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.
INTRODUCTION

Arcus senilis, also referred to as corneal arcus, is a gray-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 separated 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 corneal arcus, including hyperlipidemia, hypertension, higher body mass index (BMI), diabetes mellitus and cigarette smoking (5).

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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).
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 xanthelasma 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>
<thead>
<tr>
<th>Parameter</th>
<th>Subjects with Arcus Senilis (n=75)</th>
<th>Subjects without Arcus Senilis (n=75)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL (log)</td>
<td>3.2±0.5</td>
<td>3.3±0.5</td>
<td>0.528</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>112.0±43.3</td>
<td>118.7±37.0</td>
<td>0.307</td>
</tr>
<tr>
<td>TG (log)</td>
<td>4.7±0.5</td>
<td>4.8±0.4</td>
<td>0.760</td>
</tr>
<tr>
<td>HDL (log)</td>
<td>4.0±0.3</td>
<td>4.0±0.3</td>
<td>0.720</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>209.6±46.5</td>
<td>189.2±41.6</td>
<td>0.116</td>
</tr>
</tbody>
</table>

HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein; log: logarithmic transformation.
arcus senilis was 1.21 permml/L for total cholesterol, 1.94 permml/L for LDL, 3.85 permml/L for peripheral artery disease, 1.14 permml/L for chronic kidney disease and 1.29 permml/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 affects 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=0.41, 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