Pseudoexfoliation syndrome

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Introduction

Pseudoexfoliation (PEX) syndrome is a daily challenge for ophthalmologists because of aggressive secondary glaucoma and cataract surgery complications caused by its presence. Although it has been known since the beginning of the 20th century, the interest for its research has been increasing during the last few decades. It has been found that PEX syndrome exists in diseases of other organs and systems. In addition, the origin and nature of PEX material has not been explained yet, which further arouses the interest of scientists.

Discovery of pseudoexfoliation syndrome

Research of Finnish ophthalmologist John G. Lindberg was inspired by the works of his senior colleague, the German ophthalmologist Axenfeld, who described changes in the iris of older people. Obeying his own research needs, Lindberg worked on the thesis, examining the patients at the slit lamp, which he constructed himself. Thus, he observed and described the changes in the form grayish villi and flakes at the pupillary edge and lens in patients with cataract older than 50. In patients with chronic glaucoma, changes were found in 50% of cases. In his doctoral thesis, presented in 1917 at the University of Helsinki, Lindberg described in detail the observed changes in the iris and lens, and he personally illustrated his work.

A few years later, Lindberg gave a copy of his thesis to his Swiss colleague A. Vogt. But Vogt published his first work on PEX and glaucoma, not even once mentioning Lindberg and his work. Lindberg also borrowed his thesis to the Swedish ophthalmologist, Malling, who shortly afterwards published papers on this subject, also without mentioning Lindberg and his discovery.

Lindberg received a full recognition posthumously, a few decades later, thanks to Finnish ophthalmologists. Interest in PEXs was awakened later, in the 80s and in 1998, the International Association for the Study of PEX was established, which was named after Lindberg - the Lindberg's Society.

At first, it was thought that PEXs originated from anterior lens capsule [exfoliation superficialis capsule anteriors (Malling, Vogt)], and then they were only deposited on the front lens capsule (Busacca). Georgiana Dvorak-Theobali first suggested the term PEX (1954), in order to make the difference with the lamellar exfoliation of the lens capsule within glass blowers. In 1964, Bertelsen, Drablos and Flood found deposits located in the very lens epithelial cells and suggested the term fibrillopathia epiteliocapsularis. Today, we use the term pseudoexfoliation syndrome (PEX syndrome, PXF syndrome, XFS, PXS, PES) and, less frequently, exfoliation syndrome and senile lens exfoliation.

Clinical diagnosis of pseudoexfoliation syndrome

PEX syndrome is a systemic disorder of basement membrane. Until recently, as a direct cause of disease, the syndrome has been recognized only in the eye, where it causes aggressive secondary glaucoma and cataract surgery complications.

Initially, the syndrome is typically manifested unilaterally. However, electron microscopy indicates that subclinical changes mostly exist in the other eye, as well. In the later course, PEX syndrome becomes clinically manifested in both eyes. A patient usually has no symptoms or complains about sight quality, caused by cataract or a deficit in the visual field due to glaucoma. The diagnosis is made by standard ophthalmic examinations. It is sufficient to use biomicroscope
with slight light (sensitivity of the examination is 85% and specificity of up to 100%)\(^4\). PEXs can be clearly seen on the pupillary margin. Overview of the anterior eye segment, with pharmacological mydriasis, recognizes “3-ring” or “eye bull” sign on the front surface of the lens. It comprises a central disc and peripheral ring covered with PEX material and pure annular zone between them. Pure zone is probably caused by pupillary movement, leading to removal of PEX from the part of lens capsule and its dispersal into the environment. Total, white cataract may make it difficult to see this sign.

Pupilla pure dilates with the use of mydriatics. The entire anterior segment of the eye is ischemic to a certain degree and iris neovascularization is possible \(^5\), \(^6\). PEXs are found in the front parts of hyaloid membrane of the vitreous body, ciliary processes, lens zonules, cornea and trabeculum. Primarily, they are created by epithelium of ciliary body, iris pigment epithelium and pre-equatorial lens epithelium. It is possible that corneal endothelium, the trabecular cells and vascular endothelium are included in the creation of PEX material. PEX are also found in the orbit, conjunctiva, bulbar motors, vorticous veins, central retinal artery, optic nerve envelopes and skin of eyelids \(^7\), \(^8\).

