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Is Alzheimer disease related to age-related macular degeneration?

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Background/aim: To compare the cognitive functions and define the frequency of Alzheimer disease (AD) between participants with and without age-related macular degeneration (AMD).

Materials and methods: Fifty-nine patients with late-stage AMD (74.3 ± 7.3 years) and 49 age-, sex-, and education-matched control subjects were compared for the presence of AD according to the guidelines of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). Detailed neuropsychological tests were performed for all subjects.

Results: Neuropsychiatric tests scores were lower in the AMD group than the control group. The frequency of AD was higher in patients with AMD (40.7% in AMD and 20.4% in control group, P = 0.03), and particularly higher in late dry (nonvascular) AMD (d-AMD) patients (71.4% in d-AMD and 31.1% in late wet (vascular) AMD, P = 0.007). d-AMD patients performed worse than controls on all tests. There was also an association between age, sex, and low education and neuropsychiatric tests scores (P < 0.01). However, there was no association between visual acuity and neuropsychiatric tests scores.

Conclusion: The increased frequency of AD in patients with AMD is significant. This study demonstrated the importance of cognitive assessment in patients with AMD, particularly in the d-AMD type.

Key words: Alzheimer disease, dementia, age-related macular degeneration, cognitive impairment

1. Introduction

Alzheimer disease (AD) is an irreversible neurodegenerative disease and the most frequent cause of dementia, characterized by extracellular senile plaques that are principally formed of β-amyloid peptides, intracellular accumulation of hyperphosphorylated tau protein, and neurofibrillary tangles (1). The prevalence of AD doubles every 5 years over the age of 65 (2). AD affects more than 38 million people worldwide and this rate is anticipated to reach 115 million in 2050 (3). Clinically, it is characterized by memory loss, dementia, and cognitive impairment. AD causes one of the most relevant social and health problems because of its social impact and nonreversible nature (4).

Age-related macular degeneration (AMD) is a neurodegenerative retinal disease and is the main cause of legal blindness among people older than 65 years of age, resulting from the dysfunction and death of retinal pigment epithelial cells and adjacent photoreceptors in the macula (5,6). It is reported that 50 million people worldwide suffer from AMD symptoms and one-third of them are blind or have severe visual impairment (7,8).

Aging is the main risk factor for both AD and AMD. AD and AMD share some clinical and pathological characteristics, comprising oxidative stress and inflammation and impaired proteasomal and lysosomal function, which cause formation of intra- and extracellular deposits. In both AD and AMD, the same destructive aggregated protein deposits occur primarily in the gray matter of the brain and the macula of the retina (9–12). It is also suggested that both diseases share similar environmental risk factors such as systemic hypertension, cigarette smoking, obesity, unhealthy diet, and hypercholesterolemia (9,13).

In some studies, cognitive impairment has been reported in AMD patients (14–16). Since AD also affects the same age group, at least in some patients this cognitive impairment may be due to an incipient dementia. As the aging population increases in developing countries such as Turkey, knowing if such a relationship exists between AD and AMD is important.

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The purpose of this study is to compare cognitive functions and the rate of AD between individuals with and without AMD, and to analyze cognitive performances of patients with different pathologies based on AMD types.

2. Materials and methods

2.1. Study population and procedure

The study was conducted at the neurology, ophthalmology, and psychiatry clinics of a university hospital. Informed consent was obtained from all subjects according to the Declaration of Helsinki. The study was approved by the Süleyman Demirel University Faculty of Medical Sciences ethics committee.

Fifty-nine patients with late-stage AMD and 49 age-, sex-, and education-matched healthy subjects were included in this study. All individuals aged 65 years or older who had not previously received a diagnosis of AD were recruited among patients admitted to the outpatient clinic of the ophthalmology department. AMD patients who had sufficient visual acuity (VA) (VA ≥ 20/100 in the better eye) that would not compromise administration of neuropsychological tests were included in the study. The exclusion criterion was having neurological and psychiatric diseases or any other medical conditions that might affect cognition.

