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Original Article

Does the Stage and Involvement of Age-related Macular Degeneration Affect the Prevalence of Alzheimer's Disease?

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ABSTRACT

Objective: Age-related macular degeneration (AMD) and Alzheimer's disease (AD) are degenerative diseases that increase in prevalence with older ages.

Materials and Methods: In our prospective cross-sectional study, the patients in the dry AMD group consisted of 296 early and 284 late-stage patients. The neovascular AMD group included 285 early and 277 late-stage patients. The control group consisted of 300 patients similar in age and gender. AMD patients were grouped as dry and neovascular types, and early and late-stage. Patients were questioned about their use of medication for AD and it was recorded that those who used it had the disease. If there was no medication use, detailed inquiries were made for AD. If one of the complaints seen in AD was present, the patient was referred to a neurologist and the presence of AD was confirmed.

Results: AD was detected in 3% (n=9) of the control group. In the early dry type 7.1%(n=21) and late-dry type 7.4% (n=21) AD were detected, and the difference was significant when compared with the control group (p=0.03, p=0.02). In the early neovascular type 6.6% (n=19) and late-neovascular type 6.5% (18) AD were determined and the difference was significant (p=0.04, p=0.04).A significant association was determined between age and the frequency of AD in both types of AMD(p=0.03, p=0.04). No significant difference was found between unilateral and bilateral involvement,and between early- and late-stage AMD diseases (p>0.05). Also, the frequency of AD was found to be 2.89 times higher in those with dry type AMD, and 2.14 times higher in those with neovascular type AMD(p=0.03, p=0.04).

Conclusion: Common pathways in the etiologies of wet and dry AMD and AD may explain the higher risk of AD in these AMD. Also, in our study, we concluded that this risk does not vary depending on the stage and involvement of the disease.

Keywords: Age-related macular degeneration, Alzheimer's disease, amyloid, drusen, frequency

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INTRODUCTION

Age-related macular degeneration (AMD) is generally listed among the common causes of vision loss over the age of 65 and blindness in later stages [1,2]. Recently, AMD has been reported in some publications as a neurodegenerative disease affecting the macula [3]. This disease is seen as a degenerative disease affecting the choriocapillaris, Bruch's membrane, retinal pigment epithelium and photoreceptors, and

abnormal extracellular materials called drusen accumulate in the macula [4]. There are generally dry and neovascular types of AMD. The dry type contains pigment epithelial changes, drusen, and geographic atrophy may be seen at the end of the disease of dry type AMD [5, 6]. The neovascular type contains pigment epithelial changes, drusens, pigment epithelial detachment, neovascular membranes, and disciform scar may be seen at the end of the disease of neovascular type AMD [7, 8].

Alzheimer's disease (AD) is one of the neurodegenerative diseases frequently seen in neurological outpatient clinics, and its incidence is increasing day by day [9]. AD is an irreversible brain disease and progressive that slowly destroys memory, cognitive skills and, in later stages, the ability to perform even the simplest tasks. AD is seen in 3-11% of people over 65 years of age and the incidence increases with age [10]. AD is associated with increased amyloid deposition in the cortex and hippocampus of the brain and the formation of extracellular senile plaques and neurofibrillary tangles [11]. Both AD and AMD contain abnormal extracellular materials including β-amyloid, such as plaque and drusen, respectively and non-fibrillar β-amyloid oligomers have been shown in drusen in some studies [12-15].

To our knowledge, there is no study simultaneously investigating the relationship between AMD stages and involvement and AD. Therefore, in our study, we aimed to investigate the association between early and late stages of AMD, as well as unilateral and bilateral involvement, and the frequency of AD.

MATERIALS AND METHODS

Patients diagnosed with AMD at the ophthalmology outpatient clinic between 1 March 2022 and 1 March 2023 were included in our prospective cross-sectional study. The study was conducted in accordance with the Declaration of Helsinki and the ethics committee has approved it. A total of 584 patients in the dry AMD group, 300 in the early-stage and 284 in the late-stage, were included in the study. A total of 586 patients were included in the neovascular group, 295 in the early-stage and 286 in the late-stage. Our study's control group included 300 patients, similar in mean age and gender ratio and determined randomly.

The AMD group was divided into dry type and neovascular type, as well as early- and late-stage disease. The control group included patients without AMD and in a similar age group with no AMD detected on examination. If there were drusen and pigment epithelial changes, it was recorded as dry type early-stage AMD, and if there was geographical atrophy, it was recorded as dry type late-stage AMD [5, 6]. Early-stage wet type was accepted as the presence of drusen and pigment epithelial changes as well as macular neovascular membranes, pigment epithelial detachment and fluid (intra or subretinal), and late-stage wet type was accepted as the presence of disciform scar [7, 8].

