ORIGINAL ARTICLES

UDC: 616.133-004.6::617.7-007.681
DOI: 10.2298/VSP150320058J

The importance of developing atherosclerosis in pseudoexfoliation glaucoma

Značaj ateroskleroze u pseudoeksfolijativnom glaukomu

Katarina Janićijević*, Sanja Kocić*, Sladjana Pajović*, Nemanja Zdravković†, Tatjana Šarenac Vulović†, Mirjana Janićijević Petrović†

***Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia; †Clinic of Ophthalmology, Clinical Center of Kragujevac, Kragujevac, Serbia**

Abstract

Background/Aim. Pseudoexfoliation syndrome (XPS) is an age-related systemic disorder characterized by increased production and accumulation of elastic microfibrillar material in different tissues of the body: skin, connective tissue portions of visceral organs, periphery blood vessels and the eye, as well. The aim of our study was to determine the significance of atherosclerotic changes in the carotid arteries in the development of XFS and pseudoexfoliation glaucoma (XFG). **Methods.** The study included 120 patients – 40 patients *per* each of the three defined groups: XFS group, XFG group and age- and sex-matched control subjects (control group) without XFG. Blood samples were collected from the patients before cataract surgery. Serum levels of total cholesterol, low-density lipoprotein – LDL, high density lipoprotein – HDL and triglycerides were analyzed by standard laboratory techniques. Standard ultrasonography of the carotid blood vessels was performed in all the participants. **Results.** Lipid's profile was disturbed in the patients with XFS and XFG with statistical significance p control group ($p < 0.01$). Systolic and diastolic pressure was elevated in the patients with XFS and XFG ($p < 0.01$). Resistance index was increased in the patients with XFG ($p < 0.01$). Intima-media thickness was prolonged in patients with XFG ($p < 0.01$). **Conclusion.** A disturbed lipid profile with elevated resistancy index and intima-media thickness and increased systolic and diastolic pressure were compulsory findings in patients with developed XFG. So, these factors could be considered as risk. It seems to be difficult to inhibit the process of pseudoexfolation production in the whole body, but it appears that with proper therapy (antihypertnesive, cardiotoncs, etc.) and adequate nourishing, the process of XFG development could be interrupted.

Key words:
exfoliation syndrome; atherosclerosis; carotid arteries.

Apstrakt

Uvod/Cilj. Pseudoeksfolijativni sindrom je sistemski poremećaj starijeg životnog doba, koji se karakteriše povećanom proizvodnjom i akumulacijom elastičnog mikrofibrilarnog materijala u različitim tkivima tela: koži, vezivnom tkivu unutrašnjih organa, perifernim krvnim sudovima i oku. Cilj istraživanja bio je da se utvrdi značaj aterosklerotičnih promena u karotidnim arterijama u razvoju pseudoeksfolijativnog sindroma i pseudoeksfolijativnog glaukoma. **Metode.** Studijom je bilo obuhvaćeno 120 bolesnika, po 40 bolesnika u svakoj od tri definisane grupe: sa pseudoeksfolijativnim sindromom (XFS), sa pseudoeksfolijativnim glaukomom (XFG) i kontrolna grupa bez XFG (uparena po starosti i polu). Uzorci krvi su sakupljeni kod bolesnika pre operacije katarakte. Nivo (ukupnog holesterola, *low-density lipoprotein* – LDL, *high density lipoprotein* – HDL i triglicerida u serumu analizirani su standardnim laboratorijskim tehnikama. Standardna ultrasonografija karotidnih arterija urađena je kod svih ispitanika. **Rezultati.** Lipidni profil bio je poremećen kod bolesnika sa XFS i XFG, sa statističkom značajnošću u odnosu na kontrolnu grupu ($p < 0,01$). Sistolni i dijastolni pritisak bio je statistički značajno povišen kod bolesnika sa XFS i XFG ($p < 0.01$). Indeks rezistencije bio je povećan kod bolesnika sa XFG ($p < 0,01$), dok je intimamedija komples bio statistički značajno produžen kod bolesnika sa XFG ($p < 0.01$). **Zaključak.** Poremećen profil lipida sa povišenim indeksom rezistencije i debljinom intimomedija kompleksa kao i povišenim sistolnim i dijestolnim pritiskom su ključni nalazi kod bolesnika sa razvijenim XFG. Zbog toga ih treba uzeti u obzir kao faktore rizika. Čini se da je teško da se inhibira proces proizvodnje pseudoeksfolijacija u celom telu, ali i da se uz pravilnu terapiju (antihipertnenzivni lekovi, kardiotonici, itd) i uz adekvatan režim ishrane, proces razvoja pseudoeksfolijativnog glaukoma može da prekine.