All patients and controls were questioned for basic information, including demographics, presence of concomitant diseases, drug usage, and exposure to potential risk factors for AMD or AD. Following that, all patients and controls underwent detailed ophthalmological, neurological, and psychiatric examinations on the same day.

2.2. Ophthalmic assessment

The ophthalmological examination included the best-corrected VA, slit lamp biomicroscopy, dilated fundus examination, and optical coherence tomography. In addition, retinal photography and angiography with fluorescein were performed for AMD patients.

The diagnosis of AMD was made according to the criteria proposed by the Age- Related Eye Disease Study (16). In the retina examination, soft drusen, retinal pigment epithelial depigmentation, increased retinal pigment, geographic atrophy, and signs of exudative macular degeneration (subretinal hemorrhage, subretinal fibrous scar, retinal pigment epithelium detachment, and/or serous detachment of the sensory retina) findings were used for diagnosis of AMD. The AMD patients were classified as follows: 1) early AMD: presence of a few (<20) medium-sized drusen or retinal pigmentary abnormalities; 2) intermediate AMD: at least 1 large drusen, numerous medium-sized drusen, or geographic atrophy that does not extend to the center of the macula; 3) late dry (nonvascular) AMD (d-AMD): drusen and geographic atrophy extending to the center of the macula; 4) late wet (vascular) AMD (w-AMD): choroidal and retinal neovascularization and its sequelae, such as subretinal fluid, lipid deposition, hemorrhage, retinal pigment epithelium detachment, and fibrotic scar. In the patient group, the eyes with lower VA were used in the statistical analysis (except for 3 patients with equal VA in both eyes).

2.3. Neuropsychological assessment

All participants were submitted to a detailed neuropsychological evaluation. Neuropsychological evaluations were performed by one of the investigators individually in a single session. All tests were applied in a predefined order to all patients and controls. First, for the assessment of mood status, all subjects were given the Yesavage Geriatric Depression Scale (GDS), which was developed as a basic screening measure for major and minor depression in older adults and specifically designed to assess the presence or absence of depressive symptoms (17). General cognitive performance was also evaluated with the Mini-Mental State Examination (MMSE) (18). Since the education level of the study sample was predicted to be low, tests requiring reading/writing and drawing abilities were not included and only tests that could be administered auditorily/verbally were included for the assessment. For verbal memory, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list was used (19). Attention and executive functions were evaluated with digit span (forward and backward) (20) and CERAD verbal fluency (animals, and K, A, S) (19). A short version of the Boston naming test (including equally distributed frequent, intermediate, and rare items, a total of 15) (19) and the Frontal Assessment Battery were also administered (19,21). AD was diagnosed according to the guidelines of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (22).

2.4. Statistical analysis

All statistical analyses were performed using SPSS 15.0 for Windows. Comparisons between the groups for categorical variables were done with the chi-square test. The normality of data was assessed via Kolmogorov–Smirnov test. The independent t-test was used to compare the parametric variables between the groups. The Pearson correlation coefficient was used for quantitative relationships. Analysis of variance (ANOVA) was used to compare the same independent variable between 3 groups (patients with d-AMD, patients with w-AMD, and controls). Bonferroni corrections for post hoc comparisons were used to compare among these 3 groups' means at baseline. The significance level for the tests was 0.05.

3. Results

The sociodemographic and clinical characteristics of all subjects are shown in Table 1. The subjects were divided into 2 groups: patients affected by AMD (n = 59) and controls (n = 49). The distributions of sex, age, and duration of education of AMD patients and controls were similar. Ocular findings in both eyes of AMD patients are given in Table 2. VA was better in other eyes of late-staged AMD patients (P < 0.001). The AMD group was also classified as dry type (n = 45) and wet type (n = 14). Out of the other eyes of 45 w-AMD patients, 4 were wet (8.9%), 14 were early (31.9%), and 27 were intermediate (60.0%) type, while in d-AMD patients 1 was early (7.1%) and 13 were intermediate (92.9%). The mean VA was lower in d-AMD patients than in w-AMD patients (Table 3). There was an association between age, sex, and short education duration and neuropsychiatric tests scores (P < 0.01). However, there was no association between visual acuity and neuropsychiatric tests scores.

