Correlation Between Age-related Macular Degeneration and Pseudoexfoliation Syndrome in the Population of Crete (Greece)

Vassilios P. Kozobolis, MD; Efstathios T. Detorakis, MD; Miltiadis K. Tsilimbaris, MD; Ioannis G. Vlachonikolis, PhD; Ioannis C. Tsambarlakis, MD; Ioannis G. Pallikaris, MD

EPISTEMOLOGY AND BIOSTATISTICS

Objective: To evaluate the epidemiological correlation between age-related macular degeneration and pseudoexfoliation syndrome in the population of Crete (Greece).

Subjects and Methods: A total of 777 persons (315 men and 462 women, aged 40-99 years), representing a randomized sample (1.43%) of the Cretan population, underwent slitlamp and fundus examinations according to protocol. The results were statistically analyzed.

Results: The prevalence of pseudoexfoliation was 16.1% (21.3% in men and 12.6% in women) and that of maculopathy, 7.9% (11.7% in men and 5.2% in women). The conditions were significantly correlated with each other ($P = .002$). Also, both displayed a significant direct correlation with age and altitude (for pseudoexfoliation, $P < .001$ and $P = .002$ for age and altitude, respectively; for age-related macular degeneration, $P < .001$ for age and for altitude) and an increase in bilateral incidence with progressing age.

Conclusions: The observed prevalences of pseudoexfoliation and maculopathy were lower than those reported in the mainland of Greece and other Mediterranean regions. The correlation between age-related macular degeneration and pseudoexfoliation syndrome may be explained by the relationship of each disease with age and altitude.


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SUBJECTS AND METHODS

This in situ study was carried out in the island of Crete between February 1993 and January 1996. The target population was all residents of rural areas aged 40 years or older. A random sample of 1100 was determined by power calculation based on prevalences reported previously in other studies. This sample size would correspond to a sampling fraction for each village of approximately 5%.

The sample was drawn as follows: At first, 13 villages in all 4 prefectures of Crete were randomly selected to represent the geographic and population distribution of rural areas of Crete. In each selected village, a list of a randomized sample was prepared under our instructions by the local birth register office. This was a stratified random sample based on sex and 10-year age groups. The participants to be examined were selected by means of tables of random numbers. This ensured a representative sample of people born and living in these locations, with the same sex and age distribution as the 1991 general census target population. Recruitment was accomplished by sending personal invitations to the selected participants explaining briefly the purposes of the study and announcing the day and time the Mobile Ophthalmological Unit would be in their village.

The final accomplished sample of 777 persons represents a 70.6% response rate, varying between 60% and 80% in different villages. These 777 persons (315 men and 462 women) represent 1.4% of the total population of Crete. Because of rounding, percentages may not all total 100.

The age (mean ± SE) was 68.4 ± 0.3 years (range, 43-99 years); it was 70.5 ± 0.531 (range, 43-95 years) in men and 66.9 ± 0.44 (range, 43-99 years) in women. The age by sex specific distribution of the final sample showed that the group with the smallest attendance rate was men aged 40 to 49 years. A slight discrepancy between the male-female ratio of the final sample and that of the target population was observed. This was probably caused by the nonresponse. No further information from the nonrespondents was available.

Our group with the Mobile Ophthalmological Unit visited each village on a predetermined date. The examination was carried out in the local Primary Health Care Centers. The working conditions were satisfactory, as the Mobile Ophthalmological Unit was fully equipped and facilities were provided in the Primary Health Care Centers of the villages, such as a dark examination room and a waiting room. All patients were examined before and after the pupils were dilated with 0.5% tropicamide and 5% phenylephrine hydrochloride. The examination included measurement of visual acuity, slitlamp examination with ×10 and ×16 magnification, and fundus examination with 3-mirror lens (Goldmann [OG3HA; Ocular Instruments Inc, Bellevue, Wash] and/or Volk 78D and 90D lenses [Volk Optical Inc, Mentor, Ohio]). All details of the posterior and of the anterior segment (chamber angle, iris color, pupil dilation, lens opacities, etc) were recorded strictly according to protocol. All 777 participants were examined by 1 of us (V.P.K.), and the ocular fundus was examined by 3 of us (V.P.K., E.T.D., and M.K.T.).