OCT test was used to diagnose AMD and divide it into types. If OCT was insufficient to make the diagnosis, additional fundus fluorescein angiography was performed. If, as a result of these tests, there was an early-stage in one eye and a late-stage in the other eye, it was recorded as a late-stage. Again, to avoid confusion, patients with dry type in one eye and neovascular type in the other eye were not included in the study. In terms of differential diagnosis of AMD, the presence of retinal angiomatosis proliferation, polypoidal choroidal vasculopathy, pachychoroid neovasculopathy, vitelliform dystrophy diseases were checked. Again, patients with cornea, lens, vitreous and retina diseases that would prevent the diagnosis of AMD by preventing the macula and retina from being seen were excluded in the study.

The patients to be included in the study were questioned about the use of medication for this disease, and if they were using this medication, this disease was recorded as present. As a result of the evaluation in the neurology outpatient clinic, probable AD was diagnosed according to NINCDS-ADRDA criteria in patients with progressive cognitive impairment (attention, language, memory, visual-spatial functions, gnosis and executive functions praxis) that impairs daily living activities [16]. Since biopsy and histopathological (biopsy) evidence would be required for definitive diagnosis, patients were evaluated as probable Alzheimer's Disease. For the diagnosis and differential diagnosis of Alzheimer's disease, other possible primary (dementias with Lewy bodies, fronto temporal dementia, dementias accompanying movement disorders such as Parkinson's disease) and secondary dementia causes (vascular dementia, infectious causes) are performed on patients by brain MRI, routine blood tests and psychiatric evaluation, intracranial space-occupying lesions, subdural and epidural hemorrhages, toxic metabolic causes such as vitamin B12 deficiency and hypothyroidism, psychiatric disorders such as depression) were excluded and the patients were defined as probable AD.

Statistical Analysis

Statistical analyses were performed by using the Statistical Package for Social Sciences (SPSS) for Windows 15.0. (IBM® SPSS Collaboration Deployment Services.) In our study, the Shapiro-Wilk test was used to evaluate the distribution of the data. The t-test was used to evaluate continuous data, and the Chi-square (X^2) test was used for categorical data. Binomial logistic regression analysis was done to determine the relationship between variables. When performing statistical tests, statistically significant value was accepted as $p<0.05$.

Table 1. Alzhiemer's disease according to AMD type and stage

	Control Group (n=300)	Early Dry AMD (n=296)	p	Late Dry AMD (n=284)	p	Early Neovascular AMD (n=285)	p	Late Neovascular AMD (n=277)	p
AD, n (%)	9 (3)	21 (7.1)	0.03	21 (7.4)	0.02	19 (6.6)	0.04	18 (6.5)	0.04

AD: Alzhiemer's disease; AMD: Age related macular degeneration.

RESULTS

In our study, 302 (51%) of the dry type group were female and 278 (49%) were male, and the mean age was 67.8±6.7. In the neovascular type group, 295 (52.5%) were men and 267 (47.5%) were women, and the mean age was 66.9±5.8 years. The control group of our study consisted of 156 (52%) men and 144 (48%) women, and the mean age was 68.8±6.8 years. When the existing groups were compared, no difference was seen between them in terms of age and gender (p>0.05).

AD was determined in 3% (n=9) of the control group and in 6.8% (n=23) of the total AMD group and the difference was not found (p=>0.05). In the early dry type AMD 7.1% (n=21) and late-dry type 7.4% (7.4) AD were found and there were differences compared to the control group (p=0.03, p=0.02, respectively). AD was detected in 6.6% (n=19) in early neovascular type AMD and 6.5% (n=18) in late neovascular type AMD, and a significant difference was found when compared with the control group (p=0.04, p=0.04). The frequency of AD in the neovascular and dry AMD groups is shown in Table 1.

The effects of age and gender, disease stage, AMD types and ocular involvement on the incidence of AD are shown in Table 2. The association was found between both dry type and wet type and the frequency of AD (p=0.03, p= 0.04)). However, as a result of the analysis, no association was found with other factors (p>0.05). In terms of involvement, no association was found between unilateral and bilateral eye involvement and AD, and in terms of disease stage, no association was found between early-stage and late-stage AD (p>0.05).

As a result of the binomial regression analysis done to determine the relationship between AMD types and Alzheimer's, the incidence of Alzheimer's was found to be 2.89 times higher in those with dry type AMD and 2.14 times higher in those with neovascular type AMD. Details are shown in Table 3.

