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RESEARCH

THE ASSOCIATION OF ARCUS SENILIS WITH EXFOLIATION SYNDROME AND CARDIOVASCULAR DISEASE IN ELDERLY POPULATION

ABSTRACT

Introduction: This study aimed to evaluate the relationship between commonly observed ocular conditions in older aged population, arcus senilis and exfoliation syndrome and to evaluate their association with systemic vascular disease.

Materials and Method: Seventy-five patients with arcus senilis (Group 1) and 75 patients without arcus senilis (Group 2) were included in the study. The proportion of cases with exfoliation syndrome, levels of serum cholesterol, triglycerides, high density lipoprotein, low density lipoprotein and very low density lipoprotein as well as rates of vascular disease were compared between two groups.

Results: Patients in both groups were similar with respect to age (65.7±8.5 years, 62.9±6.2 years; p=0.394). Exfoliation syndrome prevalence in group 1 (14.7%) was lower than that of group 2 (29.3%) (p=0.030). There were no significant differences between the two groups with respect to levels of serum cholesterol (200.6±46.5 mg/dl vs.189.2±41.6 mg/dl; p=0.116), serum triglycerides (4.7±0.5 log vs. 4.8±0.4log; p=0.760), high density lipoprotein (4.06±0.3log vs. 4.08±0.3log; p=0.720), low density lipoprotein (112.0±43.3 mg/dl, 118.7±37.0 mg/dl; p=0.307) and very low density lipoprotein (3.2±0.5log vs. 3.3±0.5log; p=0.528). Statistically significant differences with respect to coronary artery disease (10.7% vs. 12.0%, p=0.797) or diabetes mellitus (18.7% vs. 30.7%; p=0.088) were not detected between the two groups. Hypertension was observed more frequently in patients without arcus senilis (12.0% vs. 37.3%; p<0.001).

Conclusion: Exfoliation syndrome was observed more frequently in patients without arcus senilis. Arcus senilis and exfoliation syndrome do not appear to be associated with coronary artery disease.

Key Words: Arcus Senilis; Coronary Artery Disease; Exfoliation Syndrome; Hyperlipidemias.

ARAŞTIRMA

YAŞLI HASTALARDA ARKUS SENİLİSİN EKSFOLİASYON SENDROMU VE KARDİYOVASKÜLER HASTALIKLAR İLE İLİŞKİSİ

ÖZ

Giriş: Bu çalışmada, yaşlı nüfusta sık görülen arkus senilis ile eksfoliasyon sendromu birlikteliğinin, sistemik vasküler hastalıklar ile ilişkisinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya arkus senilis bulunan 75 olgu (Grup 1) ile arkus senilis tespit edilmeyen 75 olgu (Grup 2) dahil edilmiştir. Tüm olguların eksfoliasyon sendromu varlığı ve serum kolesterol, trigliserid, yüksek yoğunluklu lipoprotein, düşük yoğunluklu lipoprotein, çok düşük yoğunluklu lipoprotein değerleri saptanmış, vasküler hastalıkları değerlendirilmiştir.

Bulgular: Yaş ortalamaları her iki grupta benzer bulunmuştur (65,7±8,5 yaş, 62,9±6.2 yaş; p=0,394). Eksfoliasyon sendromu prevelansı grup 1 de (%14,7) grup 2'den (%29,3) düşük bulunmuştur (p=0,030). Gruplar arasında serum kolesterol düzeyi (200,6±46,5 mg/dl, 189,2±41,6 mg/dl; p=0,116), serum logaritmik trigliseridleri (4,7±0,5 log, 4,8±0.4log; p=0,760), logaritmik yüksek yoğunluklu lipoprotein (4,06±0.3log, 4,08±0.3log; p=0,720), düşük yoğunluklu lipoprotein (112,0±43,3 mg/dl, 118,7±37.0 mg/dl; p=0,307) ve logaritmik çok düşük yoğunluklu lipoprotein (3,2±0.5log, 3,3±0.5log; p=0,528) açısından fark saptanmamıştır. İki grup arasında koroner arter hastalığı (%10,7, %12,0, p=0,797) ve diabetes mellitus (%18,7, %30,7; p=0,088) açısından istatistiksel anlamlı fark saptanmamıştır. Hipertansiyonun arkus senilis bulunmayan grupta daha sık görüldüğü saptanmıştır (%12,0, %37,3; p<0,001).