Patients with suspected ARMD had their maculas photographed with a fundus camera (Kowa Pro I [Kowa Company Ltd, Tokyo, Japan], Kodak Ektachrome 64 ASA [Eastman Kodak Co, Rochester, NY], magnification ×2.5). Two 35° photographs, centered on the macula of each eye, were performed. Photographs (returned as slides) were examined in detail in our department by the same 3 of us who decided to perform the photography, by means of a portable viewer with ×5 magnification. The total magnification was ×12.5.

Table 1. Numbers of Patients Examined by Sex and Age Group

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>Total No. of Patients</th>
<th>Sex, No. (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Men</td>
</tr>
<tr>
<td>40-49</td>
<td>23</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td>50-59</td>
<td>127</td>
<td>35 (27.6)</td>
</tr>
<tr>
<td>60-69</td>
<td>248</td>
<td>95 (38.3)</td>
</tr>
<tr>
<td>70-79</td>
<td>298</td>
<td>126 (42.3)</td>
</tr>
<tr>
<td>≥80</td>
<td>81</td>
<td>54 (66.7)</td>
</tr>
<tr>
<td>Total</td>
<td>777</td>
<td>315 (40.5)</td>
</tr>
</tbody>
</table>

*Because of rounding, percentages may not all total 100.

The prevalence of ARMD in the age groups 50 to 59, 60 to 69, 70 to 79, and 80 or more years was 2.4%, 4.4%, 9.1%, and 24.7%, respectively. In detail (Table 3), in the age group 50 to 59 years, the 3 patients (1 man [2.9%] and 2 women [2.2%]) diagnosed as having ARMD displayed drusen and pigment disturbances. In the age group 60 to 69 years, the 11 patients (5 men [5.3%] and 6 women [3.9%]) diagnosed as having ARMD displayed both drusen and pigment disturbances. In the age group 70 to 79 years, 23 patients (15 men [11.9%] and 8 women [4.7%]) diagnosed as having ARMD displayed both drusen and pigment disturbances.

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Thirty-nine participants (5.0%) (25 men [7.9%] and 14 women [3.0%]) refused to undergo fundus photography. In 11 persons (1.4%), the photographs of only 1 eye could be graded. The remaining 727 participants (285 men and 442 women) had both ocular fundi evaluated with gradable photographs. Two of the 25 men without gradable fundus photographs, both aged 70 to 79 years, were only clinically characterized as having the early variant of maculopathy. None of the 14 women without gradable fundus photographs were clinically characterized as having any variant of maculopathy.

The ARMD grading was performed jointly after the slides were evaluated by the above-mentioned 3 of us. The percentage of exact agreement ranged from 91% to 98%. Nevertheless, a final consensus regarding the grading was taken after a detailed discussion in all cases.

CLASSIFICATION OF ARMD

In the present study, ARMD was classified on the basis of the Wisconsin Age-Related Maculopathy Grading System and on the Rotterdam Maculopathy Study. Age-related macular degeneration was diagnosed on the basis of morphologic changes observed, without indication that they were secondary to other disorders.

The ARMD grading was performed by checking an area of 3000 µm from the foveola. Areas of decreased and increased pigmentation and drusen were graded in relation to their diameter. Drusen with a diameter less than 63 µm were characterized as small. Drusen with a diameter equal to or greater than 63 µm were characterized as large.

The ARMD was classified into early disease and late disease (the latter divided into dry and exudative variants). The early variant was characterized as having no signs of geographic atrophy or neovascularization and also showing either (1) soft indistinct or reticular drusen or (2) any drusen type except hard indistinct plus decreased or increased areas of pigmentation in the macular area. The dry variant was characterized as showing a well-demarcated atrophic area of retinal pigment epithelium without signs of neovascularization. The wet form of ARMD was manifested by serous or hemorrhagic retinal pigment epithelial detachment, a subretinal neovascular membrane, a subretinal hemorrhage, and/or a periretinal fibrous scar. Patients likely to have the exudative form of ARMD subsequently underwent a fluorescein angiography to confirm the diagnosis.

Pseudoexfoliation syndrome was also investigated in detail. Patients were considered to have PEX only when pseudoexfoliative deposits were present on the anterior lens surface and/or on the typical central disk or peripheral zone after the pupil was dilated. Participants were also questioned about their personal and family medical and ophthalmic history.