Ključne reči:
eksfolijativni sindrom; ateroskleroza; aa.carotis.

Correspondence to: Katarina M. Janićijević, Faculty of Medical Sciences, University of Kragujevac, Svetozara Markovića 69, 34 000 Kragujevac, Serbia. Phone: +381 34 369 828, Fax: +381 34 370 043. E-mail: kaja.andreja@yahoo.com

Introduction

Pseudoexfoliation syndrome (XPS) is an age-related systemic disorder characterized by increased production and accumulation of elastic microfibrillar material in different tissues of the body: skin, connective tissue portions of visceral organs, periphery blood vessels and the eye, as well [1].

In the eye, pseudoexfoliation (PEX) is associated with high risk for the development of glaucoma, called pseudoexfoliative glaucoma (XFG) [2].

As PEX can be found in the whole body, especially in the blood vessel wall, it can be associated with different vascular diseases [3]. Exfoliation material was physiologically detected in vessel wall, myocardium, smooth and striated muscle cells, skin and visceral organs [3, 4].

Today, it is not yet clear what is the key factor in the pathogenesis of different vascular diseases. Iris and conjunctival vasculopathy is documented by indocyanin green angiography [5, 6]; exfoliation material is physiologically presented in the vessel's wall and pericytes in the whole body [3, 4, 7] as well as elevated homocystein level in the serum of the patients with PEX [8]. PEX is indicated for high risk for vascular disease: like stroke, myocardial infarction, and venous occlusions. It is also known that PEX can be found in patients with aortic aneurism which can be explained by abnormal fiber accumulation in the vessel wall [9].

Atherosclerosis is the process closely related with a vascular disease [10].

Abnormal lipid's profile, deregulated glycemia and high blood pressure can be the potential risk factor for vascular disease in the whole body [11]. The systemic manifestations of XFS and XFG, with emphasis on changes in the blood vessels (carotids) as well as changes in the metabolism of lipid material, can be defined as an atherosclerosis risk factor. The aim of our study was to determine the significance of atherosclerotic changes in carotid arteries in the development of XFS and XFG.

Methods

The study included 120 patients – 40 patients *per* each of the three defined groups: the XFS group, the XFG group and age/sex-matched control subjects without PEX. Complete ophthalmological examination was performed for each participant: measurement of best-corrected visual acuity (Snellen charts), intraocular pressure (IOP) measured by Goldmann applanation tonometry, detailed slit-lamp examination, gonioscopy, perimetry (Octopus 900; Haag Strait, Koeniz, Switzerland), and indirect ophthalmoscopy. Slit lamp examination, as well as gonioscopy, was the basis for the diagnosis of PEX in the eye – exfoliation material on the anterior lens capsule or pupillary margin in at least one eye; and high pigmented iridocorneal angle.

PEX deposition with elevated IOP, optic disc glaucomatous changes [(neuroretinal rim and inferior-superior-nasal-temporal (ISNT rule)] and functional failure of the visual field (generalized depression, paracentral scotoma, arcuate or Bjerrum scotoma, nasal step, altitudinal defect temporal wedge, central island) were the entries for XFG group. The patients with the history of inflammatory eye disease, ocular trauma, ocular infection, severe retinal disease, myopia, intraocular surgery within the last 12 months, or laser surgery within the last 3 months were excluded from the study.

Blood samples were collected from the patients before cataract surgery. Biochemical analyses were done for responders fasting for at least 12 hours. Standard laboratory techniques were used for analyzing serum levels of lipid profiles including total cholesterol, low density lipoproteins (LDL), high density lipoproteins (HDL) and triglycerides.