The movements of the irises and pupillary dynamics do not only lead to the removal of PEX from lens capsule, but also to the pigment dispersion from the pigment layer of iris. In this way, there are some places of iris transparency and pupillary edge atrophy. Pigment granules accumulate in the chamber angle. Chamber angle is intensely and inhomogeneously pigmented and pigmentation of the angle is most pronounced in the Schwalbe’s line and in front of it (Sampaolesi line).

Lens capsule is thin and easily and unexpectedly torn during capsulorhexis of cataract surgery. Lens suspensory zonules (Zinni zonules) are weakened, leading to a tendency towards dislocation of the lens during minor trauma, and during the operational lens extraction. Split of the lens capsule, prolapsed vitreous body and lens or intraocular artificial lens dislocation are common complications of cataract surgery in subjects with the syndrome \(^4\), \(^9\). Changes on the corneal endothelium predispose the development of endothelial decompensation during cataract surgery and corneal edema during the postoperative period.

Aimed at preventing some operational complications, in longer use are several instruments and surgical modifications in cataract extraction, which increase comfort to an ophthalmologist during surgery and, to some extent, affect the incidence of some early and late postoperative complications \(^10\).

Weak suspensory zonules allow movement forward of the entire lens, so in some persons with PEX syndrome the anterior chamber looks shallow and chamber angle narrowed. In advanced stages of the syndrome, phacodonesis is visible (lens shakes while moving eyes).

Cataract is frequently associated with the PEX syndrome \(^4\), \(^9\), \(^10\). It is a mixed, cortico-nuclear type, with large, pigmented nucleus (brunescent). The findings that PEX syndrome is a risk factor for age-related macular degeneration are not consistent \(^4\), \(^12\), \(^13\).

**Pseudoexfoliation glaucoma**

Today, it is believed that PEX syndrome is the most common cause of open angle glaucoma. It is expected that up to 50% of people with PEX syndrome have elevated intraocular pressure. In people with PEX syndrome, intraocular pressure is significantly higher, even when it was within normal limits \(^9\), \(^14\), \(^15\). The risk of conversion of intraocular hypertension to glaucoma is twice as high in patients with PEX syndrome. In 5 years, 7%–30% of persons with PEX syndrome will develop glaucoma \(^16\). Although PEX syndrome itself does not produce optic nerve damage, people with diagnosed PEX syndrome should be inspected once a year \(^3\), \(^4\), \(^17\). Sometimes, glaucoma may firstly develop in an eye without clinically manifest PEXs \(^16\).

PEX glaucoma is secondary open-angle glaucoma. Earlier, it was known as capsular glaucoma (glaucoma capsulare). Glaucoma can manifest as closed/narrow-angle glaucoma. Lens weakened zonules and instability of lens allow moving forward of iridolental membrane, and thus the emergence of a narrow chamber angle and shallow anterior chamber. In addition, the pupilar bloc development is helped by the presence of iridolental synechies and iris rigidity within the syndrome \(^3\), \(^4\).

Glaucoma is a secondary event. Blockage of the trabecular spaces by PEX material promotes accumulation of pigment and cellular debris, which causes obstruction of the aqueous channels and limits access to the Schlemm canal. Accumulation of PEX material in the juxtacanicular tissue adjacent to the Schlemm canal leads to narrowing of the canal lumen, collapse of its walls, disruption of its endothelium, and partial obliteration. These changes appear to be the causative factors for chronic intraocular pressure elevation and PEX glaucoma.

PEX glaucoma has an aggressive course and an unfavourable prognosis. In its course there are high values and large day-night variations of pressure, rapid deterioration of nerve fibers of the retina and optic neuropathy, rapid progression and development of blindness. Eyes with primary open-angle glaucoma (POAG) were found to have axon loss associated with more connective tissue in the septa and surrounding the central retinal vessels and a decrease in the density of capillaries as compared with eyes with PEX glaucoma where the capillary density did not change with axon loss \(^18\). Optical coherence tomography (OCT) and Heidelberg retina tomography (HRT) have been used to help in the diagnosis and follow-up of patients with glaucoma. Both OCT and HRT have shown a high correlation between the retinal nerve fiber layer thickness and the visual field mean defect during achromatic perimetry.

