INTRODUCTION

Pseudoexfoliation syndrome is the most common clinical precursor to secondary open-angle glaucoma worldwide. It is a systemic disease that is characterized by the progressive accumulation of whitish-grey fibrillar proteins in various organs, especially ocular tissues, such as the lens, pupil border, zonules, orbital tissues, and trabecular meshwork. It is a major risk factor for glaucoma development; therefore, early detection is important in order to monitor signs of disease progression and to initiate aggressive medical and/or surgical therapies.

Pseudoexfoliation syndrome prevalence increases with age and is associated with elevated intraocular pressures. Many studies, such as the Thessaloniki Eye Study and Blue Mountain Eye Study, have found that pseudoexfoliation syndrome prevalence varies from 2.3 to 11.9% amongst different populations. Furthermore, 14.2 to 55.1% of patients with pseudoexfoliation syndrome are likely to progress into open-angle glaucoma. The Early Manifest Glaucoma found that pseudoexfoliation is a strong predictor of glaucoma progression independent of elevated intraocular pressures and other risk factors. Additionally, pseudoexfoliation has also been shown to be an important independent risk factor for glaucoma development in patients with ocular hypertension. In 14 to 29% of cases, pseudoexfoliation syndrome progresses from a unilateral disease to bilateral disease.

The pseudoexfoliative deposits are composed of complex glycoprotein/proteoglycan molecules, bearing similarities to epitopes within the basement membrane and the elastic fiber system. These microfibrillar subunits are surrounded by an amorphous matrix of elastic fibers (such as elastin, tropoelastin, amyloid P, and vitronectin) and elastic microfibrils (such as fibrillin-1, microfibril-associated glycoprotein-1, and latent tumor growth factor-binding proteins). The nature of pseudoexfoliative material and the stimulus for its production are unknown. Imbalances between matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases and extensive cross-linking processes are involved in pseudoexfoliative fiber formation, whereby the pathologic material is not properly degraded but instead progressively accumulates within the tissues over time. Furthermore, the accumulation of these pseudoexfoliation deposits within the pericellular region can disrupt the underlying basement membrane and lead to a degenerative fibrillopathy and dysfunction of the vasculature. Over time, the blood vessels experience reduced contractility and elasticity, which can eventually lead to alterations in blood flow velocity (Fig. 1).

Proposed role of decreased blood flow in the development of pseudoexfoliation glaucoma

Fig. 1: In pseudoexfoliation syndrome, pseudoexfoliation material deposits in various ocular tissues. As pseudoexfoliation material accumulates in the trabecular meshwork, it increases resistance to aqueous fluid outflow, which leads to an increase in intraocular pressure. Accumulation of the same material in blood vessels leads to a decrease in vessel contractility and loss of elasticity. This can lead to an increase in vascular resistance and decrease in the ocular blood flow. Both the increase in intraocular pressure and decrease in ocular blood flow have been linked to retinal and optic nerve head ischemia and apoptosis of the retinal ganglion cells through glutamate release and NMDA receptor activation. This can account for the conversion of pseudoexfoliation syndrome to pseudoexfoliation glaucoma.
Pseudoexfoliation Syndrome and Blood Flow Abnormalities

