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Cognitive Dysfunction and Age-Related Macular Degeneration

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Abstract

Several previous studies showed that age-related macular degeneration (AMD) and Alzheimer's disease (AD) share common risk factors and histopathology changes, and there is epidemiological evidence linking AMD to cognitive impairment. We tested this theory in 51 patients with late-stage AMD and 24 controls by analyzing their neuropsychological profiles. In this study, data showed that patients affected by late-stage AMD have a worse global cognitive function than those of the controls and, in particular, show worse performances in memory tasks. Moreover, patients affected by the dry form of AMD are significantly impaired in executive functions in addition to memory. Data support the hypothesis of a possible association between AMD and cognitive impairment. In particular, patients affected by the dry form of AMD may be at greater risk of developing subsequent dementia.

Keywords

cognitive impairment, dementia, neuro-ophtalmology, vision, drusen

Introduction

Age-related macular degeneration (AMD) is a late-onset, neurodegenerative retinal disease that leads to a progressive loss of central vision due to dysfunction and death of retinal pigment epithelial (RPE) cells and adjacent photoreceptor in the macula.[1] Age-related macular degeneration is the leading cause of central blindness in the elderly patients in developed countries.[2]

Cognitive decline reflects an age-related chronic neurodegenerative process in the brain. Older adults with evident cognitive impairment are more likely to develop dementia that is defined as deterioration of multiple cognitive functions that progresses over time and is severe enough to impact daily function. Alzheimer's disease (AD) is the most common cause of dementia.[3] It is associated with increased amyloid deposition and formation of extracellular senile plaques and neurofibrillary tangles in the cortex and hippocampus of the brain.[4]

Age-related maculopathy and AD are both chronic disorders that affect a substantial proportion of elderly population, imposing a significant burden on public health and quality of life.[5] Studies suggest that these conditions share several clinical and pathological features as thoroughly discussed by some authors.[6] In particular, an association between AD and AMD has been suggested based on various common profiles of risk factors and histopathological changes.[7,8] Previous clinical studies show that hypertension[9,10] and cigarette smoking[11,12] are the risk factors for both AMD and AD; on the contrary, the apolipoprotein E (ApoE) 4 allele has been shown to be a risk for AD and protective for AMD.[13] Moreover, both conditions are characterized by similar histopathological features: deposits of β-amyloid have been found in the brains of patients affected by AD[4,14] and also in the macula of patients affected by AMD, in particular into the drusen deposits.[15-17] Drusen are abnormal accumulation of extracellular material that can be observed between the basement membrane of the RPE and the inner collagenous layer of Bruch membrane. The presence of large and numerous drusen in the macula is a common early sign of AMD, whereas the presence of sporadic and small drusen (hard drusen) occurs normally with advancing age.[15]

The aim of the current cross-sectional study is to compare neurocognitive performances (across several domains) among nondemented individuals with or without AMD, in order to highlight a potential association between AMD and cognitive impairment; moreover, we investigated neuropsychological profiles of patients with different pathology-based types of AMD.

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Method

Participants and Procedure

The study cohort consisted of 51 patients affected by AMD attending the Department of Ophthalmology of the University of Brescia and 24 controls matched for sociodemographic characteristics (age, sex, and educational level) and recruited among patients' spouses and family members.

All individuals were aged 55 and older and did not receive a previous diagnosis of cognitive decline. The 51 patients with AMD had sufficient residual visual skills to allow the execution of neuropsychological tests (visual acuity [VA] > 20 of 125 in better eye). The patients were prescribed the standard clinical therapy protocol. None of patients with AMD received injections or laser therapy or neuroprotective products off label (ie, memantine or cholinesterase inhibitors). Controls were assessed to exclude ophthalmologic diseases. A standard form for each participant was completed at baseline including demographics, data on concomitant diseases, drugs, and exposure to potential risk factors for AMD or AD. The study cohort underwent a comprehensive ophthalmic assessment and neuropsychological evaluation. Informed consent was obtained from all the patients by the clinicians. The study protocol had received approval from the Spedali Civili Ethics Committee.

Ophthalmic Assessment

All controls underwent a simple ophthalmoscopic evaluation of the fundus to rule out macular disease and neurologic visual field assessment by confrontation.

Patients with AMD underwent a neurologic visual field assessment by confrontation and a comprehensive ophthalmic evaluation: the VA was evaluated using the Early Treatment of Diabetic Retinopathy Study (ETDRS) charts (only patients with VA > 20 of 125 in better eye were included) and the reading ability (MN-read acuity charts) was used to decide the size of the characters for neurological tests (only patients with reading ability higher than 20 of 63 in binocular vision and reading speed of 200 to 300 words/min were included).