STATISTICAL ANALYSIS

The prevalences of ARMD and PEX in strata classified by age, sex, and geographic location were analyzed by the χ2 test (linear components of association were tested by the Mantel-Haenszel test). The association of ARMD (as dependent variable) with PEX, age, sex, and altitude (as independent variables) was studied by logistic regression. The calculations were carried out by the statistical software package SPSS for Windows (Release 6.0; SPSS Inc, Chicago, Ill). All analyses were also applied with the use of weights (inversely proportional to population sizes). The results of the 2 approaches were almost identical.

Table 3. Prevalence of ARMD According to Early and Late Stages (Dry and Wet Variants) by Age and Sex*  

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Total</td>
</tr>
<tr>
<td>40-49</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>50-59</td>
<td>1 (2.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>60-69</td>
<td>5 (5.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>70-79</td>
<td>15 (11.9)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>≥80</td>
<td>6 (11.1)</td>
<td>8 (14.8)</td>
</tr>
<tr>
<td>Total</td>
<td>27 (8.6)</td>
<td>10 (3.2)</td>
</tr>
</tbody>
</table>

* Data are given as number (percentage). ARMD indicates age-related macular degeneration.
†Total numbers of men and women in each age group are listed in Table 1.

The presence of ARMD was strongly related to PEX in both eyes (χ2 = 13.675, P = .003; Mantel-Haenszel test = 13.66, P = .002). Furthermore, for the left eye, χ2 = 9.2 (P = .002) and Mantel-Haenszel test equaled 9.19 (P = .002), and for the right eye, χ2 = 9.59 (P = .001) and Mantel-Haenszel test equaled 9.58 (P = .001). The prevalence of ARMD among patients with and without PEX is shown in Table 4. The correlation between ARMD and PEX by eye is shown in Table 5.

The prevalence of PEX was significantly higher among people living in places with greater altitude.
The prevalence was the highest (27% of patients examined) in a specific area of the island (Rethymné), where the average altitude is higher (470 m compared with 110 m in the prefecture of Hérakléion and 70 m in Canea and Lasithion). The same was true for patients with ARMD, the difference between low and high altitudes being significant ($\chi^2 = 12.6, P = .001$; Mantel-Haenszel test = 7.53, $P = .001$). On the other hand, the coexistence of PEX and ARMD increased with progressing age and was stable in the provinces with low altitude and in those with high altitude (Table 6). Yet the prevalence of ARMD was not higher in Rethymné than in the other provinces. On the contrary, there appeared to be a reduction of ARMD prevalence in the western provinces (3.6%) compared with the eastern provinces (12.7%), the difference being statistically significant ($\chi^2 = 24.18, P < .001$; Mantel-Haenszel test = 24.15, $P < .001$ (Table 7, Figure)). The prevalence of PEX was 18.3% in the western provinces and 13.5 in the eastern provinces.

Logistic regression was performed with PEX, age, sex, and altitude as dependent variables and ARMD as independent variable. The $P$ value of PEX after adjusting for age, sex, and altitude was not significant (Table 8). This would imply that the association between ARMD and PEX could be explained by age and altitude (Table 8).

**COMMENT**

The pathway for most photochemical reactions is free radical production mediated by blue and UV light, through excitation of electrons to a “triplet state” that prolongs their lifetime sufficiently to interact with other molecules. Antioxidant defense mechanisms, including vitamins C and E and beta carotene, various enzymes, and cofactors such as zinc and copper offer protection by reacting with free radicals to quench their reactivity.6,18,19 For both PEX and ARMD, previous studies have reported a deficiency of zinc and copper.7,12 In addition, for both PEX11,12 and ARMD6 a correlation with solar radiation has been implied. Brown iris color has been identified as a protective factor against ARMD,6 while blue irises appear to be a risk factor for PEX.20 The slightly lower prevalence of ARMD in this study compared with that of Colorado and Wisconsin16 could be attributed, apart from the randomized sample, to the fact that the Cretan population has predominantly high ocular melanin concentration and consequently brown irises. Concerning the late ARMD, our results (1.9%) are close to those of the Rotterdam study (1.7%).17 Although our aim is not to present only an epidemiological study of ARMD, our results are compared with those of Colorado and Wisconsin16 in Table 9.
The higher prevalence of ARMD and PEX in individuals living in locations with high altitude is in accordance with the reported relationship of these conditions with UV radiation and could be attributed to the environmental influences because of a common background. Nevertheless, the coexistence of the conditions is almost the same in low and high altitude.