Table 2. Factors affecting the prevalence of Alzhiemer's disease

	AD in Dry type AMD	AD in Wet type AMD
Age	p=0.03	p=0.04
	OR=1.09	OR=1.17
Gender	p=0.71	p=0.55
	OR=1.21	OR=2.01
Stage (Early/Late)	p=0.92	p=0.99
	OR=0.94	OR=0.99
Involvement (Unilateral/bilateral)	p=0.31	p=0.69
	OR=0.32	OR=1.38

AD: Alzhiemer's disease; OR: Odds ratio; AMD: Age relataed macular degeneration.

Table 3. The relationship between the prevalence of Alzhemier's disease and AMD

	Alzhiemer's Disease
AMD	p=0.07 - OR=1.75
Dry type AMD	p=0.03 - OR=2.89
Wet type AMD	p=0.04 - OR=2.14

AMD: Age -related macular degeneration; OR: Odds ratio.

DISCUSSION

Both AMD and AD are chronic degenerative diseases common in the elderly population. The prevalence of these diseases is related to age and has been increasingly diagnosed in recent years. Due to their relatively high incidence and irreversible effects, they constitute one of the most important social problems of public health. In this study, the relationship between AD and AMD types and involvement was investigated, and a relationship was found between both dry and wet AMD and AD (p=0.03, p=0.04). However, no significant relationship was found between early- and late-stage AMD and AD (p>0.05).

Similarly, no significant relationship was found between unilateral or bilateral involvement of AMD and AD (p>0.05).

Rozzini et al. [14] found a decrease in cognitive functions and memory in 51 patients with late-stage dry+neovascular type AMD compared to a non-AMD control group in their study. Al-Selam et al. [16] found a significant reduction in cognitive function in 56 neovascular type+82 dry type AMD patients compared with a non-AMD control group. In a large retrospective study of 4453 dry and 540 neovascular AMD patients, a higher risk of AD and senile dementia was found in both dry and neovascular AMD, especially the dry type, compared to non-AMD [15]. Lee et al. [17] found an increased risk of AD in AMD and glaucoma diseases in a retrospective file scan of 31,142 patients. Choi et al. [18] reported that AMD patients were at a high risk for AD and similarly found an increased risk of AD in a retrospective study with a large number of patient files. In our study, similar to other studies, the frequency of AD was found to be higher and related in both dry and neovascular AMD compared to the control group (p=0.03, p=0.04, respectively). There is no study in the literature that simultaneously investigates the relationship between early and late stages of AMD, unilateral and bilateral eye involvement, and AD.

Previous studies have suggested several mechanisms for the risk-increasing association between AMD and AD. AD is a neurodegenerative brain disease that is also progressive, and it causes a significant impairment of normal brain structure and function. Firstly, both AD and AMD are characterized by abnormal extracellular materials including β-amyloid, such as plaque and drusen, respectively and non-fibrillar β-amyloid oligomers have been shown and second, both AMD and AD patients have been associated with increased inflammatory response concentrations [4]. Third, oxidizing radicals released by dysfunctional mitochondria have been observed in brain tissues of Alzheimer's patients and in retinal pigment epithelial cells of AMD patients [19].

Also, the association between neovascular type AMD and AD has also been reported through various mechanisms. It has been demonstrated that it increases VEGF production in retinal pigment epithelial cells as a result of amyloid β-peptide accumulation [20]. VEGF-induced angiogenesis is effective in the pathogenesis of AD; VEGF levels were found to be high in the cerebrospinal fluid of patients with AD, and VEGF was also detected in the brains of these patients with amyloid β plaques [21, 22]. It has been reported that conditions that inhibit angiogenesis may have beneficial effects on AD [22]. These common mechanisms in both AMD and AD diseases may suggest that AMD may be associated with a higher risk of AD.

CONCLUSION

There are some limitations in the study. These are relatively low number of patients, and the effects of cigarettes, alcohol, etc. were not evaluated. In addition, these include not questioning whether they have received other vitamin treatments such as antioxidants.

Common pathways in the etiologies of wet and dry AMD and AD may explain the higher risk of AD in these AMDs. No studies were found in the literature that investigated the relationship between both the stages of AMD and ocular involvement and AD, and in our study, we concluded that this risk does not vary according to the stage and involvement of the disease. Further studies with more patients are needed.

DECLARATIONS

Ethics Committee Approval: The Aksaray University Clinical Research Ethics Committee granted approval for this study (date: 24.02.2022, number: 2022/04-05).

Author Contributions: Concept – EY; Design – UG; Supervision – MDB; Resource – MG; Materials – EY; Data collection and/or processing – KM; Analysis and/or interpretation – EY; Literature review – UG; Writing – MDB; Critical Review – KM.

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