The hallmark of pseudoexfoliation disease is the pathologic production and accumulation of abnormal fibrillar extracellular material in the anterior segment tissues. Pseudoexfoliation material deposits throughout the trabecular meshwork can result in blockage of the outflow channels of aqueous fluid. More specifically, abnormal accumulation of pseudoexfoliation matter in the juxtacanalicular tissue beneath the inner wall of Schlemm canal has been shown to lead to the greatest resistance to the aqueous fluid outflow. Increased outflow resistance and decreased aqueous fluid drainage results in the chronic intraocular pressure elevations. The progressive buildup of pseudoexfoliation material in the juxtacanalicular tissue has been shown to correlate with elevated intraocular pressures and the presence and increased severity of glaucomatous optic nerve changes. Pseudoexfoliation glaucoma is characterized by the presence of pseudoexfoliative debris on the lens and/or pupillary border, increased pigmentation at the angle, glaucomatous optic disk changes, and glaucomatous visual field defects. It is associated with higher mean intraocular pressures, greater diurnal fluctuations in intraocular pressure, marked pressure spikes, and poorer responses to medical intraocular pressure-reducing therapies, all of which can account for its worse prognosis than primary open-angle glaucoma. Although pseudoexfoliation syndrome significantly predisposes patients to pseudoexfoliation glaucoma, not all patients with pseudoexfoliation syndrome will develop glaucomatous signs/symptoms. Active involvement of the trabecular meshwork may lead to glaucoma development in 40 to 60% of the patients.

Pseudoexfoliation syndrome is the ocular manifestation of a systemic disease; therefore, pseudoexfoliative material deposits are not only found within orbital tissue, but can also accumulate in skin, lung, heart, liver, gallbladder, kidney, ear, optic nerve, blood vessels, and cerebral meninges. Although pseudoexfoliation syndrome is diagnosed through ocular signs/symptoms, correlations have been made between the ocular changes and systemic diseases. In this review, we will focus on the less discussed vascular and blood flow changes associated with pseudoexfoliation syndrome and its correlation with pseudoexfoliation glaucoma and other systemic vascular-related abnormalities.

THE OCULAR VASCULATURE

Pseudoexfoliation syndrome represents a disease continuum that progresses as extracellular material accumulates in the vasculature. Although pseudoexfoliation syndrome is often unilateral when first detected, recent studies illustrate the subclinical involvement within the unaffected eyes. Kivela et al found the abnormalities within the ocular vasculature are detected earlier than frank pseudoexfoliation deposits on the ciliary epithelium and lens capsule. Furthermore, the severity of pseudoexfoliation glaucoma was found to be related to the amount of pseudoexfoliation material present in the cribiform region. Nevertheless, since it is not currently possible to determine the length of time a patient has been exposed to pseudoexfoliation syndrome, varying degrees of pseudoexfoliative material accumulation may explain the differing results produced while investigating pseudoexfoliation syndrome. With advanced glaucomatous damage, there is reduced blood flow in the lamina cribrosa and the rim area but not in the peripapillary retina. Pseudoexfoliation syndrome is also associated with a thinner retinal nerve fiber layer compared to controls. Puska et al demonstrated that patients with pseudoexfoliation syndrome may experience structural optic disc changes that were unrelated to increased intraocular pressure.

Accumulation of pseudoexfoliation material has been associated with narrowing and hypoperfusion of the iris vessels, loss of normal radial iris vessels, and neovascularization. In pseudoexfoliation syndrome, affected iris vessels show prominent pseudoexfoliation material accumulations in the adventitia, gradual degeneration of smooth muscle cells, pericytes, and endothelial cells up to complete destruction of the iris vessel wall or complete obliteration of the vessel lumen. Dayanir et al studied the ocular blood flow changes in patients with unilateral pseudoexfoliation syndrome between eyes clinically affected by pseudoexfoliation syndrome versus clinically unaffected eyes and controls. In eyes affected by pseudoexfoliation material, the ophthalmic artery experienced decreases in the peak systolic and end diastolic velocities and increases in the resistive index compared to the control group. Moreover, comparison of the clinically unaffected eyes with the control group showed significant decreases in mean peak systolic velocity by 23% and in end diastolic velocity by 40% of the ophthalmic artery. Thus, even unilateral pseudoexfoliation disease seems to affect the ocular tissue and vasculature in both eyes, even if not yet clinically detectable. Unilateral pseudoexfoliation syndrome converts to pseudoexfoliation glaucoma in the contralateral eye in up to third of cases and understanding pathologic alterations in the clinically unaffected eye at the initial presentation can provide further insights into the possible pathogenesis of disease progression.