Color fundus photographs and infrared, red-free light, and autofluorescence images have been taken. Angiography with fluorescein and indocyanine green was performed for patients who needed further investigation. Finally, Optical Coherence tomography was performed in order to give a cross-sectional image of the retina with the use of reflecting light rays.

Age-related macular degeneration is a multifactorial disease in which several environmental and genetic risk factors determine many phenotypes[18]; the most prevalent phenotypes are dry (nonvascular) or wet (vascular). The diagnosis of AMD was made according to the criteria proposed by the Age-Related Eye Disease Study[19]; early AMD is characterized by the presence of a few (<20) medium-size drusen or retinal pigmentary abnormalities. Intermediate AMD is characterized by at least 1 large drusen, numerous medium-size drusen or geographic atrophy that does not extend to the center of the macula. Advanced or late AMD can be either nonvascular (dry) or vascular (wet). Dry AMD (d-AMD) is characterized by drusen and geographic atrophy extending to the center of the macula. Wet AMD (w-AMD) is characterized by choroidal and retinal neovascularization and its sequelae, including subretinal fluid, lipid deposition, hemorrhage, retinal pigment epithelium detachment, and fibrotic scar. All 51 patients affected by AMD of this cohort met diagnostic criteria for late stage AMD, both dry and wet.

Neuropsychological Assessment

Cognitive function of the study cohort was assessed using a broad neuropsychological battery.

Vision-based tests were magnified in order to compensate for eventual visual impairments.[20] Normative data are available for the neuropsychological test battery (from studies about normalization and standardization of Italian people), allowing for correction of scores to test for factors such as age, education, and gender as well as the cutoff scores which sign a performance that is considered pathological to a probability level of 95%. Diagnostic tests, made of paper-and-pencil tasks, are Mini-Mental State Examination (MMSE),[21] Montreal Cognitive Assessment (MOCA),[22] the clock test,[23] Story Recall test,[24] Rey List Immediate and Delayed,[25] Trail Making Test (TMT A and B),[26] Word and Category fluency test (word: A-F-S; categories: colors, animals, fruit, towns).[27]

The MMSE is an instrument for the assessment of global cognitive functions consisting of 30 questions that explore immediate and delayed recall, language, temporal and spatial orientation, attention, calculation, and praxis. The MOCA is a rapid screening tool for mild cognitive impairment. It assesses different cognitive domains such as attention and concentration, executive functions, memory, language, visual-constructional abilities, abstraction, and calculation.

The execution of the clock test relies on visual-spatial, constructional, and executive functions. The Story Recall test, Rey List Immediate and Delayed examine verbal long-term memory.

The TMT can provide information about visual search speed, scanning, speed of processing, mental flexibility, and executive functioning. The TMT consists of 2 parts: part A evaluates the selective attention and psychomotor speed and part B evaluates the visual-spatial divided attention. The Word and Category fluency test measures the capacity to produce words in a fixed time. Finally, depressive symptoms were collected using the Geriatric Depression Scale (GDS) short version.[28]

Statistical Analysis

Statistical analysis was performed using the SPPS.[29] Descriptive statistics are presented as mean values and standard deviation or percentages, according to the nature of the variables. Considering that score data are nonnormally distributed, comparison between the groups about education, comorbidity, depressive, and neuropsychological tests was made with

Table 1. Characteristics of Individuals Affected by Age-Related Macular Degeneration (AMD) and Controls.[a]

	AMD			Controls			
	N = 51			N = 24			
	Mean	SD	%	Mean	SD	%	*P* Value
Age, years	73.7	7.2		71.7	6.2		.24
Sex, women			53			83	.01
Education, years	8.4	4.3		7.5	2.8		.69
Civil status							
Widow			18			17	.94
Married			76			79	.94
Single status			6			4	.94
Cigarette smoking			57			25	.03
Comorbidity[b]	2.9	1.7		2.3	1.5		.07
Alcohol (at meals)			47			29	.11
Hypercholesterolemia			57			58	.55
Hypertension			53			54	.56
Diabetes			12			8	.49
Cardiopathies			31			12	.07
Nervous system's disease			14			12.5	.59
Gastrointestinal diseases			18			17	.59
Genitourinary diseases			14			8	.40
Immunitary diseases			8			4	.48
Respiratory diseases			6			4	.61
Locomotory diseases			8			8	.63
Depressive symptoms (GDS)[c]	2.3	3.3		1.8	1.9		.85

Abbreviation: SD, standard deviation; NS, nonsignificant; GDS, Geriatric Depression Scale.
[a] Comparison between groups about education, comorbidity, and depressive symptoms was analyzed using nonparametric statistical methods. The presence of each pathology was defined as self-reported use of specific medications.
[b] Comorbidity: number of diseases.
[c] GDS: Geriatric Depression Scale (15 items).

nonparametric statistical methods; chi-square test was used for dichotomous ones. One-way analysis of variance was used to compare the same independent variable between 3 groups (individuals affected by d-AMD, individuals affected by w-AMD, and controls). Post hoc comparisons, adjusted with the Bonferroni correction, were used to make comparisons between these 3 group means at baseline.