Sonuç: Bu çalışmada arkus senilis bulunmayan grupta eksfoliasyon sendromu daha sık saptanmıştır. Geriatrik yaş grubunda sıklıkla görülen arkus senilis ve eksfoliasyon sendromunun koroner arter hastalığı ile ilişkisi mevcut değildir.

Anahtar Sözcükler: Arkus Senilis; Koroner Arter Hastalığı; Eksfoliasyon Sendromu; Hiperlipidemi.

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INTRODUCTION

Arcus senilis, also referred to as corneal arcus, is a grey white yellowish opacity located at the peripheral cornea. It forms from deposition of cholesterol esters, phospholipids and neutral triglycerides at the edge of Bowman's layer and is seperated from the limbus with a lucent zone (1). Arcus senilis is an age related corneal finding and is readily detectable with biomicroscopic examination. Arcus senilis begins at the inferior and superior poles of the cornea and progresses to encircle the entire circumference of the peripheral cornea. The prevalence of corneal arcus increases with age, up to a reported prevalence of >80% in persons older than 60 years and is more common in men than women regardless of age or race (2). Arcus senilis has been shown to be associated with atherosclerotic vessel disease, obesity, dyslipidemia, insulin resistance and type 2 diabetes and thus is regarded as an alerting ocular symptom for cardiovascular disease (1,3). Previous investigators reported a higher prevalence of coronary heart disease in subjects with arcus senilis than those without, especially in those younger than fifty years of age (4). Various cardiovascular risk factors were found to be associated with corneal arcus, including hyperlipidemia, hypertension, higher body mass index (BMI), diabetes mellitus and cigarette smoking (5).

Exfoliation syndrome (XFS) is a common age-related systemic fibrillopathy of unknown etiology that mainly affects the geriatric population in certain geographic locations such as Iceland, Scandinavia, Turkey, Greece and Saudi Arabia (6). In certain populations, 5-40% of the geriatric population over 70 years of age has been shown to have ocular signs indicative of XFS (7,8). XFS arises secondary to deposition of fibrillogranular material throughout the entire anterior segment of the eye including the lens capsule, ciliary body, zonules and corneal endothelium (6). It is a known risk factor for secondary open angle glaucoma, cataract, lens subluxation and increased inflammation following intraocular procedures (9). From a systemic standpoint, XFS has been found to increase susceptibility to cardiovascular disease (10, 11), peripheral vascular disease (12), cerebrovascular disease (13), small vessel disease (14) as well as neurodegenerative disorders (15). Hypoxia has been implicated as a pathogenetic factor in the development of XFS (14). Furthermore, increased level of inflammatory markers such as IL 6, IL8, TGF-, in ocular fluids of patients with XFS suggest that inflammation could also be involved in the pathogenesis of vascular disease associated with XFS (11). Overall, the findings of previous studies suggest that both arcus senilis and exfoliation syndrome share similar mechanisms for the formation of atherosclerotic plaques. Thus, the possibility of a common underlying link such as hypoxia may exist between the XFS, arcus senilis and vascular disease (16).

In this aspect, since both arcus senilis and XFS are linked to systemic vascular disorders and are easily recognizable with routine eye examinations, they could have a potential value in alerting the physician to the presence of systemic vascular disease. Therefore, the aim of this study was to look into the possible association between arcus senilis and XFS and to determine whether arcus senilis and XFS individually or in combination could be used as potential surrogate markers for hyperlipidemia, coronary heart disease, diabetes mellitus or hypertension.