PEX glaucoma responds poorly to medical management of POAG, glaucoma simplex. Glaucoma is often unilateral, compared to POAG, and if the syndrome is manifested bilaterally, the eye with glaucoma has a more intense pigmentation of the chamber angle \(^19\). Angle pigmentation is positively correlated with the amount of IOP, but not with severity of glaucoma. Pressure rise in PEX glaucoma happens due to the increased resistance of aque-
ous humor outflow in the trabeculum and reduced uveoscleral flow 20.

Medical therapy does not lead to a long-term compensation of IOP. Initially, combinations of drugs are often used in therapy, because of the weak response to monotherapy 21. Myotics have worsening potential for the pupillary block development. Argon laser trabeculoplasty shows a great initial success, but the percentage of decompensation of pressure is up to 50%, three years after the intervention 22. Selective laser trabeculoplasty shows a similar success, but it can be repeated several times, because it does not cause thermal damage 23. Trabeculectomy and other filtration penetrant and nonpenetrant surgical procedure should be usually performed in earlier stages of the disease than in POAG. Postoperative complications in the form of inflammation, hypotony, and cataract are more common than in POAG.

Differential diagnosis include POAG and pigmentary glaucoma.

**Epidemiology of PEX syndrome and PEX glaucoma**

PEXs syndrome prevalence increases with age, but shows considerable variations, depending on geography and ethnicity. Judging from early reports, it was considered that PEX syndrome and PEX glaucoma dominate in Scandinavian countries 24. Later, analyzing the results of population studies, it was realized that these entities existed throughout the world. This syndrome is rarely manifested before 50, and it is most commonly recorded with patients between 69 and 75 years. In Scandinavian countries PEX syndrome was found in 23% of people in their seventh decade 14.

In the same study, after a 20-year follow-up period, Swedish authors 14 reported that the elevated IOP was 6 times more common in people with PEX syndrome. They found identical incidence of glaucoma in both sexes and bilateral manifestation of PEX syndrome that was initially recorded in one eye in 55% of persons observed for 2 decades. During the follow-up, 25% of those patients developed glaucoma before they were 87 years of age, and in almost 60% of cases they had characteristics of PEX glaucoma. In the same study, the prevalence of PEX syndrome in people who were 87 was even 61%.

On Iceland, PEX syndrome and PEX glaucoma has recorded annual growth of 10% in people older than 50 25. The syndrome has not been found in the Inuits living in the polar regions of Canada, but has a high prevalence in the Samis, who live on the same latitude in Europe 26. The prevalence is 4.7% in England, 6.3% in Norway, 4.4% in Germany and 1.1% in Greece. Similar prevalence exists in India, Pakistan (hospital studies) and in some African tribes 1. In China, there are only 0.4% of respondents aged between 60 and 91, hospitalized for other diseases 27. In USA, 6–12% cases of open angle glaucoma seem to be PEX glaucoma and the prevalence of PEX syndrome ranges from 0.4% to 2.7% in different regions and racial groups, with white patients predominance 28, 29.

In some areas, PEX syndrome and PEX glaucoma are manifested in several generations of the same family and suggest a genetic predisposition 12, 28, 30. However, in different populations examined, the findings suggest mitochondrial, X linked and autosomal form of inheritance 31.

Earlier papers have reported significantly more common occurrence of PEX syndrome in women 26. However, it has not been confirmed by authors 12, 13 from Iceland and Greece.

Studies on PEX syndrome have been conducted on very diverse population and also dealt with variability in the glaucoma definition, especially in early publications. These make it often difficult to compare different series, even when age-specific rates are available 31.

**Extraocular localization of pseudoexfoliations and syndrome comorbidity**

PEXs have been found in the skin, lungs, liver, heart, kidney, gallbladder and meninges, mainly in areas containing connective tissue 32, 33. They are also in blood vessels in the body, but the results documenting their frequent association with cardiovascular diseases such as angina, hypertension and stroke 33–36 or abdominal aortic aneurysm 37, are contradicted by the results of researchers who have found similar frequency in the clinical syndrome and control group 38–41. A greater number of studies with the same design, clinical and control subjects and methods of analysis are required for more consistent conclusion. Cardiac arrhythmia is the most common finding in patients with this syndrome 41. Systemic vascular endothelial dysfunction has been found in persons with PEX syndrome and PEX glaucoma 42.