Results

Table 1 shows the sociodemographic and clinical characteristics of all participants; participants were divided into 2 groups: patients affected by AMD (n = 51) and controls (controls n = 24). Female gender is more represented into the control group (AMD 53% vs controls 83%; $P = .01$) and patients with AMD are more likely to be current smokers (AMD 57% vs controls 25%; $P = .03$). No other differences have been found between the 2 groups.

Table 2 shows that participants with AMD have a worse global cognitive function than controls, measured with MMSE and MOCA (MMSE: AMD 26.8 $\pm$ 3.2 vs controls 28.3 $\pm$ 1.3; $P = .05$; MOCA*:* AMD 20.2 $\pm$ 5.8 vs controls 23.7 $\pm$ 3.2; $P = .007$). Patients with AMD show worse performances in memory tasks when analyzed with Short Story Recall (AMD 9.5 $\pm$ 4.4 vs controls 11.8 $\pm$ 3.1; $P = .04$), Rey List Immediate (AMD 29.3 $\pm$ 8.8 vs controls 38.7 $\pm$ 9.9; $P = .000$), and Rey List Delayed tests (AMD 7.3 $\pm$ 2.9 vs controls 9.5 $\pm$ 2.8; $P = .01$). The executive functions are worse in patients affected by AMD as highlighted by lower score in Word Fluency Test (AMD 24.8 $\pm$ 11.5 vs controls 31.4 $\pm$ 9.3; $P = .003$).

The AMD group was further divided into 2 subgroups: those affected by the dry clinical form (d-AMD, n = 20) and those affected by the wet clinical form (w-AMD, n = 31). These 2 groups were comparable for sociodemographic and clinical characteristics (Table 3).

Neuropsychological test scores of patients affected by late-stage AMD, either d-AMD or w-AMD, have been compared with the control group (Table 4). Patients affected by d-AMD have global cognitive scores significantly lower than controls (MMSE 26.2 $\pm$ 3.6 vs 28.3 $\pm$ 1.3: $P < .05$; MOCA 19.6 $\pm$ 6.7 vs 23.7 $\pm$ 3.2; $P < .05$).

Both d-AMD and w-AMD groups show significantly worse abilities to learn a word list as compared to the control groups (Rey list immediate scores: d-AMD 30.6 $\pm$ 9.1 vs controls 38.7 $\pm$ 9.9; $P < .05$; w-AMD 28.5 $\pm$ 8.7 vs controls 38.7 $\pm$ 9.9; $P < .001$).

In addition, deficit in recall of the same word list is observed in patients with AMD (Rey list delayed scores: d-AMD 7,2 $\pm$ 3.2 vs controls 9.5 $\pm$ 2.8: $P < .05$; w-AMD 7,4 $\pm$ 2,7 vs controls 9.5 $\pm$ 2.8; $P < .05$). Nonstatistically significant

Table 2. Neuropsychological Assessment of Individuals Affected by Age-Related Macular Degeneration (AMD) and Controls.[a]

	AMD		Controls		
	N = 51		N = 24		
	Mean	SD	Mean	SD	*P* Value
MMSE (0-30)	26.8	3.2	28.3	1.3	.05
MOCA (0-30)	20.2	5.8	23.7	3.2	.007
Short story recall (0-28)	9.5	4.4	11.8	3.1	.04
Rey list immediate (0-75)	29.3	8.8	38.7	9.9	0
Rey list delayed (0-15)	7.3	2.9	9.5	2.8	.01
Word fluency	24.8	11.5	31.4	9.3	.003
Category fluency	46.7	14.4	47.4	17.1	.49
TMT-A	78.4	57.4	60	20.9	.09
TMT-B	131.9	72.5	127.3	44.9	.92
Clock-test (0-10)	7.8	2.4	8.7	1.8	.16

Abbreviations: MMSE, Mini-Mental State Examination; MOCA, Montreal Cognitive Assessment; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; NS, nonsignificant; SD, standard deviation.
[a] Comparison between groups was analyzed using nonparametric statistical methods. The scores of neuropsychological test are adjusted for age, gender, and education.

