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Pseudoexfoliation syndrome and its antioxidative protection deficiency as risk factors for age-related cataract

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PURPOSE. *Pseudoexfoliation syndrome (PES) seems to be a systemic condition. However, to an ophthalmologist it represents a continual challenge, due to unclear etiology and pathogenesis, and because of a potential for development of an aggressive glaucoma, and cataract surgery complications. According to some findings, PES could be a factor of hastened aging, which means that it could be considered as a secondary aging factor.*
METHODS. *Frequencies of secondary aging diseases (non-insulin dependent diabetes mellitus, atherosclerotic myocardiopathy, chronic obstructive lung diseases, arterial hypertension, and PES) were investigated in 162 patients with age-related cataract and 55 age- and sex-matched control subjects, and analyzed by a logistic regression. The authors also determined elements of antioxidative protection in a group of sera from patients with cataract and PES, and compared them to those obtained from patients with cataract without PES (activity of catalase and peroxidase, glutathione, vitamins C and E), and total antioxidative protection (%iMDA). Antioxidant defense of aqueous humors, expressed as a rate of induced malondialdehyde (%iMDA), and total thiol groups in the lens corticonuclear blocks (TSH) were estimated in samples of 17 patients with PES and cataract and 55 patients with cataract only.*
RESULTS. *Logistic regression showed the highest odds ratio for PES (OR=4.516; $p<0.05$). Catalytic activity of serum catalase had significantly lower values in patients with PES ($p<0.05$). Antioxidative defense of aqueous humor and lens had lower values in patients with PES.*
CONCLUSIONS. *The results indicate that PES might be a significant factor for cataractogenesis. At least a part of pathogenesis alterations in an eye with PES could be the result of higher intensity of oxidative stress. (Eur J Ophthalmol 2006; 16:268-73)*

KEY WORDS. *Cataract, Oxidative stress, Pseudoexfoliation syndrome, Antioxidative protection*

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INTRODUCTION

Primary aging is a solely genetically determined process, and its essence is in the involutional changes that appear with age. Secondary aging is an accelerated process, because of diseases that are frequent in later period of human life, and which are mostly consequences of living habits, social, economic, ecologic, and other influences (1).

A contemporary hypothesis on aging points to oxidative stress product accumulation, which decreases resistance

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to intra- and extracellular damages (2). Oxidative stress results from increased oxidative damage, decreased antioxidative protection, or both. Oxidative stress induced by solar ultraviolet radiation (photoxidative stress) could be an important factor in age-related cataractogenesis.

Pseudoexfoliation syndrome (PES) appears in the elderly and its frequency increases with age. Since first reported by Lindberg in 1917, in association with glaucoma, it continues to be an enigma and a challenge for ophthalmologists, due to the unclear origin and composition of pseudoexfoliative material capable of ocular disease development.

The numerous changes it causes in an eye, such as uveopathy, corneal endothelopathy, zonulopathy, phakopathy, and irido- and cyclopathy, could be a source of numerous perioperative complications of cataract surgery and accidental injury, as well as of aggressive glaucoma development (3-5).

The fact that pseudoexfoliations have been found in other organs and tissues of older people directs attention to the systemic nature of PES (5-10).

However, true pathology directly connected to PES has been observed solely in the eye.

So far, PES could be considered a systemic condition, but documented as a causative agent for ocular diseases only, and thus it remains a subject of primary ophthalmologic interest.

The chemical composition of pseudoexfoliative material remains unknown. It was recognized as a complex glycoprotein/proteoglycan filamentous and fibrilous structure. It also consists of the matrix and HNK-1 carbohydrate epitope, responsible for different tissue components adhesion, including also PES material.

Yet the epitope immunoreactivity in eye differs from extraocular fibrilopathy within PES (11, 12). New methods could be helpful in investigation of the basic nature of pseudoexfoliative material, even on the elemental level (13).

Besides their specific nature, changes in an eye with PES also resemble some more pronounced degenerative changes related to aging. The instances of somewhat younger patients with cataract and PES compared to cataract patients without PES in our population also point to hastened aging (14).

Because PES and age-related cataract are both characteristic of elderly people and with regard to the contemporary hypothesis about oxidative stress and aging, interrelation of those conditions should be investigated.

METHODS

The clinical group included 162 patients with cataract, and the control one 55 healthy age- and sex-matched control subjects. An ophthalmologist and an internist examined all of them. Frequencies of secondary age diseases, such as non-insulin dependent diabetes, chronic obstructive lung diseases, arterial hypertension without complications, atherosclerotic myocardiopathy, and PES, were recorded and compared by means of a logistic regression.