According to the guidelines of NINCDS-ADRDA, 24 (40.7%) patients were diagnosed with AD among the 59 patients with AMD. There were 10 (20.4%) subjects who

Table 1. Characteristics of individuals affected by age-related macular degeneration (AMD) and controls.

	AMD		Controls		
	n = 59		n = 49		P-value
	Mean ± SD	%	Mean ± SD	%	
Age (years)	74.3 ± 7.31		73.85 ± 5.51		0.36
Sex (female)		47		48	0.9
Visual acuity (logMAR)	1.21 ± 0.75		0.39 ± 0.73		<0.001
Education (years)	3.45 ± 2.58		3.63 ± 2.84		0.73
Cigarette smoking		35.6		26.5	0.40
Alcohol		5.10		4.10	0.80
Hypercholesterolemia		30.5		28.6	0.82
Hypertension		66.1		49.0	0.07
Diabetes		23.7		36.7	0.14
Cardiac diseases		25.4		24.5	0.91
Gastrointestinal diseases		18.6		12.2	0.21
Genitourinary diseases		27.1		16.3	0.17
Respiratory diseases		16.9		8.2	0.25
Locomotor diseases		22.0		40.8	0.03
Obesity		30		20	0.21
Sun exposure		71.2		53.1	0.07
Cataract surgery		59.3		42.9	0.08
Light-colored eyes		25.4		8.2	0.02
Meaty diet		27.1		16.3	0.40

SD: Standard deviation.

Table 2. Ocular findings in both eyes of age-related macular degeneration patients.

	Advanced eye	Other eye
Visual acuity (logMAR), mean ± SD	1.21 ± 0.76	0.30 ± 0.30
Type of AMD		
Early, n (%)	0	15 (25.4)
Intermediate, n (%)	0	40 (67.8)
Late-dry, n (%)	14 (23.7)	0
Late-wet, n (%)	45 (76.3)	4 (6.81)

SD: Standard deviation.

Table 3. Characteristics of individuals affected by late stage age-related macular degeneration (AMD), dry AMD, and wet AMD.

	d-AMD		w-AMD		
	n = 14		n = 45		P-value
	Mean ± SD	%	Mean ± SD	%	
Age (years)	74.0 ± 10.1		74.4 ± 6.3		0.86
Sex (women)		78.6		40	0.01
Visual acuity (logMAR)	1.55 ± 0.36		1.11 ± 0.81		0.006
Education (years)	2.92 ± 3.19		3.62 ± 2.37		0.46
Cigarette smoking		14.3		42.2	0.37
Alcohol		0		6.7	0.99
Hypercholesterolemia		42.9		26.7	0.27
Hypertension		71.4		64.4	0.65
Diabetes		7.1		28.9	0.09
Cardiac diseases		21.4		26.2	0.68
Gastrointestinal diseases		14.3		20.0	0.62
Genitourinary diseases		21.4		28.9	0.56
Respiratory diseases		21.4		15.6	0.61
Locomotor diseases		21.9		22.2	0.93
Obesity		21.7		33.3	0.35
Sun exposure		71.4		71.1	0.99
Cataract surgery		71.9		55.6	0.21
Light-colored eyes		14.3		28.9	0.22
Meaty diet		21.5		28.7	0.85

SD: Standard deviation.

had AD in the control group. The differences between the groups were statistically significant (P = 0.03). The frequency of AD was particularly higher in patients with d-AMD (71.4% in d-AMD and 31.1% in w-AMD, P = 0.007). Neuropsychological performances of AMD patients and the control group are shown in Table 4. MMSE, word list recognition, digit span forward and total, verbal fluency for letters K and S and K-A-S total, and FAB scores were lower in the AMD group than the control group. Neuropsychological test results among the AMD subtypes and controls are summarized in Table 5. Patients with d-AMD performed worse than the controls on all tests and also worse than patients with w-AMD on all tests except digit span backward.

4. Discussion

In this study, we found that AD frequency was statistically significantly increased in the AMD group as compared to the control group. We documented the relationship between possible cognitive impairment and AMD, especially d-AMD.