Prior to blood pressure measurement the participants were asked to rest for 5 minutes. Blood pressure was measured, using an Omron M1 plus (OMRON Matsusaka Co. Ltd., Japan) digital blood pressure monitor with an appropriate-sized cuff. Arterial hypertension was diagnosed if the systolic blood pressure was 140 and/or diastolic blood pressure 90 mmHg or higher and antihypertensive drugs were used during the past 2 weeks [12]. Three consecutive measurements with a two-minute interval between measurements were performed and the mean value was used for analyses.

Measurements of the resistance index and intimaemedia thickness during the arterial pressure pulse were performed using ultrasonography (conventional ultrasound scanner – Portable Digital Ultrasound machine Scanner system 3.5 Mhz, Convex probe with 3D, Hongkong, China).

The study was conducted in accordance with the Declaration of Helsinki and it was approved by the local ethics committee. All the subjects were informed about the study procedure and they consented to participate. Informed consent was obtained from each participant.

Statistical analysis was performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

The distribution of the variables was checked with Kolmogorov–Smirnov's test. As all variables were distributed normally, they were expressed as the mean ± SD (Kruskal-Wallis test was used to compare the groups).

Results

The biochemical parameters of the elected groups are given in Figure 1. The mean serum total cholesterol (XFS/XFG: 205.32 ± 33.25/ 205.7 ± 29.38 mg/mL), LDL (XFS/XFG 125.22 ± 15.71/133.4 ± 18.42 mg/mL), and triglycerides: (XFS/ XFG: 133.5 ± 11.23/ 133.15 ± 13.84 mg/mL) levels were significantly higher and mean serum HDL (XFS/XFG: 44.25 ± 7.81/ 39.02 ± 7.38 mg/mL) level was significantly lower in the PEX groups (XFG and XFS) than in the control group (cholesterol: 141.42 ± 28.23 mg/mL, LDL: 105.42 ± 16.21 mg/mL, triglycerides: 107.93 ± 10.65 mg/mL, HDL: 46.322 ± 6.38 mg/mL ($p < 0.01$). The mean serum total cholesterol, LDL, and triglycerides levels were significantly higher and the mean serum HDL level was significantly lower in the PEX group (XFG and XFS) than in the control group ($p < 0.01$).

Systolic and diastolic pressure values were significantly higher in the PEX groups (systolic XFS/XFG 129.92 ± 13.83 mmHg/135 ± 9.84 mmHg; diastolic XFS/XFG 77.12 ± 9.81

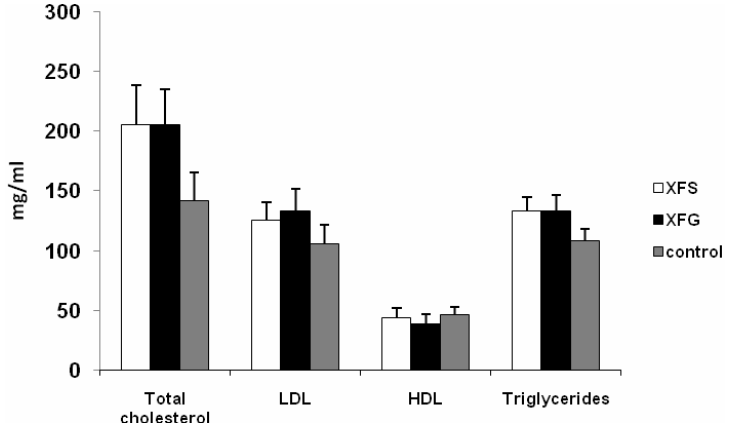

Fig. 1 – Disturbed lipid profile in the patients with pseudoexfoliation syndrome (XFS) and pseudoexfoliation glaucoma (XFG).
LDL – low density lipoproteins;
HDL – high density lipoproteins.

mmHg/80.44 ± 6.89 mmHg) than in the control group (systolic/diastolic: 118.22 ± 9.87 mmHg/135 ± 9.94 mmHg). The systolic and diastolic values are graphically shown in Figure 2. Systolic and diastolic pressure values were significantly higher in the PEX groups than in the control group ($p < 0.01$).

Resistance index was significantly higher ($p < 0.01$) in the XFG group (0.77 ± 0.04) in comparison with the XFS (0.67 ± 0.05) and the control group (0.63 ± 0.05). The patients with XFG (0.91 ± 0.13) had significantly higher values $p < 0.01$ in comparison with XFS patients (0.76 ± 0.09) and the patients from the control group (0.66 ± 0.11) and the results were presented in Figure 3. The patients with XFG had significantly higher values ($p < 0.01$) in comparison with the XFS patients and the patients from the control group.

