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Research Article

Chronic Glaucoma, Age-Related Macular Degeneration, Diabetic Retinopathy and Alzheimer's Disease: A Case-Control Study

Alexandros Tsilis[1]* and Sygkliti-Henrietta Pelidou[2]

[1]*Faculty of Medicine, University of Ioannina, Ioannina, Greece*

[2]*Department of Neurology, University of Ioannina School of Medicine, Ioannina, Greece*

***Corresponding Author:** Alexandros Tsilis, Faculty of Medicine, University of Ioannina, Ioannina, Greece.

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Abstract

Objective of the Study: The purpose of the current case-control study is to evaluate the incidence rate of chronic glaucoma (CGL), age-related macular degeneration (AMD), diabetic retinopathy (DR) and other clinical parameters with Alzheimer's disease (AD).

Materials and Methods: A case-control study was conducted from February 2020 through October 2021. A total of one hundred and sixty-five participants were enrolled. Data analysis was performed using SPSS software version 26.0.

Results: 165 persons were enrolled in the clinical study with a mean age of 75.62 ± 1.22 years. Oh these, 41 individuals were diagnosed with AD, of which 2 persons had chronic glaucoma (4.88%), 5 persons had AMD (12.20%) and 14 persons had DR (34.15%) and 124 persons were non-demented, of which 4 individuals had chronic glaucoma (3.23%), 14 individuals had AMD (11.29%) and 36 individuals had DR (29.03%) respectively. Age and total cholesterol (TCHOL) had a statistically significant positive association with AD, respectively (OR, 1.23; 95% CI, 1.13 - 1.34, OR, 1.04; 95% CI, 1.02 - 1.07), whereas triglycerides (TG), best corrected visual acuity (BCVA), alcohol and smoking had a statistically significant inverse association with AD, respectively (OR, 0.93; 95% CI, 0.89 - 0.97, OR, 0.31; 95% CI, 0.19 - 0.50, OR, 0.15; 95% CI, 0.07 - 0.33, OR, 0.17; 95% CI, 0.04 - 0.81). The association of CGL, AMD and DR with AD was estimated statistically as non-significant.

Conclusion: There is no statistical significant association between CGL, AMD and DR with AD. Age, TCHOL, TG, BCVA, alcohol and smoking had a statistical significant association with AD.

Keywords: *Alzheimer's Disease; Chronic Glaucoma; Age-Related Macular Degeneration; Diabetic Retinopathy*

Abbreviations

$A\beta_{42}$: Amyloid-β; AD: Alzheimer's Disease; AMD: Age-Related Macular Degeneration; BCVA: Best Corrected Visual Acuity; BMI: Body Mass Index; CGL: Chronic Glaucoma; DBP: Diastolic Blood Pressure; DR: Diabetic Retinopathy; IOP: Intraocular Pressure; NFT: Neurofibrillary Tangles; POAG: Primary Open-Angle Glaucoma; RGCs: Retinal Ganglion Cells; RNFL: Retinal Nerve Fiber Layer; SBP: Systolic Blood Pressure; TCHOL: Total Cholesterol; TG: Triglycerides

Introduction

Recent evidence has suggested a potential association between Alzheimer's disease (AD), chronic glaucoma (CGL), age-related macular degeneration (AMD) and diabetic retinopathy (DR) [1,2].

Dementia is a syndrome with a strong age-related incidence, which is characterized by progressive memory loss and cognitive impairment [3]. AD is the most common type of dementia [4,5] and is associated with neuropathological characteristics including extracellular senile plaques of amyloid-β ($A\beta_{42}$) and intracellular neurofibrillary tangles (NFT) consisted of hyperphosphorylated tau protein [6-10].

Glaucoma is a group of optic neuropathies that are characterized by progressive neurodegeneration of the retinal ganglion cells (RGCs) and their axons, resulting in structural changes of the optic nerve head and visual field defects [11,12]. Primary open-angle glaucoma (POAG) is the most common form of glaucoma worldwide [13] and increased intraocular pressure (IOP) is a major risk factor of the disease itself [14].

AMD is a disorder that is characterized by a progressive loss of color and central vision caused by neurodegenerative and neovascular changes in the macula [15], thus resulting to severe and irreversible vision impairment [16,17].

DR is a neurovascular disease as neurodegeneration precedes and coexists with microvascular changes [18].

Although several lines of evidence indicate that chronic glaucoma, AMD and DR may be associated with AD due to common pathophysiological mechanisms including progressive neurodegeneration, characteristic amyloid β deposits and chronic microvascular insults [1, 2], yet there is no definite answer. It is well-known that the retinas of AD patients have revealed RGC loss and retinal nerve fiber layer (RNFL) thinning followed by electrophysiological abnormalities [2]. Moreover, some epidemiological studies have reported a higher risk of glaucoma in patients with AD or a higher risk of AD in patients with glaucoma [19-24]. Other studies have reported that both AD and AMD share common risk factors, histopathologic features including amyloid β in ocular drusen and senile plaques as well as substantial glial reactivity, neuroinflammation and increased metabolic and oxidative stress [10,15,25-27].