Pseudoexfoliation deposits have been reported within the central retinal artery, short posterior ciliary arteries and vortex veins. Saatci et al pointed out that pseudoexfoliation syndrome is a risk factor for central retinal vein occlusion. Altered ocular blood flow has been widely reported in glaucoma patients and with glaucoma progression. Patients with pseudoexfoliation syndrome and iris transillumination have a significantly higher resistive index of the ophthalmic artery than controls. Pulsatile ocular blood flow, a representation of choroidal blood flow, was found to be decreased in pseudoexfoliation glaucoma compared to controls.
differences in pulsatile ocular blood flow were found between pseudoexfoliation syndrome patients when compared to pseudoexfoliation glaucoma patients. Yüksel et al used color Doppler imaging to demonstrate that pseudoexfoliation syndrome patients had decreased peak systolic velocity in the central retinal artery, decreased end diastolic blood flow velocities in the central retinal and short posterior ciliary arteries and high resistive indices in the ophthalmic and central retinal arteries. Pseudoexfoliation glaucoma patients also showed decreased blood flow velocities and increased resistive indices in the ophthalmic, central retinal and short posterior ciliary arteries when compared to controls. Moreover, patients with pseudoexfoliation glaucoma had lower blood flow velocities in the ophthalmic and short nasal posterior ciliary arteries than patients with pseudoexfoliation syndrome. Since the blood flow velocity changes are less severe in pseudoexfoliation syndrome, it may be considered a precursor to pseudoexfoliation glaucoma (Table 1). Nevertheless, it cannot be determined if these alterations in blood flow velocities contribute to the pathogenesis of pseudoexfoliation glaucoma or if they are a consequence of the disease.

A controversy remains over the differences in blood flow velocity between pseudoexfoliation and primary open-angle glaucoma. Yüksel et al found that blood flow velocities decreased to the same degree in patients of both groups. On the other hand, Martinez et al reported that blood flow abnormalities are more pronounced in primary open-angle glaucoma compared to pseudoexfoliation glaucoma (Table 1). These findings suggest that although the well-recognized parameter in the pathogenesis of pseudoexfoliation glaucoma

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PXG – pseudoexfoliation glaucoma; PXS – pseudoexfoliation syndrome; POAG – primary open-angle glaucoma; POBF – pulsatile ocular blood flowmetry/flow; PV – pulse volume; PA – pulse amplitude; CDI – color Doppler imaging; PSV – peak systolic velocity; EDV – end diastolic velocity; RI – resistive index; OA – ophthalmic artery; CRA – central retinal artery; PCA – posterior ciliary arteries; TPCA – temporal posterior ciliary arteries; NPCA – nasal posterior ciliary arteries; OPP – ocular perfusion pressure; BP – blood pressure; DPP – diastolic perfusion pressure; TCD – transcranial Doppler; TAMAX – time-averaged maximum velocity; PI – pulsatility index; MCA – middle cerebral artery; MSV – mean systolic velocity; MDV – mean diastolic velocity.
is elevated intraocular pressure and resulting glaucomatous damage, microcirculatory dysfunction and reduced blood flow velocities in the retrobulbar vessels may contribute to glaucomatous optic nerve damage in patients with pseudoexfoliation glaucoma.54