Blood for serum analyses was taken from all patients with cataract and control subjects in the morning, after a night fast. During an extracapsular cataract extraction, 80 samples of corticonuclear blocks and aqueous humors were taken from 72 cataract patients.

Vitamin C concentration in sera was estimated colorimetrically using 2.4-dinitrophenylchidralazyne (15), and results were expressed in mM/L. Vitamin E serum concentration was assayed by the fluorometric method (16), and results were expressed in μM/L. Glutathione concentration was determined using the Elman's reagent (17). Catalase activity was assayed by the Koroljuk's method (18) and serum peroxidase activity by the Trinder's method (19). Total antioxidative protection (%iMDA) based on level of non-oxidized lipids was determined by the Ledwaziv and coworkers method (20). The same method was used in the humor aqueous analysis whereas total thiol groups in the lens corticonuclear blocks were analyzed after homogenization by the Elman's reagent method without a previous deproteinization of samples (17). Data were analyzed by univariant and multivariant variance analysis (ANOVA, MANOVA).

RESULTS

The average age of the clinical group was 65.1 years, and 62.4 in the control group. There were 107 male and 55 female cataract patients, and 32 male and 23 female persons without cataract in the control group.

Among the patients with cataract, 29 had PES, versus only 2 in the control group. Diabetes was found in 27 patients with cataract and 4 without cataract, 48 patients in the clinical group had arterial hypertension and 11 of those in the control group, obstructive bronchitis or emphysema was found in 26 from the clinical and 4 in the control group, 31 patients with cataract and 5 from control group had non-ischemic atherosclerotic myocardiopathy.

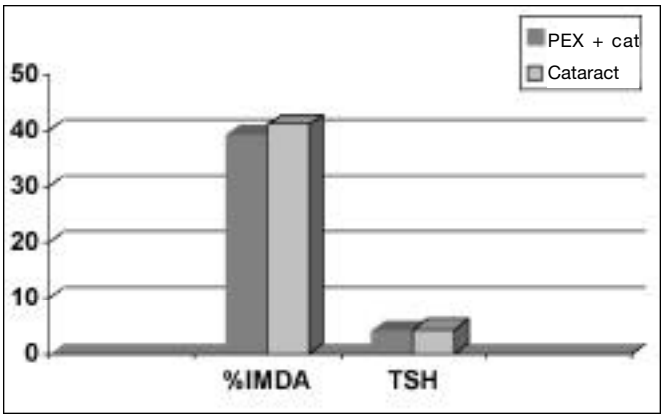

Fig. 1 - *Lower values of some antioxidative defense parameters in aqueous humour and lens corticonuclear block.*

Based on the secondary diseases frequency, a statistically significant logistic regression was obtained (χ^2=18.87; p=0.0044; const = 0.379). Odds ratio was significant for the PES only (OR=4.516; p=0.049), and it is higher than the one found in diabetic patients (Tab. I).

Patients with cataract and PES had significantly lower values of catalytic activity of the serum catalase (p<0.05) (Tab. II). Other analyzed parameters of the antioxidative defense of the sera do not significantly differ in cataract patients with and without PES.

In the local compartment, total sulfhydryl groups of corticonuclear lens blocks were somewhat lower in patients with PES (TSH=3.93±1.47 with PES, and 4.20±1.63 without PES), as well as %iMDA in their aqueous humors (%iMDA=39.45±16.28 μM/g with PES, and 40.03±18.07 without it) (Fig. 1). Neither of the results had statistical significance (p>0.05).

TABLE I - VALUES OF ODDS RATIO (OR) BASED ON THE SECONDARY AGING DISEASES IN CLINICAL AND CONTROL GROUPS

Variable	B	OR
Diabetes	0.915	2.506
Hypertension	0.589	1.807
Atherosclerosis	0.543	1.725
Lung diseases	0.714	2.048
PES*	1.501	4.516

*p<0.05
PES = Pseudoexfoliation syndrome

DISCUSSION

Frequency of PES in patients with cataract is less analyzed than the frequency of the syndrome alone, or as a risk for glaucoma development (5, 21-23), although it has been recognized as a risk factor for cataract (24, 25). Yet not all authors find association between PES and cataract (26).

Could it be that PES-induced systemic or intraocular changes compromise lens metabolism more than other mentioned diseases? Should PES be considered as a possible secondary aging factor?

Catalase is a hemoprotein enzyme present in almost all mammalian tissues, but it shows the highest activity in the liver and erythrocytes. It is one of the most significant antioxidative enzymes. An increase of catalase activity has been observed in numerous liver and some other diseases (27).

A decreased catalase activity has been found in patients with malignant diseases, diabetes, anemia, and other conditions (28). Catalase acts in alcohol, formiate, and nitrites reduction. It has a catalytic and peroxidatic activity. Most frequently it reflects the hepatocytes state. However, besides the above mentioned, we found no clinical evidence of liver or other diseases in our clinical group.