MATERIALS AND METHOD

An observational case-control study was undertaken at a single university based hospital from September 2011 to October 2012. The research adhered to the tenets of the Declaration of Helsinki, informed consent was obtained from all participants and the study was carried out with approval from the Institutional Ethical Review Board. Patients who were over the age of 40 years and whose medical data was evaluable for evaluation were consecutively included in both groups. Arcus senilis was defined as deposition of whitish-grey lipid material in the peripheral corneal stroma seperated from the limbus with a clear zone. Subjects with arcus senilis were designated as cases (Group 1, n=75 patients) and those without arcus senilis constituted the controls (Group 2, n=75 patients) (Table 1). Patients in both groups were consecutively recruited into the study. All patients underwent a complete ocular examination consisting of slit-lamp biomicroscopy, fundus examination and intraocular pressure evaluation. The presence of arcus senilis and XFS were specifically evaluated. The diagnosis of XFS was established upon the detection of fibrillogranular material deposited on the anterior lens capsule and/or the pupillary border (Figure 1). Data from patients' lipid profile were recorded. All patients had to have prior blood samples obtained within 12 months of their eye examination to be included into the study. Subjects without a serum lipid profile [total cholesterol, triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL)] within the last 12 months were excluded. Detailed medical history details of all participants were recorded. Pertinent details included hypertension, diabetes mellitus, coronary heart disease and their medication history. A positive history of myocardial infarction, coronary

Table 1— Demographic and Clinical Characteristics of Subjects Included in the Study.

Parameter	Subjects with Arcus Senilis (n=75)	Subjects without Arcus Senilis (n=75)	p
Age (years)	65.7±8.5	62.9±6.2	0.394
Gender (F/M)	30/45	51/24	0.001*
Presence of XFS n (%)	11 (14.7)	22 (29.3)	0.030*
Coronary Artery Disease n (%)	8 (10.7)	9 (12.0)	0.797
Diabetes Mellitus n (%)	14 (18.7)	23 (30.7)	0.088
Hypertension n (%)	9 (12.0)	28 (37.3)	<0.001*

XFS: Exfoliation syndrome; F: Female; M: Male.
* Significant p<0.05.

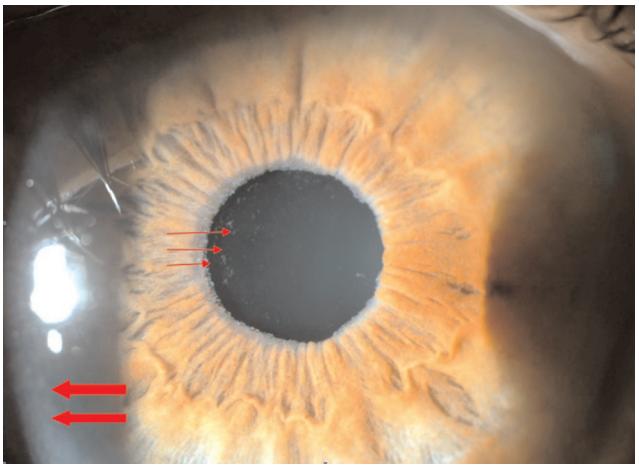

Figure 1— Slit lamp biomicroscopic appearance of an eye with arcus senilis (thick arrows) and exfoliation syndrome (arrows).

artery bypass surgery, angioplasty and angina pectoris was considered as positive markers for the presence of cardiovascular disease. Hypertension was defined as a diastolic blood pressure of ≥90 mm/Hg and a systolic blood pressure of ≥160 mm/Hg. SPSS v.18.0 (IBM, New York, USA) was used for all statistical analyses. Student's t test, Pearson correlation analysis or Mann Whitney U test were used for group comparisons. A p value of less than 0.05 was considered significant.

Results

The baseline characteristics of all patients are highlighted in Table 1. There were no significant differences between the mean ages of group 1 and group 2 (p=0.394). XFS was observed in 22.0% of all subjects (n=150) and was more frequent in subjects *without* arcus senilis (29.3%) than those with arcus senilis (14.7%) (p=0.030) (Figure 2).