Although color Doppler indices are direct measurements of blood flow velocities, these can only be used as estimations for actual blood flow. Since direct visualization of ocular blood flow is not currently available, clinical practitioners can use blood pressure and intraocular pressure measurements to calculate ocular perfusion pressure to quantify vascular changes in glaucomatous patients. Ocular perfusion pressure is defined as 2/3 of the mean arterial blood pressure minus intraocular pressure. This can be further broken down into the systolic and diastolic components by taking the systolic or diastolic blood pressure minus the intraocular pressure, respectively. Hence, ocular perfusion pressure can be decreased by raising the intraocular pressure or reducing the blood pressure. Recently, Galassi et al reported that both the ocular perfusion pressure and diastolic perfusion pressures were lower in the pseudoexfoliation glaucoma group than in primary open-angle glaucoma patients or controls.56 In the same study, decreased end diastolic velocities and increased resistive indices were found in the ophthalmic, central retinal, and short posterior ciliary arteries in patients with pseudoexfoliation glaucoma.56 The perfusion pressure was further negatively related to the resistive index of the ophthalmic artery in patients with pseudoexfoliation glaucoma, with no similar relationships in patients with primary open-angle glaucoma or controls.56

THE CEREBRAL VASCULATURE

Since both the brain and the retina have the same embryologic development, there are close similarities between their vasculatures. Often, the middle cerebral artery blood flow is used as a representation of overall cerebral blood flow. In patients with pseudoexfoliation glaucoma, middle cerebral artery blood flow velocities were decreased and the resistive and pulsatility indices were increased when compared to controls.27 Yüksel et al compared middle cerebral artery blood flow amongst patients with pseudoexfoliation syndrome, pseudoexfoliation glaucoma and control subjects.65 In the pseudoexfoliation glaucoma group, the mean systolic and diastolic velocities in the middle cerebral artery were found lower than the control group.65 No difference was found between the group of subjects with pseudoexfoliation glaucoma or syndrome65 (Table 1). Decreases in cerebral blood flow have been reported in various types of glaucoma, such as normal-tension, low-tension and primary open-angle glaucoma, and not just in pseudoexfoliation glaucoma.66-68 Studying the effect of intraocular pressure on cerebral blood flow found that patients with ocular hypertension did not have similar changes in cerebral blood flow as patients with glaucoma.69 This implies that increases in intraocular pressure are not the only factor connected to the decrease in cerebral blood flow, and that disease itself is related to the decrease in blood flow. In addition, magnetic resonance imaging of normal-tension glaucoma patients demonstrates diffuse cerebral small vessel ischemic change, cerebral infarcts, or corpus callosum atrophy.69,70 Therefore, altered cerebral blood flow velocities are not only associated with pseudoexfoliation disease, but also with various forms of glaucoma.

Repo et al evaluated the effect of pseudoexfoliation syndrome on the vascular tissue in patients who had at least one transient ischemic attack.52 Iris transillumination and pseudoexfoliation syndrome were significantly higher in these patients with transient ischemic attacks compared to healthy subjects.52 This may suggest pathologic changes in the blood supply of pseudoexfoliation syndrome eyes. Ritland et al investigated the survival and cause of death of 1147 patients with pseudoexfoliation glaucoma or primary open-angle glaucoma.61 There was increased comorbidity but not mortality in patients with pseudoexfoliation glaucoma and acute cerebrovascular disease, as well as with chronic cerebral diseases such as senile dementia, cerebral atrophy and chronic cerebral ischemia.61

Recently, it has been reported that pseudoexfoliation syndrome was associated with Alzheimer’s disease. Strom et al71 suggests pseudoexfoliation-associated lesions are also located in the brain of patients suffering from dementia. The Alzheimer’s peptide (Aβ) has been detected in the aqueous humor of pseudoexfoliation patients.71 In Alzheimer’s disease, Aβ peptides are deposited in the neuritic plaques and cerebral vessel walls and are associated with a reduction of cerebrovascular blood flow.72,73 Although age, gender, systemic blood pressure, carotid artery stenosis, diabetes mellitus, blood viscosity, increased intracranial pressure, and systemic
medications can affect blood flow velocities, most studies attempt to eliminate these differences in their patient populations in order to determine statistically significant variations. Therefore, it is possible that these two diseases share some common pathophysiology and similar biochemical and etiological features.70,74