The fact that ARMD was not more prevalent in the prefecture of Rethymne (with the higher average altitude, where PEX was significantly more prevalent) could possibly be attributed to genetic factors. In support of this concept is the almost linear decrease in ARMD prevalence toward the western provinces of the island.

Pseudoexfoliative material is thought to result from abnormal basement membrane production by degenerated epithelial cells. An immunological relationship of wearing toward the western provinces of the island. PEX material with elastic tissue was also shown, suggesting an abnormal stimulus or defective regulation of matrix synthesis exists in the disease. In the case of ARMD, there is accumulation of abnormal extracellular matrix at the interface of the retinal pigment epithelium and the Bruch membrane. Furthermore, animal studies have shown discontinuation of the elastic layer of the Bruch membrane in the aged macula. It appears, therefore, that both pathological entities are related, in some degree, with abnormalities of the basic membranes. Concerning inheritance, several authors have described the familial occurrence of PEX, which is further supported by the correlation with specific HLA antigens. In the case of ARMD, the association with maternal or sibling history of macular disease was shown by several studies.

Table 8. Logistic Regression of ARMD Association With Age, Sex, Altitude, and PEX*

<table>
<thead>
<tr>
<th></th>
<th>β (Coefficient)</th>
<th>SE of β</th>
<th>Wald Test</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.0707</td>
<td>0.188</td>
<td>14.1407</td>
<td>1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.4615</td>
<td>0.3189</td>
<td>2.0943</td>
<td>1</td>
<td>.15</td>
</tr>
<tr>
<td>Altitude</td>
<td>-1.0649</td>
<td>0.3473</td>
<td>9.4011</td>
<td>1</td>
<td>.002</td>
</tr>
<tr>
<td>PEX</td>
<td>0.3420</td>
<td>0.3807</td>
<td>0.8070</td>
<td>1</td>
<td>.37</td>
</tr>
<tr>
<td>Constant</td>
<td>-6.7810</td>
<td>1.4198</td>
<td>22.8111</td>
<td>1</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* ARMD indicates age-related macular degeneration; PEX, pseudoexfoliation syndrome.

Table 9. Comparison of the Prevalence of ARMD in Population-Based Studies*

<table>
<thead>
<tr>
<th></th>
<th>Beaver Dam (NHW)†</th>
<th>NHW</th>
<th>H</th>
<th>Crete</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any ARMD</td>
<td>Any ARMD</td>
<td>LATE ARMD</td>
<td>Early ARMD</td>
</tr>
<tr>
<td></td>
<td>10.3</td>
<td>15.0</td>
<td>0.1</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>60-74</td>
<td>60-74</td>
<td>60-74</td>
<td>60-74</td>
</tr>
</tbody>
</table>

* ARMD indicates age-related macular degeneration; NHW, non-Hispanic whites; and H, Hispanic.
†From Cruickshanks et al.16
as well as to increased ocular pigmentation in the Cretan population examined. In the present study, a correlation between these 2 pathological entities was found. We believe that this association is not caused by chance, because our sample is statistically sufficient and representative of the population and the study was well designed from the beginning in all details. The value of this study is enhanced by the fact that the population of the island is epidemiologically isolated. On the other hand, the number of participants is not as large as in other previous studies, ie, in Wisconsin and Colorado or the Rotterdam Study. Another variable that should be considered is the use of non-stereoscopic photographs, which could have led to an underestimation of the ARMD prevalence and interfered with the association of PEX and ARMD.

Pseudoexfoliation syndrome and ARMD affect vision in different ways. Age-related macular degeneration affects primarily central vision, while PEX predominantly influences the intraocular pressure. However, the epidemiological correlation between the 2 pathological entities shown in this study, as well as the previously reported similarity in predisposing factors and in the pathological and biochemical findings implicated, could mean that there is a common genetic defect predisposing to both conditions, possibly a disturbance in basic membrane and elastic tissue turnover. Nevertheless, there are differences emphasizing the diversity and complexity of the pathogenesis of ARMD and PEX.

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Corresponding author: Vassilios P. Kozobolis, MD, Department of Ophthalmology, University of Crete, School of Medicine, POB 1352, Herakleion, Crete, 71110 Greece (e-mail: kozoboli@med.uch.gr).

REFERENCES