SYSTEMIC MANIFESTATIONS OF PSEUDOEXFOLIATION

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ABSTRACT

Objective: The aim of our study was to establish a correlation between pseudoexfoliation and its systemic manifestation.

Findings: Pseudoexfoliation syndrome is an age-related systemic disorder that leads to the overproduction and accumulation of the pseudoexfoliated materials in the visceral organs and in the eye. Many vascular diseases are closely related with pseudoexfoliation manifestations. Our results indicated that there were no statistically significant differences (p>0.05) among patients regarding the presence of hypertension in all groups: PEX glaucoma – 45% (9 patients); PEX syndrome-40% (8 patients); and control groups-35% (7 patients). Ischemic heart disease was statistically significant present in the sPEX syndrome-20% (5 patients) and PEX glaucoma-25% (5 patients) patient groups, in comparison with those of the control group-10%, (p<0.05). Aortic aneurism was statistically significant present in patients with PEX (syndrome-5% or glaucoma-15%), compared to those in the control group, which included no patients with aneurisms, (p<0.05). Our results indicated that a statistically significant number of patients with aneurism were in the group of patients who developed PEX glaucoma (p<0.05). Cerebrovascular diseases were detected in all groups of patients, but a significant decrease in this metric was noted in the control group-5% (2 patients), compared with patients with PEX syndrome-15% and PEX glaucoma-25%, (p<0.05). Hearing loss, as a concomitant sign of PEX manifestation, was recorded in all patients, but in the group with PEX (syndrome-55% or glaucoma-75%), these results showed a statistically significant increase (p<0.05) in comparison with those of patients in the control group (10%). Among the patients with PEX (syndrome and glaucoma), there were no statistically significant differences in the selected categories of systemic manifestations (p<0.05). This result indicates that the main risk for systemic manifestation is the presence of PEX and that other ocular and vascular complications are, in fact, consequences of PEX.

SAŽETAK

Cilj: Cilj našeg ispitivanja je bio da se utvrdi korelacija između pseudoexfolijacija i njihovih sistemskih manifestacija

Rezultati: Pseudoexfolijacije su sistemska poremećaj, starijeg životnog doba, koji karakterišu povećana produkcija i nakupljanje pseudoexfolijativnog materijala u viseralnim organima, i u oku vezane za starije. Mnoge vaskularne bolesti su u neposrednoj povezanosti sa prisustvom pseudoexfolijacija u oku. Naši rezultati ukazuju da nije bilo statistički značajne razlike u incidenci hipertenzije kod pripadnika sve tri ispitivane grupe, (p>0.05): PEX glaukom-45% (9 pacijenata); PEX sindrom-40% (8 pacijenata) i kontrolna grupa-35% (7 pacijenata). Ishemijska bolest srca je statistički značajno zastupljena u grupi bolesnika sa PEX sindromom-20% (5 pacijenata) i PEX glaukomom-25% (5 pacijenata) u poranđenju sa bolesnicima iz kontrolne grupe-10%, (p<0.05). Kod bolesnika sa PEX (sindrom-5% i glaukom-15%) uočeno je statistički značajan (p<0.05) broj bolesnika sa aneurizmom aorte u odnosu na kontrolne grupe, gde nisu usetljive. Cerebrovaskularne bolesti su statistički značajno umanjena, (p<0.05) u kontrolnoj grupi 5% (2 pacijenta) u poranđenju sa ispitnicima iz grupa bolesnika sa PEX: sindrom-15% i PEX glaukom-25%, (p<0.05). Gutitak sluha, koji se sreće kod bolesnika sa PEX, je zabeležen kod svih ispitnika, ali je statistički značajan broj (p<0.05) u grupi bolesnika sa PEX (sindrom-55% i glaukom-75%) u odnosu na pripadnike kontrolne grupe (10%). Naše ispitivanje ukazuje da je prisustvo PEX faktor rizika za različite vaskularne komplikacije.

Zaključak: Pseudoexfolijacije su u neposrednoj povezanosti sa brojnim vaskularnim poremećajima. Bolesnici koji imaju PEX bi trebalo da budu detaljno ispitani od strane specijaliste interne medicine i neurologa. Njihova detaljna ispitivanja, naročito u ranoj fazi bolesti, bi bila od velike pomoći u prevenciji teških vaskularnih komplikacija sistemskih manifestacija PEX.
INTRODUCTION

Pseudoexfoliation syndrome (PXS) is an age-related systemic disorder involving the overproduction and accumulation of pseudoexfoliation materials (PEX) in the visceral organs and in the eye (1). It is characterised by an intensive production of abnormal fibres and their accumulation in the whole body and in the eye (1). PEX flakes can be detected around the blood vessels of connective tissue and have been identified using electron microscopy (2) and immunohistochemistry (3) in the lung, liver, kidney, gall bladder, and cerebral meninges (4). Some cardiovascular and cerebral diseases (angina, aortic aneurysm, dementia, etc.) have been associated with pseudoexfoliations (5). Pseudoexfoliation can be detected using a slit lamp in every part of the anterior segment of the eye, including the corneal endothelium, iridocorneal angle, pupillary margin, and iris anterior capsule of the lens. By histological examination, PEX can be detected in extra-ocular tissues, such as the conjunctiva, extra-ocular muscles, and retro-ocular tissue (1). The fibres can accumulate during the outflow through the trajectories of the aqueous humor, causing enhanced resistance and further increasing intraocular pressure (4). Glaucoma occurs more commonly in eyes with PEX than in those without PEX (6). Glaucoma in patients with PEX has a more serious clinical progression and worse prognosis than primary open-angle glaucoma (6).