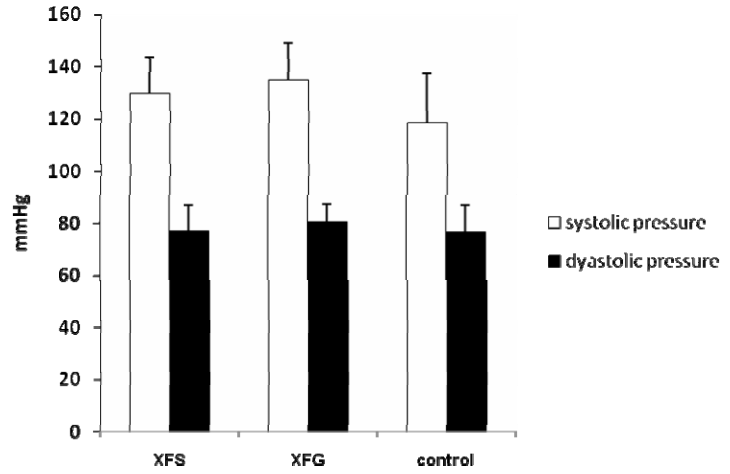

Fig. 2 –Elevated systolic and diastolic pressure in the patients with pseudoexfoliation syndrome (XFS) and pseudoexfoliation glaucoma (XFG).

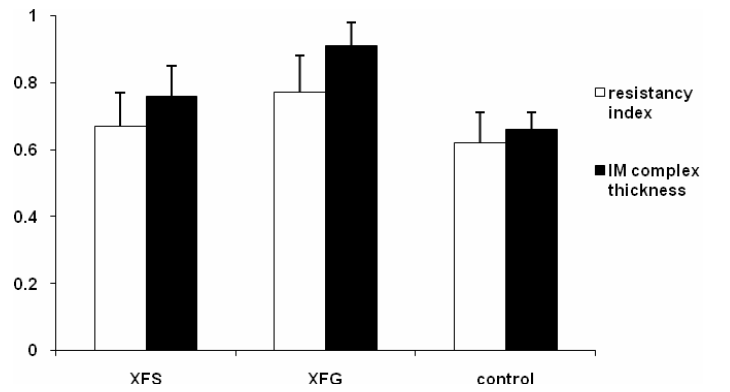

Fig. 3 – Increased resistance index in the patients with pseudoexfoliation glaucoma (XFG). Prolonged intima-media (IM) complex thickness in the patients with XFG.

Disscusion

Pseudoexfoliation syndrome is an age-related disorder in which white flakes accumulate in different tissues in the anterior eye as well as in the whole body, caused by a generalized fibrillopathy [7]. Its pathogenesis is not completely known, but it results in electron-dense microfibrils tissue deposition [13]. The gray-white material can be presented on anterior lens surface and pupillary margin, and can be scraped by papillary movement [14, 15]. Concomitant pigment dispersion with its deposition on anterior chamber structures can be obtained by detailed slit-lamp examination and gonioscopy [15]. Exfoliation material can be found in many different organs: skin, heart, liver, brain, kidney, and eye, too [1]. Earlier studies indicated that iris vasculopathy was described in XFS/XFG [5, 6]; PEX material can be histologically detected in the vessel wall, and pericytes in the whole body [3, 4] and homocystein concentration was elevated [1]. All those findings indicate that vascular diseases could be in a tight junction with XFS/XFG including transient ischemic attacks, hypertension, angina, myocardial infarction, cerebrovascular and cardiovascular disease, aortic aneurysm, Alzheimer-disease and hearing loss [8]. Deregulated parasympathetic vascular control and baroreflex sensitivity, increased vascular resistance and decreased blood flow velocity, arterial endothelial dysfunction, high levels of plasma homocystein and arterial hypertension have been described in PEX patients [16].