AMD and AD are both chronic degenerative disorders affecting the elderly population. AD and AMD have similar environmental and genetic risk factors (9). In our study, hypertension, cigarette smoking, obesity, and meaty diet rates were higher in the AMD group, but we did not find a statistically significant difference between the groups. Sun exposure, cataract surgery, and light-colored eyes have been reported as risk factors for AMD (4). We also found higher levels of sun exposure, cataract surgery, and light-colored eyes in the AMD group; light-colored eyes were statistically significant.

Vision is the most important warning for cognitive function and poor vision due to AMD may negatively affect the vision-associated parts of the brain cortex (15). The association between visual impairment and cognitive function may be due to the optic nerve and retinal degeneration. It has been reported that in AD visual pathways are impaired as compared to in persons without AD (23). Additionally, optimal cognitive function relies on processing and recall of information obtained via the visual sensory system. Thus, performance on assessment

Table 4. Neuropsychological assessment of individuals affected by age-related macular degeneration (AMD) and controls.

	AMD n = 59 Mean ± SD	Controls n = 39 Mean ± SD	P-value
GDS (30)	6.38 ± 4.04	5.93 ± 4.05	0.56
MMSE (30)	24.3 ± 3.88	26.5 ± 3.16	0.002
Verbal memory			
Encoding (n/30)	12.9 ± 4.77	13.8 ± 3.59	0.29
Recall (n/10)	3.27 ± 2.38	3.65 ± 1.70	0.33
Recognition (n/20)	16.2 ± 2.91	17.4 ± 2.55	0.02
Verbal fluency			
Animals (n/min)	13.7 ± 5.50	15.0 ± 5.66	0.21
K (n/min)	6.08 ± 2.47	8.44 ± 3.27	<0.001
A (n/min)	5.79 ± 2.36	6.73 ± 2.65	0.05
S (n/min)	5.67 ± 2.40	7.10 ± 2.87	0.006
KAS total	17.5 ± 6.93	22.0 ± 7.68	0.002
Digit span			
Forward	5.79 ± 1.95	7.12 ± 1.73	< 0.001
Backward	2.74 ± 1.40	3.28 ± 1.76	0.08
Total	8.54 ± 3.12	10.3 ± 3.12	0.004
Naming (n/15)	11.9 ± 2.12	12.5 ± 1.74	0.12
FAB (18)	12.0 ± 3.24	13.8 ± 2.76	0.004

SD: Standard deviation; MMSE: Mini-Mental State Examination; FAB: Frontal Assessment Battery; GDS: Geriatric Depression Scale.
The scores of neuropsychological tests were adjusted for age, sex, and education.

neuropsychological tests presumably is affected (24). Our results showed that there was reduced vision and worse cognitive function in AMD patients, and especially in d-AMD patients.

Several studies have shown different results for a potential relationship between AMD and dementia or cognitive impairment (13–15,25–27). In the Rotterdam study, Ott et al. (27) analyzed people 75 years and older for the relation of AMD to cognitive function. They found a weak association between late AMD and incident AD, but no association for early AMD and AD. The Blue Mountains Eye Study found an association between late AMD and cognitive impairment by using the modified MMSE (27). However, Wong et al. (26) suggested a weak relationship between cognitive function and early AMD. In their study, mean scores were lower for delayed word recall and digit symbol subtest in the late AMD group but were similar for word fluency test. Baker et al. (13) found a positive association between cognitive impairment that depended on digit symbol substitution test and early AMD. A case-control study (15) reported that AMD patients showed lower global cognition scores than controls. Among cognitive functions, visuospatial function, verbal memory, visual memory, and frontal function were impaired in AMD patients relative to normal controls. The rate of mild cognitive impairment was higher in AMD patients than in controls. Geographic atrophy was associated with the highest risk of mild cognitive impairment and a clinically significant reduction in MMSE scores (15).

In our study, MMSE, digit span total, verbal fluency for the letters K and S and K-A-S total, word list recognition, and FAB total scores were lower in the AMD group than the control. We found that d-AMD of the AMD types was associated with the worst cognitive functions and AD. This is probably because there is slow, progressive degeneration of photoreceptors and retinal pigment epithelium in d-AMD and its clinical properties are more similar to the phenotype of AD than are those of w-AMD (26).