Table 3. Characteristics of Individuals Affected by Late stage Age-Related Macular Degeneration (AMD), Wet AMD, and Dry AMD.[a]

	d-AMD			w-AMD			
	N = 20			N = 31			
	Mean	SD	%	Mean	SD	%	*P* Value
Age, years	75.5	5.9		72.6	7.8		.18
Sex, women			65			45	.13
Education, years	8.6	4.8		8.3	4.1		.68
Civil status							
Widow			30			10	.18
Married			65			84	.18
Single status			5			6	.18
Cigarette smoking			45			55	.94
Visual acuity	20/32	2.38		20/25	2.10		.15
Comorbidity[b]	1.8	1.6		2.9	3.1		.15
Alcohol (at meals)			50			45	.47
Hypercholesterolemia			55			58	.52
Hypertension			55			52	.52
Diabetes			5			16	.23
Cardiopathies			25			35	.31
Nervous system's disease			20			10	.26
Gastrointestinal diseases			20			16	.50
Genitourinary diseases			20			10	.26
Immunitary diseases			15			3	.16
Respiratory diseases			10			3	.33
Locomotory diseases			10			6	.51
Depressive symptoms (GDS)[c]	2.5	2.5		2.4	3.7		.63

Abbreviations: NS, nonsignificant; GDS, Geriatric Depression Scale; AMD, age-related macular degeneration; SD, standard deviation; d-AMD, dry AMD; w-AMD, wet-AMD.
[a] Comparison between groups about education, comorbidity. and depressive symptoms was analyzed using nonparametric statistical methods. The presence of each pathology was defined as self-reported use of specific medication.
[b] Comorbidity: number of diseases.
[c] GDS: 15 items.

differences in terms of ability to learn and recall a word list were found between d-AMD and w-AMD subgroups.

Divided attention and visualspatial abilities in the d-AMD group are worse than in the control group (TMT-B 133.7 ± 32.9 vs 127.3 ± 44.9; $P < .05$; the clock-test 7.1 ± 2.6 vs 8.7 ± 1.8; $P < .05$). No significant differences between d-AMD and w-AMD groups are found in these tests.

Table 4. 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.[a]

	d-AMD		w-AMD		Controls	
	N = 20		N = 31		N = 24	
	Mean	SD	Mean	SD	Mean	SD
MMSE (0-30)	26.2[c]	3.6	27.2	2.8	28.3[c]	1.3
MOCA (0-30)	19.6[c]	6.7	20.6	5.3	23.7[c]	3.2
Short story recall (0-28)	9.4	4.8	9.5	4.3	11.8	3.1
Rey list immediate (0-75)	30.6[c]	9.1	28.5[d]	8.7	38.7[c,d]	9.9
Rey list delayed (0-15)	7.2[c]	3.2	7.4[e]	2.7	9.5[c,e]	2.8
Word fluency	24.1	11.7	25.2	11.5	31.4	9.3
Category fluency	44.1	13.2	48.3	15.1	47.4	17.1
TMT-A (seconds)	74.8	37.2	80.4	66.4	60.0	20.9
TMT-B (seconds)	133.7[c]	32.9	130.9	88.4	127.3[c]	44.9
Clock-test (0-10)	7.1[c]	2.6	8.3	2.1	8.7[c]	1.8

Abbreviations: ANOVA, analysis of variance; MMSE, Mini-Mental State Examination; MOCA, Montreal Cognitive Assessment; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; SD, standard deviation.
[a] ANOVA model adjusted with the Bonferroni correction. The scores of neuropsychological test are adjusted for age, gender, and education.
[b] $P < .05$.
[c] $P < .001$.
[d] $P < .05$.

Discussion

Different studies[5,30,31] reported an association between AMD and cognitive decline. Our study confirms these findings and highlights new aspects of the relationship between these 2 conditions.

Both AMD and dementia are chronic degenerative disease with significant impact on elderly population. The prevalence of these diseases correlates with age and appears to be increasing in the last decade. They constitute one of the most important social problem of public health because of the numerical impact in the general population and their irreversible nature.[5] Previous studies[8,32] have raised the hypothesis of a possible association between AMD and cognitive impairment, investigating the presence of common etiopathogenic factors. However, little is known about the association between late AMD and deficits in specific cognitive domains.

Data emerging from the study reinforce the hypothesis of a possible association between AMD and cognitive impairment, as shown by the performances in neuropsychological tests.