The association between different systemic vascular diseases and XFS/XFG remains controversial, despite earlier exposed data [1, 3, 4]. Thus, studies in this ophthalmological field are inconsistent. Our study indicates an association between elevated serum total cholesterol, LDL and triglycerides levels, and the mean systolic and diastolic blood pressures, which were significantly higher where the mean serum HDL level was significantly lower in PEX patients than in control subjects. We can find earlier data about elevated homocystein concentration [8], as well as human cartilage glycoprotein-39 (YKL-40) levels, a new biomarker of inflammation and vascular dysfunction [17, 18], so it can be interlocked with a high incidence of vascular disease in XFS/XFG subjects. Some studies indicated disturbed lipid's profile in PEX patients [18, 19], so previously stated facts can be implicated in the pathogenesis of PEX cardiovascular diseases. Our results concurred with some of numerous studies, in which serum total cholesterol, LDL, and triglycerides levels were significantly higher and the serum HDL level was significantly lower in the PEX groups (XFG and XFS) than in the control group ($p < 0.01$). On the other hand, some data show no significant differences between cholesterol and triglyceride levels in patients with and without PEX [16]. Also, higher arterial pressure, which we observed in our study, represents the risk factor for the development of serious vascular disease [16, 18]. Atherosclerosis is a compound process in the vessel wall, and final effect is the increased resistance and decreased blood flow, so tissue nourishment can be unsettled [19, 20]. Some atherosclerosis markers are the elements of lipid's profile and are useful to evaluate blood flow in the tissue. Also, ultrasonography research is a very important method for rating blood flow in the blood vessel and in the tissue, too. A high resistance index and elevated intima-media thickness are in tight junction with atherosclerotic process and can signify for decreased blood flow, which corresponds to our results. They are also directly associated with disturbed lipid's status. Glaucoma is an ocular disease characterized by disturbed oxidative/antioxidative status activated by increased intraocular pressure and decreased blood flow in the retinal blood vessel, and with the loss of retinal ganglion cells by the apoptotic process [21, 22]. Decreased blood flow of the optic head is the main step of its glaucomatous changes with appropriate functional visual field changes [21, 22]. Increased IOP in XFG is due to accumulated PEX material in the outflow of the humor aqueous; and decreased blood flow in the optic head [2]. Decreased blood flow of the head of optical nerve is due to increased vascular resistance in the carotid and other smaller cranial arteries due to disturbed lipid's profile, elevated homocystein and YKL-40 level [8, 16, 18].

Systemic and ocular blood flow changes, vascular resistance and arterial endothelial dysfunction, high levels of plasma homocystein and arterial hypertension have all been demonstrated in PEX subjects [23–25].

Conclusion

Based the obtained results, as well as on some earlier results, we can suggest new strategies for restraining of pseudoexfoliation glaucoma development. **A** disturbed lipid profile with elevated resistancy index and intima-media thickness and increased systolic and diastolic pressure were compulsory findings in patients with developed XFG. So, these factors could be considered as risk.

In this moment, it seems to be difficult to inhibit the process of pseudoexfoliation production in the whole body, but it appears that with proper therapy (antihypertnesive drugs, cardiotonics, etc.) and adequate nourishing, the process of pseudoexfoliation glaucoma development can be arrested.