An important factor is that the coexistence of AMD and AD may cause much worsening in the quality of life in the elderly. This was contrary to initial expectations that the depression score would not differ between AMD patients

Table 5. Neuropsychological assessment of individuals affected by dry age-related macular degeneration (d-AMD), individuals affected by wet age-related macular degeneration (w-AMD), and controls.

	d-AMD n = 14 Mean ± SD	w-AMD n = 45 Mean ± SD	Controls n = 49 Mean ± SD	P (* / ® / #)
GDS (30)	6.42 ± 2.53	6.37 ± 4.43	5.93 ± 4.05	0.84 (0.91 / 0.86 / 0.99)
MMSE (30)	20.71 ± 4.71	25.46 ± 2.80	26.59 ± 3.16	<0.001 (0.001 / 0.19 / 0.008)
Verbal memory				
Encoding (n/30)	9.35 ± 4.81	14.11 ± 4.21	13.83 ± 3.59	0.001 (0.001 / 0.94 / 0.001)
Recall (n/10)	1.57 ± 1.91	3.65 ± 1.70	3.80 ± 2.28	0.001 (0.002 / 0.93 / 0.001)
Recognition (n/20)	13.21 ± 3.01	17.17 ± 2.16	17.46 ± 2.55	<0.001 (<0.001 / 0.83 / <0.001)
Verbal fluency				
Animals (n/min)	10.14 ± 5.03	14.84 ± 5.20	15.06 ± 5.66	0.01 (0.009 / 0.97 / 0.01)
K (n/min)	4.35 ± 1.73	6.62 ± 2.44	8.44 ± 3.27	<0.001 (<0.001 / 0.006 / 0.02)
A (n/min)	4.14 ± 1.83	6.31 ± 2.29	6.37 ± 2.65	0.003 (0.002 / 0.67 / 0.01)
S (n/min)	3.29 ± 2.05	6.22 ± 2.25	7.10 ± 2.87	<0.001 (<0.001 / 0.21 / 0.01)
KAS total	12.50 ± 5.58	19.13 ± 6.59	22.02 ± 7.68	<0.001 (<0.001 / 0.11 / 0.007)
Digit span				
Forward	4.42 ± 1.60	6.22 ± 1.86	7.12 ± 1.73	<0.001 (<0.001 / 0.04 / 0.004)
Backward	1.92 ± 1.26	3.00 ± 1.36	3.28 ± 1.76	0.01 (0.01 / 0.64 / 0.06)
Total	6.35 ± 2.81	9.22 ± 2.92	10.34 ± 3.12	<0.001 (<0.001 / 0.17 / 0.007)
Naming (n/15)	10.07 ± 2.43	12.12 ± 1.97	12.53 ± 1.74	<0.001 (<0.001 / 0.98 / <0.001)
FAB (18)	9.57 ± 3.13	12.84 ± 2.89	13.81 ± 2.76	<0.001 (<0.001 / 0.23 / 0.001)

SD: Standard deviation; MMSE: Mini-Mental State Examination; FAB: Frontal Assessment Battery; GDS: Geriatric Depression Scale
The scores of neuropsychological test were adjusted for age, sex, and education.
P: P-value for ANOVA.
*: P-value between controls and d-AMD.
®: P-value between controls and w-AMD.
#: P-value between d-AMD and w-AMD.

and normal controls. Whitson et al. (28) reported that the comorbidity of visual and cognitive impairment leads to a higher risk of disability than each of impairment alone.

The important limitation of our study is the relatively small sample. Additionally, although we included AMD patients who had sufficient VA (VA ≥ 20/100 in the better eye) to allow for conducting neuropsychological tests in the study, reduced vision may have influenced the success of neuropsychological tests.

In conclusion, this study showed a possible association of AMD, and especially d-AMD type, with cognitive impairment and AD. The risk of cognitive impairment and AD should also be considered in patients with AMD, particularly in the d-AMD type.

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