PEX syndrome is often associated with Alzheimer’s disease 43, 44. Due to similarities in the pathogenesis, some authors call pseudoexfoliation glaucoma “eye Alzheimer’s disease”. However, the syndrome does not result in an increased rate of mortality from cerebrovascular disease 40, 41. Quality testing of cerebral blood flow in patients with PEX glaucoma shows a reduced speed and increased resistance 46, and magnetic resonance imaging test is periocular zone of damage, regardless of optic neuropathy in patients who have not only PEX syndrome, but also PEX glaucoma 47, 48.

Hearing disorders have also been detected in patients with this syndrome, especially in hearing the frequency range of human voice 49.

PEX syndrome is rare in patients with diabetic retinopathy 50 yet initiated a series of new tests. However, better selection of groups of respondents, particularly in relation to age, has showed that diabetes is not rare in patients with this syndrome 41, 42 or even that it is more common 50.

**Origin and composition of pseudoexfoliation material**

Today, the accepted concept suggests that PEX syndrome is a pathological process of the extracellular matrix, which is characterized by the excessive production of abnormal extracellular material aggregating and accumulating, but not decomposing in the organism. Based on known
characteristics of PEX material, PEX syndrome is one of the systemic elastosis that primarily affects elastic microfibrils.  

PEX material belongs to glycoprotein or proteoglycan. It consists of a protein core surrounded by a mass of conjugated complex sugars. It contains glycosaminoglycans (heparan sulfate, chondroitin sulfate, dermatan sulfate and hyaluron acid), as well as many components of noncollenagen ingredients basement membrane and elastic microfibrile (elastin, vitronectin, amyloid P, laminin, nidogen, fibrillin 1, latent TGF binding protein 1 and 2, microfibrile associated glycoprotein 31). It is not known which are integral parts of molecules and which are adhered. Human natural killer 1 carbohydrate component is considered to be responsible for the adhesive nature of PEX. The components are connected among themselves by enzymes and they stabilize the complex. Proteolytic imbalance observed in syndrome may be caused by a disturbed relationship between matrix metalloproteinases and their tissue inhibitors. Because of similarities in the painting composition, PEX material is often described as amyloid 4, 31, 32.

The origin of syndromes is associated with different risk factors. In addition to these age and genetic predisposition, other factors with potential cumulative but mutually dependent effects are also mentioned: ultraviolet radiation, oxidative stress, chronic inflammation in the autoimmune process, infections caused by herpes viruses, hepatitis C virus and Helicobacter pylori bacteria, as well as diet habits 4, 23, 30, 52–57.


Hyperhomocysteinemia has been found in persons with PEX syndrome and PEX glaucoma 29, 51, 58. Genetic polymorphism lysil oxidase like 1 gene and its homozygous presence represent the risk for the disorder of homocysteine metabolism, abnormal hepatic fibrosis and aggregation of elastic components of PEX, especially in a disturbed folate status in the body. Similar disturbances in the plasma levels of homocysteine, folic acid and vitamins B6 and B12 are evident with Alzheimer’s disease and certain cardiovascular diseases. However, hyperhomocysteinemia exists in patients with POAG and normotensive glaucoma.

Elevated serum levels of connective tissue growth factor in a number of diseases accompanied by fibrosis has been detected in patients with PEX syndrome 57. Again, matrix metalloproteinases are involved in its regulation. Transforming growth factor β1, as a regulator of most genes that are expressed in PEX syndrome, is increased in aqueous humor of patients with this syndrome and is considered to be one of the key mediators in the fibrotic process syndrome 29.

The system of production and accumulation of PEX makes it complex and interdependent set of elements of such a specific, stress-induced elastosis 31.

Conclusion

Considering population aging worldwide, including our country, we can expect an increasing prevalence of PEX syndrome and PEX glaucoma. Although there is no clear pathogenesis, since the first PEX glaucoma is prevalent among other types of secondary open angle glaucoma, it should be studied during the regular medical studies.

Diseases mentioned in comorbidity of syndrome, which include the risk of mortality and disability with a significant reduction in quality of life, can be suspected earlier if the ophthalmologic overview of the anterior eye segment is done. The possibility of preventing such diseases or reducing their progression is the chance that should be taken. Further studies PEX syndrome origin and nature may help in shedding light on its etiology and pathogenesis, which may open new perspectives in its prevention.

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