Catalase activity in a local compartment and on a systemic level seems to be of little importance in prevention of pure age-related cataract. It was found that catalase levels in red blood cells were not modified, whereas activity of superoxide dismutase was significantly increased in patients with age-related cataract versus in healthy subjects (29). Catalase was also less effective than glutathione peroxidase in the prevention of cataract in cultured rat lenses,

TABLE II - MEAN VALUES ± STANDARD DEVIATIONS OF INVESTIGATED SERUM ANTIOXIDATIVE PARAMETERS IN PATIENTS WITH CATARACT, ACCORDING TO PES PRESENCE

Parameter	With PES	Without PES
Vitamin C	52.21±13.42	50.44±13.26
Vitamin E	22.18± 4.21	22.22± 4.36
Peroxidase	61.79±40.32	62.81±29.56
Glutathione	15.59± 4.80	13.99± 5.96
Catalase*	17.82±14.83	24.73±15.23
%i MDA	49.31±18.68	47.48±20.93

*p<0.05
PES = Pseudoexfoliation syndrome

if the cataract was caused by H_2O_2 and photochemical injury under physiologic conditions (30). On the other hand, catalase activity level and Cu, Zn-superoxide dismutase level was found to be significantly lower in diabetic cataractous lenses then in senile cataractous lenses (31).

Paying attention to the diabetes and PES connection, lower prevalence of PES and pseudoexfoliation glaucoma was recognized in the group of patients with diabetes (32-34). Some other studies did not find a connection between PES and diabetes, either positive or negative (26, 35). However, in one recent report a high incidence of PES in diabetic patients compared with non-diabetic ones of the same age was found (36).

Diabetes increases oxidative stress. But with regard to antioxidative protection, the most consistent results in diabetes and cataract patients were related to decreased glutathione and protein thiols concentration (37-39). However, an exhaustion of antioxidant system, and especially glutathione metabolic system, was also observed in cataract patients with diseases of liver and chronic alcohol intoxication, cardiovascular diseases, and gastrointestinal diseases (40).

Ringvold and Davanger described changes observed in the iris vascular bed of eyes with PES that resulted in tissue hypoxia (41).

Do similar changes appear in other vessels in body? A large population-based Blue Mountain Eye Study has found significant association of PES with a history of angina or hypertension or a combined history of angina, acute myocardial infarction, or stroke (42). Other authors suspect that PES is a systemic disorder associated with transient ischemic attacks, stroke, systemic hypertension, and myocardial infarction (25). There was also found a significant association between PES and aneurysms of the abdominal aorta (43). However, in an Icelandic families study, the PES association with genetics was very indicative, but there were no associations of PES with cardiovascular and cerebrovascular diseases, systemic hypertension, or diabetes (32).

Authors from Spain (26) found that heart failure, geographic macular atrophy, and antiglaucomatous treatment multiply risk for PES several times.

Testing a hypothesis that ocular PES is a part of generalized disorder that could increase mortality, Ringvold et al found no association between the presence of ocular PES and mortality (44). Two large population-based studies from Norway did not reveal significant differences in rates of death caused by vascular diseases and cancer in patients with pseudoexfoliation glaucoma compared to primary open-angle glaucoma, but they found an increased mortality rate in connection with acetazolamide usage (45, 46). Other works demonstrated significantly more common chronic cerebral diseases in patients with pseudoexfoliation glaucoma (47), while others did not find association between ocular PES and cardiovascular and cerebrovascular mortality (48). However, having diseases, which are frequent in secondary aging, do not obligatorily mean increased mortality rate (1), and that could be equally valid for PES.

Recently, PES has been found to be more common in patients with Alzheimer's disease. PES is considered to be useful in an early diagnosis of that type of dementia. Similarities between PES material in eye and amyloid material are actualized again (6, 47, 49). An increased cataractogenesis was pointed out in the Abeta-transgenic mouse model for Alzheimer disease (50). Cerebral Abeta deposition occurs also in cataract in patients with Alzheimer disease. It is interesting that cataract amelioration was achieved by addition of synthetic catalase and superoxide dismutase mimetic (50).

According to our results, PES has a role in cataractogenesis. The results of lower catalase activity we could interpret as a decreased antioxidative defense only. Investigated lens and aqueous humor antioxidative parameters reflect intensity of oxidative stress in an eye only, but without any specificity for particular diseases. Almost any other secondary aging disease, which was observed in our work, raises the oxidative stress intensity in the eye at a somewhat similar level to PES. However, evidence of oxidative damage, as well as decreased antioxidative protection, has been documented in the pathobiology of ocular PES (51).

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