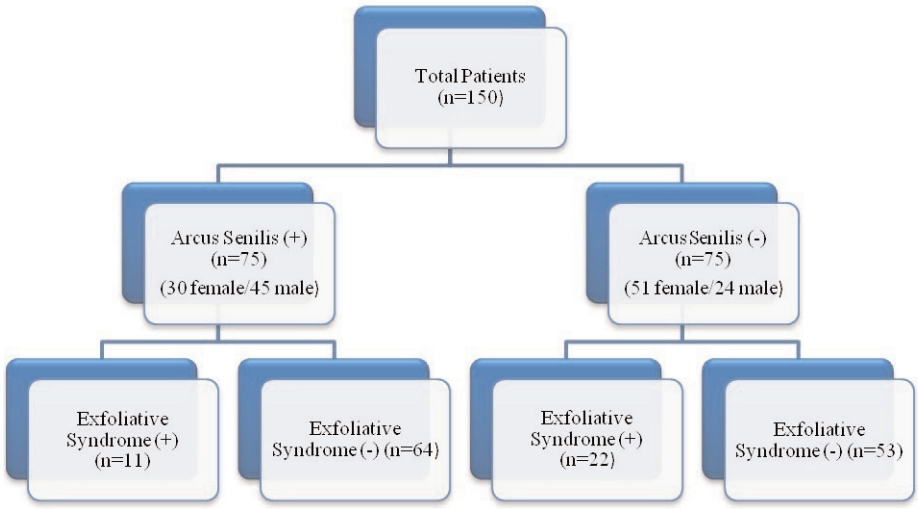

Figure 2— The study design and the number of study subjects allocated to each study group is demonstrated.

Additionally, arcus senilis conferred a protective effect for XFS (OR=0.414, 95%CI, p=0.0329). The distribution of subjects in the two groups with respect to systemic illness such as diabetes mellitus and coronary artery disease was not significantly different (Table 1). Hypertension was observed more frequently in subjects without arcus senilis (p<0.001). The mean serum lipid levels of both groups were also found to be similar (Table 2).

DISCUSSION

Arcus senilis represents deposits of cholesterol ester rich lipid particles, which are selectively trapped in the extracellular matrix in the corneal stroma. Arcus senilis formation is believed to be accelerated in the presence of high plasma LDL levels as LDL is the major source of the cholesterol esters that accumulate in the cornea (17). In our study, LDL levels were comparable between subjects with arcus senilis (112.0±43.3 mg/dl) and those without (118.7±37.0 mg/dl) (p=0.307). Arcus senilis has also been associated with diabetes mellitus, smoking, blood pressure, obesity and age (17). We found that among subjects with arcus senilis, 8 patients (10.7%) had coronary artery disease, 14 had (18.7%) diabetes mellitus and 9 had hypertension (12.0%) and that the prevalence of these diseases were not different in subjects without arcus senilis (Table 2), suggesting that the presence of arcus senilis does not increase the probability of the above mentioned vascular diseases. However, in previous population based investigations and hospital based studies, arcus senilis was found to be associated with older age, male sex, hyperlipidemia, dyslipoproteinemias including familial hypercholesterolemia, atherosclerosis and coronary artery disease (17,18). Thus, our findings could be representative of the Turkish population.

In a study of Christoffersen et al. in which 12745 people aged 20-93 years were followed for 31 to 33 years, the risk of ischemic heart disease was reported to be stronger when both xanthelasmata and arcus senilis were present (19). In another study by Vurgese et al. in which randomly selected 952 people were evaluated, arcus senilis was found to be significantly associated with age, lower intraocular pressure, thinner central cornea and hyperopic refractive error (3). However, in the same report, arcus senilis was not associated with serum levels of HDL, cholesterol, creatinine, glucose and glycosylated hemoglobin. It was concluded that arcus senilis was not a clinical biomarker for major metabolic disorders (3). Our data appears to be in agreement with the results of Vurgese et al.

Chen et al. followed 238 patients aged 30-60 years who were evaluated for the association of arcus senilis, serum lipid profile and coronary artery disease. In that study, systolic blood pressure was inversely correlated with arcus senilis (4). In our study we also found an inverse correlation for hypertension and arcus senilis.

In a population based cross sectional study by Ang et al. involving 3397 people aged 40-80 years, it was found that arcus senilis was associated with coronary artery disease, independent of other risk factors in ethnic Indian adults, even in those at low risk for vascular disease (1). Hickey et al. followed 534 patients who were investigated for the association of arcus senilis, serum lipid profile and coronary artery disease (20). Frequency and degree of arcus were positively associated with age and with lifetime alcohol intake. In another study by Pe'er et al. in which randomly selected 150 people were evaluated, no associations were found between arcus senilis and other coronary artery disease risk factors such as high triglyceride, HDL, LDL, VLDL levels, obesity and smoking (18).