In particular, patients affected by AMD have worse performances on memory and verbal fluency tests when compared to controls, as previously demonstrated in a study conducted at a low vision rehabilitation clinic, suggesting that the high prevalence of cognitive impairment may compromise the success of low vision rehabilitation interventions among patients with macular disease.[33]

Furthermore, these findings remain consistent with the previous research,[34] suggesting that patients affected by the d-AMD have worse performances in executive functions (TMT-B and the clock test), and this impairment of multiple cognitive domains is confirmed by the worse performances in MMSE and MOCA tests.

Several previous studies demonstrated that an impairment in episodic memory (ie, the ability to learn and retain new information) associated with deficit in executive functions is seen most commonly in patients affected by mild cognitive decline who subsequently progress to a diagnosis of AD dementia.[35,36]

In this line, patients affected by late-stage AMD have a different pattern of cognitive decline: patients with w-AMD show statistically significant deficit of memory performances compared with controls, whereas patients with d-AMD can be impaired in executive functions in addition to memory. Therefore, patients affected by the d-AMD may be at greater risk of developing dementia.

The hypothesis to interpret these clinical results could be the presence of numerous and large drusen in the retina of patients with d-AMD; these abnormal accumulations of extracellular material with β-amyloid protein among their components, in association with incipient memory impairment and executive dysfunction, could give support to the hypothesis of a common etiopathogenic pathway between AD and AMD.[7,37]

These results could provide additional evidence that the dry and wet types of macular degeneration, although they represent 2 clinical forms of the same ocular disease, are characterized by the occurrence of different clinical abnormalities. Although sharing the same pathological manifestations in the early stages, they show a dissimilar evolutionary process. In fact, the wet form of macular degeneration is marked by a tumultuous course with acute phases and remissions associated with the presence of retinal neovascularization, whereas the dry form has a chronic, slow, and gradual evolution of the initial framework, leading to a worsening of the lesions already present in the early stadium (drusen and atrophy), without the onset of further clinical manifestations.[38] The evolution of symptoms

in dry form seems similar to the progression of dementia characterized by insidious onset and slow and gradual progression.

The current study has some limitations that should be considered when interpreting the findings reported. First, the sample size was small and should be increased. Second, the magnified tests were administered to the cases and not to the controls, thus the portion of the retina covered by a magnified test was different in the patients compared to the controls.

Third, although central scotomas are cardinal symptoms of late-stage AMD, information about scotomas was not collected with specific tests such as microperimetry and computer-based visual field test because of clinical setting limitations. However, we performed neurological visual field assessment by confrontation, which allowed us to exclude major visual field deficits but not minor absolute or relative scotomas. Due to this limitation, we used the reading ability and speed as inclusion criteria because some authors demonstrated[39] a significant correlation between the size of absolute scotomas and reading speed as well as reading acuity. Thus, with the evaluation of reading ability, we aimed at excluding patients with larger absolute scotomas from our cohort.

Finally, considering the impact of variants in the ApoE gene on both AMD and AD,[13] as well as on outcome of specific treatments such as antivascular endothelial growth factor drugs for vascular AMD,[40] it would have been interesting to have data available about status relative to ApoE for patients and controls.

In conclusion, AMD can be considered a chronic degenerative disease affecting elderly population which shares some striking similarities of AD. Histological analysis has revealed the presence of β-amyloid deposits in the macula of patients affected by AMD, in particular into the drusen, which are the retinal lesions typical of this disease.

These evidences lead to hypothesize that AMD and AD could be 2 forms of a larger spectrum of disease caused by accumulation of β-amyloid and characterized by common acquired risk factors and pattern of evolution. In this study, cognitive functions of patients with AMD have been assessed using a comprehensive neuropsychological battery, focusing on the evaluation of the cognitive functions typically altered in patients affected by AD, such as learning, long-term memory, executive functions, and visualspatial abilities.

The results highlight that patients affected by AMD perform worse in the global cognitive tasks than those of the controls; however, all test scores are included into the range of normality and do not meet criteria for dementia. Additionally, patients affected by the d-AMD have lower scores in tests assessing global cognitive functions, in particular showing impairment in memory and executive tasks. A broad ophthalmologic checkup demonstrated that drusen in the retina of patients affected by the d-AMD are more numerous than in the retina of patients affected by the w-AMD and of elderly controls. A possible explanation of this finding is that drusen could be a reflection of the degree of β-amyloid accumulation in the central nervous system, disclosed by both visual deficit and cognitive impairment.

Further studies are needed to elucidate this correlation and to demonstrate the utility of a cognitive status screening for patients affected by AMD in routine clinical practice, in order to detect early cognitive impairment in this population.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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