanisms of action include endothelial dysfunction, platelet aggregation and perturbation of clotting factors. In addition, alteration of the extracellular matrix of several tissues (mainly vessels), elastolysis and oxidative stress may be implicated.

Hyperhomocysteinemia has been suggested as a possible cause for increased vascular risk because of the potential to trigger the abnormal matrix accumulation in PEX patients. High levels of plasma homocysteine have been found in patients with PEX syndrome and PEX glaucoma[75-84]. Homocysteine concentration has been found to be elevated[83] or unaffected[77] in aqueous humor of patients with PEX glaucoma, while increased in PEX glaucoma patients' tears[84]. Vitamins B6, B12 and folate, which are involved in homocysteine metabolism and negatively correlated with total plasma homocysteine levels, have been reported to be decreased in PEX glaucoma patients[85], though not differing between PEX and control groups in another study[77]. On the contrary, Turacli *et al*[86] did not confirm the relationship between plasma homocysteine and PEX syndrome. Hyperhomocysteinemia has also been implicated in the decrease of both LOX activity and expression in vascular endothelial cells[87]. LOX downregulation has been associated with endothelial dysfunction, characteristic of earlier stages of the atherosclerotic process[88]. A possible association between SNPs in the *LOXL1* gene (which is linked with PEX syndrome) and spontaneous cervical artery dissection has also been proposed[89].

Arterial hypertension

It is known that hypertension is a major risk factor for stroke, myocardial infarction, heart failure, aneurysms of the arteries (*e.g.*, aortic aneurysm), peripheral arterial disease and chronic kidney disease. At least two studies have demonstrated a higher rate of arterial hypertension in patients with PEX[14,90]. Endothelial damage, impairment of the parasympathetic vascular regulation and elastosis have been implicated. Renal artery stenosis with subsequent arterial hypertension has also been reported[91]. However, reports are conflicting and no clear association has yet been proven, as other studies failed to demonstrate any significant relationship between PEX and arterial hypertension[15,16,17,23-26,61,92], or found arterial hypertension to be less common in PEX subjects[28,93,94].

Aortic aneurysm

Impairment in systemic macro- and microcirculation in PEX patients has been suggested. Abdominal aortic aneurysms have been attributed to atherosclerosis, though other factors are involved in their formation. An association between aneurysms of the abdominal aorta and PEX syndrome has been proposed. Histopathological examination of aortic-wall samples from patients with ocular PEX syndrome revealed accumulation of focal PEX deposits in the adventitial and subendothelial connective tissue, pronounced fibrosis, and elastosis of the tunica intima[95]. Abdominal aorta aneurysm was observed with a higher frequency in PEX patients than in control group[91,96], although, other studies failed to demonstrate any significant association[97,98].

OTHER COMMON PATHOGENETIC SIGNS

Apart from epidemiologic studies and the presence of PEX deposits on vessel wall, a possible relation between PEX material and cardiovascular disease may be supported by similar features in their pathogenesis. In addition to vascular endothelial dysfunction, hyperhomocysteinemia and blood flow changes mentioned above, disorders of the extracellular matrix by growth factors, matrix metalloproteinases, cytokines and altered enzymic action constitute part of atherosclerosis[99] and PEX fibrillopathy process. Altintas *et al*[100] demonstrated higher serum antiphospholipid antibodies (a risk factor for cardiovascular and cerebrovascular disease) in patients with PEX and PEX glaucoma than in healthy controls and in patients with POAG. In support of the above, serum asymmetric dimethyl arginine and YKL-40 levels (both independent cardiovascular risk factors) have been found higher in

PEX patients than those of the control group[101,102].

Atherosclerosis is associated with a number of oxidative events like low density lipoproteins oxidation, production of intracellular reactive oxygen species (ROS) and reactive nitrogen species (RNS), as well as, endothelial dysfunction and plaque disruption[103]. The oxidative-antioxidative balance is disturbed in patients with PEX syndrome as supported by reduced levels of antioxidants such as ascorbic acid, glutathione, trace elements, antioxidative enzymes in aqueous humor and serum and increased levels of oxidants such as hydrogen peroxide or nitric oxide, as well as, oxidative stress markers[104].

Inflammation plays a major role in all phases of atherosclerosis. Inflammatory cells like macrophages and lymphocytes both migrate from the blood and multiply within the atherosclerotic plaques. Activation of these cells leads to lytic enzymes, cytokines, chemokines and growth factors release that induce further damage[105]. Stress-induced, temporally restricted subclinical inflammation in anterior segment tissues is detected during the early stages of the fibrotic PEX process[10]. Moreover, inflammatory markers such as alpha-1 antitrypsin, Interleukin-6, high-sensitivity C-reactive protein and Tumor Necrosis factor alpha have been reported to be increased in PEX subjects[106-108].

CONCLUSION

Although more data is still required, an increased incidence of cardiovascular disorders in PEX patients and several common features in their pathogenesis suggest that PEX may be an independent risk factor for cardiovascular disease or it may occur as part of a systemic disorder with cardiovascular implications. The pathogenesis of PEX glaucoma and CAD in PEX patients may reflect different manifestations of the same process. Patients with PEX syndrome should be informed and examined frequently as cardiovascular risk may be present throughout.

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P- Reviewer: Cumurcu T, Speckauskas M **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

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