PATIENTS AND METHODS

Our cross-sectional comparison study included 60 patients at the Clinic of Ophthalmology, Clinical Centre, Kragujevac, Serbia who were referred for cataract surgery. The study design was approved by the local ethics committee, and all enrolled patients gave their written consent at the beginning of the study.

All patients were divided in three groups according to the presence of PEX in their eyes: patients with PEX syndrome, those with PEX glaucoma and a control group (no PEX). The presence of PEX was confirmed by slit-lamp examination, measurements of intraocular pressure, and gonioscopy; to establish PEX glaucoma, fundus and visual field examination was needed. Exclusion criteria were a history of intraocular surgery, ocular trauma, uveitis, prophylactic laser photoagulation, and myopio- or cryo-treatment. Directly before the surgical treatment, a detailed disease history was taken from every patient, including the following items: hypertension (HT), diabetes mellitus (DM), cerebrovascular stroke, ischemic heart disease (IHD), and hearing loss. Reports from an internal medicine specialist and otolaryngologist with detailed disease summary and recommended therapy were also required, and any vascular surgery was recorded. The presence of diabetes mellitus was defined as previous (detailed medical history with therapy) or newly diagnosed (no medical history). Cardiovascular disease was defined by the presence of an earlier heart attack, bypass surgery, angioplasty, cardiomyopathy or angina. Hypertension was defined by an earlier disease history with detailed therapy (systolic blood pressure of more than 160 mm/Hg or a diastolic blood pressure more than 90 mm/Hg). An otolaryngologist discovered and explained any hearing loss in our patients using standard audiometry.

The participants in the control group included patients with cataracts who were age–matched and resisted the exclusion criteria.

STATISTICAL ANALYSIS

The unpaired Student’s t-test and Mann–Whitney test were performed using the SPSS 19.0 statistical software package (SPSS Inc., Chicago, IL ). The results were expressed as the percentage values. All P values were 1-sided, and a P value <0.05 was considered statistically significant (significance levels as indicated in the table legends).

RESULTS

Among the participants of the study, a female majority (15, 3:1) was noted in the first group of the PXS syndrome.
In the group of patients with PXS glaucoma, 14 patients were female (2.33:1), whereas in the control group, the gender ratio was approximately equal (11, 1.22:1).

The mean age of all patients was 72.2 ± 7.4 years (the youngest was 48 years; the oldest, 90 years). The group of patients with PEX glaucoma had a mean age of 77.2±3.9; the PXS group, of 73.4±6.5; and the control group, of 63.4±4.2 years, Table 1.

Our results indicated that there were no statistically significantly differences (p=0.081) among patients regarding the presence of hypertension in any of the groups: PEX glaucoma-45% (9 patients); PEX syndrome-40% (8 patients) and control groups-35% (7 patients). Ischemic heart disease was statistically significantly present in the PEX syndrome group- 20% (5 patients) and in the PEX glaucoma group-25% (5 patients), compared with controls-10%, (p=0.049). Aortal aneurisms were statistically significantly present in patients with PEX (syndrome-5% or glaucoma-15%) in comparison with patients from the control group, in which no patients had aneurisms (p=0.018). Cerebrovascular diseases were detected in all groups of patients, but in the control group- 5% (2 patients), this number was statistically significantly lower than in patients with PEX syndrome- 15% or PEX glaucoma-25% (p=0.026). Hearing loss as concomitant sign of PEX manifestation was recorded in all patients, but in the group with PXS (syndrome-5% or glaucoma-75%), those numbers were statistically significantly increased (p=0.033) in comparison with the patients in the control group (10%). Among those patients with PXS (syndrome or glaucoma), there were no statistically significantly differences among any of the selected categories of systemic manifestation (p=0.0728), Table 2.

**DISCUSSION**

PEX deposits can be found in many tissues in the body, especially in connective tissue or transverse organ septa (1). PEX can be presented in the eye or localised around either eye (7). Ocular PEX is associated with high rates of cataract and glaucoma (6).

PEX can be described as the abnormal production and accumulation of fibres, accompanied by the presence of fibroblasts around small blood vessels, as indicated for systemic manifestations (2). The process of this production can be activated by increased levels of different growth factors (8), a disrupted oxidative-anti-oxidative status (9), and enhanced metalloproteinase (MMP) activities (10). Homocysteine levels in the plasma are increased in patients with PEX (11). All of these parameters signify the systemic manifestations of PEX.