Therefore, we conducted a case-control study in order to contribute to a further elucidation of the association between these four disorders. Also, we estimated the association of various clinical parameters with AD.

Materials and Methods

Study design

A hospital-based case-control study was conducted from February 2020 through October 2021. We included new patients with or without clinical symptoms of AD who were examined in the Outpatient Department of the Neurological Clinic of the General Hospital of Corfu. Then, all patients and control subjects were examined in the Outpatient Department of the Ophthalmology Clinic of the General Hospital of Corfu in order to investigate whether they were exposed to CGL, AMD or DR. The diagnosis of AD was based on clinical features according to the criteria defined by the NINCDS-ADRDA [28] and all patients and control subjects fulfilled the diagnostic criteria for POAG [12], AMD [29,30] and DR [31], respectively. Each participant was submitted to pupillary dilation in both eyes with 0.5% tropicamide and 5% phenylephrine hydrochloride.

Eligibility criteria

We excluded patients and control subjects with ophthalmic or orbital trauma, optic nerve atrophy, uveitis, myopia or hyperopia > 3.00 diopters and astigmatism > 1.00 diopters. Also patients with exfoliative glaucoma, acute glaucoma, or congenital glaucoma were excluded.

Statistical analysis

The relationship between CGL, AMD, DR and other clinical parameters with AD was estimated by using stepwise forward binary logistic regression analysis according to the Wald method. All statistical analyses were performed with SPSS software version 26.0.

Results

In total, 165 persons (83 men, 82 women), aged 59 - 97 years were enrolled into the study (mean age: 75.62 ± 1.22 years). Of these, 41 subjects were diagnosed with AD, 22 men and 19 women (mean age: 82.68 ± 1.96 years) and 124 were non-demented participants, 61 men and 63 women (mean age: 73.3 ± 1.46 years). Of the 41 patients with AD and 124 controls, 2 (4.88%) and 4 (3.23%) persons had chronic glaucoma, 5 (12.20%) and 14 (11.29%) persons had AMD and 14 (34.15%) and 36 (29.03%) persons had DR, respectively (Figure 1).

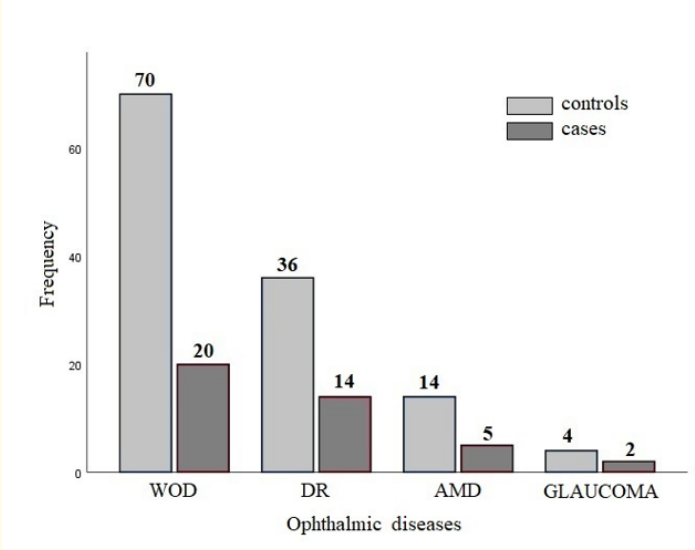

Figure 1: *Distribution of ophthalmic diseases between controls and AD patients.*

Age and TCHOL had a statistically significant positive association with AD, respectively (OR, 1.23; 95% CI, 1.13 - 1.34, OR, 1.04; 95% CI, 1.02 - 1.07). On the contrary, TG, BCVA, alcohol and smoking had a statistically significant inverse association with AD, respectively (OR, 0.93; 95% CI, 0.89 - 0.97, OR, 0.31; 95% CI, 0.19 - 0.50, OR, 0.15; 95% CI, 0.07 - 0.33, OR, 0.17; 95% CI, 0.04 - 0.81) (Table 1). Systolic (SBP) and diastolic blood pressure (DBP) had not a statistically significant association with AD respectively (OR, 0.99; 95% CI, 0.92 - 1.07, OR, 1.04; 95% CI, 0.93 - 1.15) (Table 2). In addition, weight, height, mean IOP, mean c/d ratio, body mass index (BMI), sex, hypertension and diabetes had not a statistically significant association with AD, respectively (OR, 1.09; 95% CI, 0.98 - 1.20, OR, 2.56; 95% CI, 0.43 - 12.54, OR, 1.10; 95% CI, 0.97 - 1.27, OR, 0.92; 95% CI, 0.83 - 1.26, OR, 1.35; 95% CI 0.79 - 2.19, OR, 0.84; 95% CI, 0.41 - 1.70, OR, 2.11; 95% CI, 0.90 - 4.98, OR, 1.17; 95% CI, 0.60 - 2.44) (Table 2). Also, both CGL and AMD had not a statistically significant association with AD (OR, 1.37; 95% CI, 0.50 - 3.72) (Table 2). Finally, DR had not a statistically significant association with AD (OR, 1.36; 95% CI, 0.62 - 3.01) (Table 2). The predictive power of AD significant variables such as age, TCOL, TG, BCVA, alcohol and smoking is shown in figure 2.