In the Singapour Malay Eye Study in which 3280 subjects aged 40-80 years were investigated, the serum C-reactive protein (CRP) levels as well as the presence of chronic kidney disease and peripheral artery disease were determined (5). Arcus senilis was determined from anterior segment images taken with a slit-lamp camera. The odds ratio of demonstrating

Table 2— Serum Lipid Profiles of the Patients Included in the Study.

Parameter	Subjects with Arcus Senilis (n=75)	Subjects without Arcus Senilis (n=75)	p
VLDL (log)	3.2±0.5	3.3±0.5	0.528
LDL (mg/dl)	112.0±43.3	118.7±37.0	0.307
TG (log)	4.7±0.5	4.8±0.4	0.760
HDL (log)	4.06±0.3	4.08±0.3	0.720
Total Cholesterol (mg/dl)	200.6±46.5	189.2±41.6	0.116

HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein; log: logarithmic transformation.

arcus senilis was 1.21 permmol/L for total cholesterol, 1.94 permmol/L for LDL, 3.85 permmol/L for peripheral artery disease, 1.14 permmol/L for chronic kidney disease and 1.29 permmol/L for smoking. This study confirmed that arcus senilis was associated with systemic inflammatory markers, peripheral artery disease and chronic kidney disease (5).

XFS is a complex systemic fibrillopathy with an inflammatory component which primarily effects eye and visceral organs (6,7,13). In previous studies, both XFS and arcus senilis were found to be independently associated with age, vascular disease and inflammation (1,6). However, the findings of our study revealed a statistically significant inverse association between XFS and arcus senilis (p=0.030) and suggest that from a clinical standpoint, arcus senilis develops independently of XFS. Furthermore, the findings of our study suggest that arcus senilis may be protective for XFS (OR=0.414, 95%CI, p=0.0329). In previous studies, XFS has been also found to be related to vascular, cerebrovascular and cardiovascular diseases (9) although not all studies have confirmed these associations (21,22). In our study AS was not found to be statistically associated with coronary artery disease (p=0.797).

In the Blue Mountain Eye Study, XFS was seen in 81 (2.3%) patients of 3546 participants. Its prevalence was increased with age, in females, and in subjects with a history of angina, acute myocardial infarction and stroke (23). Of importance, arcus senilis was predictive of cardiovascular disease and coronary artery disease in elderly individuals due to its association with age. The findings suggested that arcus senilis and XFS are both ocular markers for proatherogenic changes (12,17). Our study is unique in that, to the best of our knowledge, it was the first study to analyze the possible association of XFS with arcus senilis. Our findings were unable to reveal a meaningful negative relationship between these two disorders. Thus, we conclude that these two ocular conditions that arise in the aging population have different pathogenetic mechanisms and the presence of one condition does not have any predictive value as to the presence of the other.

In conclusion, the results from this study reveal that arcus senilis is not associated with coronary artery disease, diabetes mellitus, hypertension and blood lipid levels in Turkish elderly population. Arcus senilis appears to be a protective factor for the development of XFS. Further investigations are necessary to understand whether the relationship between arcus senilis and cardiovascular risk factors/disease is affected by race and/or geographic location.