Many earlier studies have suggested an important relation between PEX and different systemic diseases, but their results are contradictory (12). This fact can be explained by differences among populations and selected groups. Generally, a large number of associations have been found between PXS and peripheral vascular diseases (13).

It has been established that iris vasculopathy is an obligatory finding in eyes with PEX and may cause hypoxia of the anterior segment of the eye (14). Indocyanin green was used to support this finding (15). Some similar diagnostic procedures were used to establish blood flow in other tissues in the body. Cutaneous capillary perfusion was examined to demonstrate impaired vascular perfusion in the fingers of patients with PEX (16). This study indicated that the cutaneous capillary flow was significantly lower in patients with PEX than in the age-matched control group. Additionally, this study demonstrated a reduced cardiovascular regulatory function among PEX patients. Another study, using Color Doppler imaging, indicated that brachial and dorsal pedis artery circulation could be improved (12). This finding was sustained by a low ankle brachial index (ABI). Low ABI is one of the risk factors for the development of peripheral vascular disease and is strictly connected with PEX. A

<table>
<thead>
<tr>
<th>Age</th>
<th>PEX syndrome (%)</th>
<th>PEX glaucoma (%)</th>
<th>Cataract (%)</th>
<th>Means±SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-60.</td>
<td>1 (1.67)</td>
<td>0 (0)</td>
<td>11 (18.33)</td>
<td>54.23±3.2</td>
<td>p=0.023 *</td>
</tr>
<tr>
<td>60-75.</td>
<td>10 (16.67)</td>
<td>6 (10)</td>
<td>9 (15)</td>
<td>70.57±5.21</td>
<td>p=0.078</td>
</tr>
<tr>
<td>75-90.</td>
<td>9 (15)</td>
<td>14 (23.33)</td>
<td>0 (0)</td>
<td>83.45±4.34</td>
<td>p=0.038 *</td>
</tr>
<tr>
<td>Mean age</td>
<td>73.41±6.54</td>
<td>77.2±3.9</td>
<td>63.4±4.2</td>
<td>72.2±7.4</td>
<td>p=0.029*</td>
</tr>
</tbody>
</table>

Table 1. Distribution of the patients according to age. Our results indicated that the older population was at a greater risk for PEX production, fibre accumulation and development of glaucoma. Our results indicated that the older population was at a greater risk for PEX production, fibre accumulation and development of glaucoma.

<table>
<thead>
<tr>
<th>Arterial hypertension (%)</th>
<th>Ischemic heart disease (%)</th>
<th>Aortal aneurism (%)</th>
<th>Cerebrovascular disease (%)</th>
<th>Sensorineural hearing loss (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEX glaucoma</td>
<td>9 (45)</td>
<td>5 (25)</td>
<td>3 (15)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>PEX syndrome</td>
<td>8 (40)</td>
<td>4 (20)</td>
<td>1 (5)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Control group</td>
<td>7 (35)</td>
<td>2 (10)</td>
<td>0 (0)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>P values</td>
<td>p=0.081</td>
<td>p=0.049*</td>
<td>p=0.018*</td>
<td>p=0.026*</td>
</tr>
</tbody>
</table>

Table 2. Systemic manifestations of the ocular pseudoxfoliation. Patients with PEX (syndrome and glaucoma) had a greater incidence of ischemic heart disease, aortal aneurism, cerebrovascular disease and hearing loss, in comparison with patients without PEX.
biopsy of the cutaneous tissue showed pseudoexfoliation materials around the blood vessels.

Toxic agents, acoustic trauma, solicitude and other less studied causes can contribute to sensorineural hearing loss (SNHL) (17). The hair cells (inner and outer hair cells), which are placed on the basilar membrane and overlaid with the tectorial membrane, are the fragments of the compound organ of Corti. SNHL in PXF syndrome may be caused by deposits of this material in inner ear structures (organ of Corti), which can decrease the alterations in small vibrations actuated by sound analogues (18).

The present study was performed to establish a correlation between PEX patients (syndrome or glaucoma) and a control group, according to the potential systemic manifestations of PEX. Arterial hypertension was equally represented in all selected groups. Our results indicated statistically significant differences in the number of patients with ischemic cardiac disease, cerebrovascular disease, and the presence of aortal aneurism or sensorineural hearing loss between the PEX group (syndrome or glaucoma) and controls. There were no statistically significant differences between the two subgroups of the PEX group (syndrome or glaucoma). This result indicated that the main risk for systemic manifestation is the presence of PEX. Other ocular and vascular complications constitute consequences of PEX. Our results are similar to the results of recent studies, the data from which have been published (5, 7, 12). These studies suggest that ocular PEX carries a great risk for peripheral vascular disease development with sensorineural hearing loss, as was seen in the concomitant otolaryngologist’s findings.

Our study showed a statistically significant association between PEX and different cardio- and cerebrovascular diseases, similar to other previous studies (5, 12, 19, 20).

Pseudoexfoliation is strongly related to systemic vascular disturbances. A detailed examination of patients with PEX by a specialist in internal diseases or a neurologist should be made. Such examinations can be helpful in the prevention of vascular disease development among patients with PEX, especially at early stages.

REFERENCES