Discussion

In this case-control study we have reported that the association between CGL, AMD, DR and AD was not statistically significant. Furthermore, we have evaluated the incidence rate of some clinical parameters with AD. Patients with AD when compared to control subjects were significantly older ($p < 0.001$), an expected observation, as the AD appearance is age-related [5,32].

Variable	OR	95% CI	P value
Age	1.23	1.13 - 1.34	< 0.001
Total cholesterol	1.04	1.02 - 1.07	0.002
Triglycerides	0.93	0.89 - 0.97	0.002
Best corrected visual acuity	0.31	0.19 - 0.50	< 0.001
Alcohol	0.15	0.07 - 0.33	< 0.001
Smoking	0.17	0.04 - 0.81	0.025

Table 1: *Statistical significant variables associated with AD.*

Variable	OR	95% CI	P value
SBP	0.99	0.92 - 1.07	0.66
DBP	1.04	0.93 - 1.15	0.39
Weight	1.09	0.98 - 1.20	0.37
Height	2.56	0.43 - 12.54	0.10
Mean IOP	1.10	0.97 - 1.27	0.11
Mean c/d ratio	0.92	0.83 - 1.26	0.24
BMI	1.35	0.79 - 2.19	0.96
Sex	0.84	0.41 - 1.70	0.16
Hypertension	2.11	0.90 - 4.98	0.11
Diabetes	1.17	0.60 - 2.44	0.92
DR	1.36	0.62 - 3.01	0.88
CGL and AMD	1.37	0.50 - 3.72	0.76

Table 2: *Statistical non-significant variables with AD.*

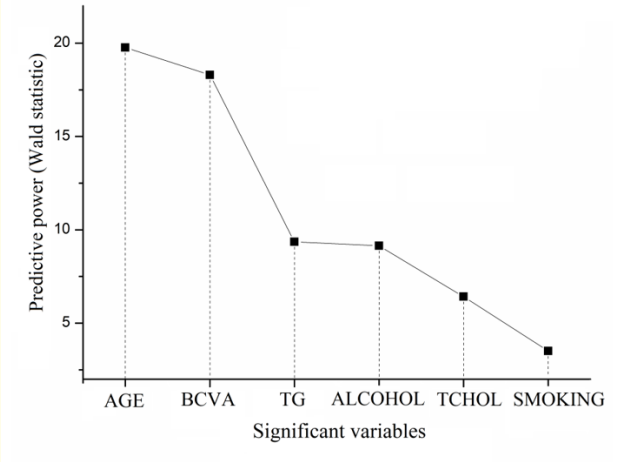

Figure 2: *The predictive power of AD significant variables.*

Although several studies have reported that a number of cardiovascular risk factors including hypertension, total and high cholesterol level, triglycerides, diabetes, smoking and obesity are associated with a higher risk of AD [4,5,33-42], our findings have reported mixed results ranged from statistically significant positive (TCHOL) to statistically significant inverse (TG, smoking) or even non-statistically significant associations with AD, respectively (hypertension, diabetes, BMI). Additionally, although several lines of evidence have reported that alcohol is a risk factor for AD [43,44], our findings have showed a statistical significant inverse association. Also, we have showed that SBP and DBP were not associated with AD, whereas cross-sectional studies have reported mixed results [45-47]. Finally, our findings have showed that height, IOP and c/d ratio had not a statistically significant association with AD, but no formal data of this association is currently available.

Patients with AD had a significantly lower triglyceride levels when compared to the control group, which can be attributed to the dietary habits of the patients, to an anti-lipidemic medication or to reduced appetite. The observed decrease in blood triglycerides in these patients may be associated with weight loss in patients with AD. Alcohol and smoking was more prevalent in control subjects than in participants with AD. This can be explained, most likely, by medical considerations to the patients with AD about compliance to a more healthy way of living or because of the amnesia of depreciation of the habit.

Conclusion

In summary, we have reported that there is no association between CGL, AMD or DR with AD. Age, TCHOL, TG, BCVA, alcohol and smoking had a statistical significant association with AD, whereas other clinical parameters had not a significant association with AD. Large prospective designs with long follow-ups are needed to clarify this potential association in both directions, particular among CGL, AMD or DR patients who get diagnosed with AD and AD patients who get CGL, AMD or DR.

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