OTHER VASCULAR SYSTEMS

Many studies have demonstrated a correlation between pseudoexfoliation syndrome and cardiovascular disease. Mild to moderate hyperhomocysteinemia has been suggested as one possible cause for an increased vascular risk in pseudoexfoliation patients.18 Pathologic elevation of plasma homocysteine concentrations in patients with pseudoexfoliation syndrome independent of glaucomatous change has been demonstrated in different studies.75-79 Homocysteine can play a role in altering extracellular matrix metabolism through the dysregulation of matrix metalloproteinases, their inhibitors, and in vascular endothelial dysfunction.18 Vitamins B6, B12, and folate are involved in homocysteine metabolism and they have been reported to be markedly decreased in patients with pseudoexfoliation glaucoma.18 Since they are also negatively correlated with total plasma homocysteine levels, deficiencies of these vitamins may explain hyperhomocysteinemia in these patients.18 In a different report folate and serum vitamin B6 and B12 levels did not differ statistically between the pseudoexfoliation group and the control group.78 But further research will be necessary to confirm this association, since another study did not find a statistically significant correlation between homocysteine and vitamins B6, B12, and folate levels in pseudoexfoliation patients.

Furthermore, cutaneous microcirculation of patients with pseudoexfoliation shows altered response to cold and warm conditions compared to patients with primary open-angle glaucoma and controls. The altered response may suggest damage to the vascular autonomic innervation and/or damage to the microcirculatory effector system.80 Visontai et al recently reported that increased carotid artery stiffness and reduced baroreflex sensitivity in patients with pseudoexfoliation syndrome and glaucoma.64 These findings can suggest altered parasympathetic vascular control in pseudoexfoliation disease which increases with age. The findings suggest that ocular pseudoexfoliation is a part of a general disorder of the extracellular matrix and that these patients may suffer from increased comorbidity.18 In the Blue Mountain Eye Study, pseudoexfoliation syndrome was associated with a history of angina or hypertension or a combined history of angina, acute myocardial infarction, or stroke, which further emphasizes the systemic and potentially vascular nature of pseudoexfoliation syndrome.60 Citrik et al61 reported higher presence of pseudoexfoliation syndrome in patients with coronary artery disease and a higher occurrence of coronary artery disease in patients with pseudoexfoliation syndrome. They suggest that all patients with pseudoexfoliation syndrome be screened for coronary artery disease and patients with coronary artery disease be screened for pseudoexfoliation syndrome.81

CONCLUSION

In the past few years, it becomes clear that glaucoma in a multifactorial disease and lowering intraocular pressure is not always sufficient.82,83 Growing evidence supports the role of vascular abnormalities in glaucoma disease and progression.49,84 It seems that pseudoexfoliation syndrome and glaucoma have a vascular component to disease development and progression. Although pseudoexfoliation glaucoma is differentiated from primary open-angle glaucoma both clinically and histopathologically, both have similar blood flow abnormalities and elevated intraocular pressure. It is possible that the ocular blood flow is influenced by the elevated intraocular pressure, but pseudoexfoliation material found in the vascular walls may also lead to impaired blood flow both systemically and locally in the eye (see Fig. 1). It is unknown whether the vascular changes seen in pseudoexfoliation are adherent abnormalities or perhaps secondary to altered dysregulation due to endothelial dysfunction. Ocular blood flow reduction can be seen in the pseudoexfoliation syndrome and glaucoma. Perhaps both the vascular and intraocular pressure components have to occur mutually as the pseudoexfoliation material accumulates during development of glaucoma disease and progression. It seems that variations in optic nerve head blood supply and in ocular blood flow regulation play also a role in pseudoexfoliation glaucoma.56 With further research, future clinical practices may include routine ophthalmologic examinations to identify this important marker for patients at risk for cerebrovascular and cardiovascular disease.

REFERENCES


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I want it said of me by those who knew me best, that I always plucked a thistle and planted a flower, where I thought a flower would grow.

— Abraham Lincon