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References

1. Ang M, Wong W, Park J, et al. Corneal arcus is a sign of cardiovascular disease, even in low-risk persons. Am J Ophthalmol 2011;152(5):864-71. (PMID:21742308).
2. Friedlaender MH, Smolin G. Corneal degenerations. Ann Ophthalmol 1979;11:1485-95. (PMID:318034).
3. Vurgese S, Panda-Jonas S, et al. Corneal arcus and its associations with ocular and general parameters: the Central India Eye and Medical Study. Invest Ophthalmol Vis Sci 2011;52(13):9636-43. (PMID:22110074).
4. Chen HT, Chen HC, Hsiao CH, et al. Corneal arcus and cardiovascular risk factors in middle-aged subjects in Taiwan. Am J Med Sci 2009;338(4):268-72. (PMID:19707111).
5. Wu R, Wang JJ, Tai ES, Wong TY. Cardiovascular risk factors, inflammation, and corneal arcus: the Singapore Malay Eye Study. Am J Ophthalmol 2010;150:581-7. (PMID:20630492).
6. Elhawy E, Kamthan G, Dong CQ, Danias J. Pseudoexfoliation syndrome, a systemic disorder with ocular manifestations. Hum Genomics 2012;10:22-6. (PMID:23157966).
7. Irkec M. Exfoliation and carotid stiffness. Br J Ophthalmol 2006;90(5):529-30. (PMID:16556616).
8. Ringvold A. Epidemiology of the pseudoexfoliation syndrome. Acta Ophthalmol Scand 1999;77:371-5. (PMID:10463402).
9. Arnarsson A, Damji KF, Sverrisson T, Sasaki H, Jonasson F. Pseudoexfoliation in the Reykjavik Eye Study: prevalences and related ophthalmological variables. Acta Ophthalmol Scand 2007;85:822-7. (PMID:18028119).
10. Sekeroglu MA, Bozkurt B, Irkec M, et al. Systemic associations and prevalence of exfoliation syndrome in patients scheduled for cataract surgery. Eur J Ophthalmol 2008;18:551-5. (PMID:18609473).
11. Stafiej J, Malukiewicz G, Lesiewska-Junk H, RoÊç D, Kaêmierczak K. Endothelial cell markers in patients with pseudoexfoliation syndrome. The Scientific World Journal 2012;2012:863949. doi:10.1100/2012/863949. (PMID:22593709).
12. Praveen MR, Shah SK, Vasavada AR, et al. Pseudoexfoliation as a risk factor for peripheral vascular disease: a case-control study. Eye (Lond) 2011;25:174-9. (PMID:21127507).
13. Schlötzer-Schrehardt U, Naumann GO. Ocular and systemic pseudoexfoliation syndrome. Am J Ophthalmol 2006;141:921-37. (PMID:16678509).
14. Koz OG, Turkcu MF, Yarangumeli A, Koz C, Kural G. Normotensive glaucoma and risk factors in normotensive eyes with pseudoexfoliation syndrome. J Glaucoma 2009;18:684-8. (PMID:20010248).
15. Linnér E, Popovic V, Gottfries CG, et al. The exfoliation syndrome in cognitive impairment of cerebrovascular or Alzheimer's type. Acta Ophthalmol Scand 2001;79:283-5. (PMID:11401639).

16. Repo LP, Teräsvirta ME, Koivisto KJ. Generalized transluminance of the iris and the frequency of the pseudoexfoliation syndrome in the eyes of transient ischemic attack patients. Ophthalmology 1993;100:352-5. (PMID:84600005).
17. Fernández A, Sorokin A, Thompson PD. Corneal arcus as coronary artery disease risk factor. Atherosclerosis. 2007;193:235-40. (PMID:17049531).
18. Pe'er J, Vidaurri J, Halfon ST, Eisenberg S, Zauberman H. Association between corneal arcus and some of the risk factors for coronary artery disease. Br J Ophthalmol 1983;67:795-8. (PMID:6671093).
19. Christoffersen M, Frikke-Schmidt R, Schnohr P, et al. Xanthelasmata, arcus corneae and ischaemic vascular disease and death in general population: prospective cohort study. BMJ 2011;343:5497-515. (PMID:21920887).
20. Hickey N, Maurer B, Mulcahy R. Arcus senilis: its relation to certain attributes and risk factors in patients with coronary heart disease. Br Heart J 1970;32:449-52. (PMID:5433305).
21. Tarkkanen A. Is exfoliation syndrome a sign of systemic vascular disease? Acta Ophthalmol 2008;86:832-6. (PMID:19086926).
22. Speãkauskas M, Tamo‰ci nas A, Ja‰cinskas V. Association of ocular pseudoexfoliation syndrome with ischaemic heart disease, arterial hypertension and diabetes mellitus. Acta Ophthalmol 2012;90:470-5. (PMID:22550962).
23. Mitchell P, Wang JJ, Smith W. Association of pseudoexfoliation syndrome with increased vascular risk. Am J Ophthalmol 1997;124:685-7. (PMID:9372724).