R E F E R E N C E S

1. *Scharfenberg E, Schlötzer-Schrehardt U.* PEX syndrome. Clinical diagnosis and systemic manifestations. Der Ophthalmologe 2012; 109(10): 952−61.
2. *Ritch R, Schlotzer-Schrehardt U, Konstas A.* Why is glaucoma associated with exfoliation syndrome. Prog Ret Eye Res 2003; 22(3): 253−75.
3. *Schlötzer-Schrehardt UM, Koca MR, Naumann GO, Volkholz H.* Pseudoexfoliation syndrome. Ocular manifestation of a systemic disorder. Arch Ophthalmol 1992; 110(12): 1752−6.
4. *Streeten BW, Li ZY, Wallace RN, Eagle RC, Keshgegian AA.* Pseudoexfoliative fibrillopathy in visceral organs of a patient with pseudoexfoliation syndrome. Arch Ophthalmol 1992; 110(12): 1757−62.
5. *Asano N, Schlötzer-Schrehardt U, Naumann GO.* A histopathologic study of iris changes in pseudoexfoliation syndrome. Ophthalmology 1995; 102(9): 1279−90.
6. *Parodi MB, Bondel E, Saviano S, Ravalico G.* Iris indocyanine green angiography in pseudoexfoliation syndrome and capsular glaucoma. Acta Ophthalmol Scand 2000; 78(4): 437−42.
7. *Naumann G.* Pseudoexfoliation syndrome for the comprehensive ophthalmologist Intraocular and systemic manifestations Historical image. Ophthalmology 1998; 105(6): 951−68.
8. *Leibovitch I, Kurtz S, Shemesh G, Goldstein M, Sela B, Lazar M*, et al. Hyperhomocystinemia in Pseudoexfoliation Glaucoma. J Glaucoma 2003; 12(1): 36−9. 1
9. *Schumacher S, Schlotzer-Schrehardt U, Martus P, Lang W, Naumann GO.* Pseudoexfoliation syndrome and aneurysm of the abdominal aorta. Lancet 2001; 357(9253): 359−60.
10. *Rathcke CN, Vestergaard H.* YKL-40, a new inflammatory marker with relation to insulin resistance and with a role in endothelial dysfunction and atherosclerosis. Inflamm Res 2006; 55(6): 221−7.
11. *Mitchell P, Wang JJ, Smith W.* Association of pseudoexfoliation syndrome with inceased vascular risk. Am J Ophthalmol 1997; 124(5): 685−7.
12. *Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G,* et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2007; 28(12): 1462−536.
13. *Schlotzer-Schrehardt U, von der Mark K, Sakai LY, Naumann GO.* Increased extracellular deposition of fibrillin-containing fibrils in pseudoexfoliatin syndrome. Invest Ophthalmol Vis Sci 1997; 38(5): 970−84.
14. *Ritch R, Schlötzer-Schrehardt U.* Exfoliation syndrome. Surv Ophthalmol 2001; 45(4): 265−315.
15. *Hoeks AP, Brands PJ, Smeets FA, Reneman RS.* Assessment of the distensibility of superficial arteries. Ultrasound Med Biol 1990; 16(2): 121−8.
16. *Visontai Z, Merisch B, Kollai M, Holló G.* Increase of carotid artery stiffness and decrease of baroreflex sensitivity in exfoliation syndrome and glaucoma. Br J Ophthalmol 2006; 90(5): 563−7.
17. *Kastrup J, Johansen JS, Winkel P, Hansen JF, Hildebrandt P, Jensen GB,* et al. High serum YKL-40 concentration is associated with cardiovascular and all-cause mortality in patients with stable coronary artery disease. Eur Heart J 2009; 30(9): 1066−72.
18. *Turkyılmaz K, Oner V, Kırbas A, Sevim MS, Sekeryapan B, Zgur GO,* et al. Serum YKL-40 levels as a novel marker of inflammation and endothelial dysfunction in patients with pseudoexfoliation syndrome. Eye 2013; 2(7): 854−9.
19. *Damji KF, Bains HS, Stefansson E, Loftsdottir M, Sverrisson T, Thorgeirsson E,*et al.Is pseudoexfoliation syndrome inherited? A review of genetic and nongenetic factors and a new observation. Ophthalmic Genet 1998; 19(4): 175−85.
20. *Ross R.* The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993; 362(6423): 801−9.
21. *Tezel G.* Oxidative stress in glaucomatous neurodegeneration: mechanisms and consequences. Prog Retin Eye Res 2006; 25(5): 490−513.
22. *Liu T, Clark RK, McDonnell PC, Young PR, White RF, Barone FC,* et al. Tumor necrosis factor-alpha expression in ischemic neurons. Stroke 1994; 25(7): 1481−8.
23. *Andrikopoulos KG, Alexopoulos KD, Gartaganis PS.* Pseudoexfoliation syndrome and cardiovascular diseases. World J Cardiol 2014; 26(8): 847−54.
24. *Agafonova VV, Frankovska-Gerlak MZ, Sokolovskaia TV, Brizhak PE, Bessarabov AN.* Occurrence and characteristics of cardiovascular pathology in patients with pseudoexfoliative glaucoma. Vestn Oftalmol 2013; 129(6): 34−7. (Russian)
25. *Benda T.* Cardiovascular diseases occurrence in patients with pseudoexfoliative syndrome and pseudoexfoliative glaucoma. Cesk Slov Oftalmol 2011; 67(1): 12−5. (Czech)

Received on March 20, 2015.
Revised on July 8, 2015.
Accepted on August 25, 2015.
Online First April, 2016.