MINI-COGNITIVE TESTING IN PATIENTS WITH AGE-RELATED MACULAR DEGENERATION

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Purpose: To compare Mini-Cognitive (Mini-Cog) Screening test results between patients with age-related macular degeneration (AMD) and age-matched controls.

Participants: Two hundred and twenty-nine patients were included in the study. Patients were divided into 3 groups: 56 patients with exudative AMD, mean age of 76 ± 8 years; 82 patients with dry AMD, mean age of 77 ± 9 years; and 91 controls, mean age of 75 ± 8 years.

Methods: The Mini-Cog test, used to screen patients with early cognitive impairment, was introduced to the three groups of patients at the settings of an ophthalmology outpatient clinic. Test scores were compared between the groups.

Results: The mean for the Mini-Cog test scores was 3.5 (95% confidence interval, 3.15–3.85) for the dry AMD group, 3.95 (95% confidence interval, 3.51–4.39) for the exudative AMD group, and 4.63 (95% confidence interval, 4.45–4.80) for the control group. There was no statistically significant difference between the scores of AMD groups, however, both AMD groups received significantly lower scores than controls ($P < 0.0001$).

Conclusion: Patients with age-related macular degeneration in this study demonstrated lower mean scores in the Mini-Cog test than age-matched controls. The Mini-Cog test may be easily applied at an office setting of ophthalmology outpatient clinics, and may help in the early diagnosis of cognitive impairment in the patients with AMD.

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Normal aging carries some degree of physical, cognitive, and decreased problem-solving ability.[1,2] Age-related macular degeneration (AMD) is a principal cause of blindness in the United States and other industrialized nations. An estimated 10 million Americans are afflicted with AMD.[3] The prevalence of AMD steadily increases with age, affecting 2% of the population at age 40 years, and 1 in 4 people by age 80 years.[3] There are two types of AMD, the "dry" and "wet" forms. Dry AMD is a chronic disease that usually causes some degree of visual impairment and sometimes progresses to severe blindness. In contrast, wet AMD affects only 10% to 15% of patients with AMD, emerges abruptly, and rapidly progresses to blindness if left untreated.[4,5]

Cognitive impairment is an acquired deficit in memory function, problem-solving and orientation; it reduces an individual's ability to function independently and is a major component of age-related deterioration.[1,2] Cognitive impairment has been recognized to be one of the early manifestations of Alzheimer disease.[6–8]

Age-related macular degeneration and Alzheimer disease were implied to share common epidemiological risk factors, such as old age, female gender, white race, cardiovascular disease, hypercholesterolemia, UV light exposure, and smoking.[9] The Rotterdam Study found that late AMD was associated with 2-year higher incidence of Alzheimer disease in white individuals 75 years or older.[10] Several other large-scale epidemiological studies suggested an association between early AMD and cognitive impairment.[6,11]

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For early screening of cognitive impairment, the mini-cognitive (Mini-Cog) test that is a 3-minute instrument was used.[12] The choice of the test was based on many reasons. Firstly, the test is not affected by subject ethnicity, language, and education, and can detect a variety of different dementias.[12] In other words, the test is easy to perform; it can be used for illiterate people and multicultural populations.[12,13] It is unique from other dementia screening tests with its acceptable sensitivity of 53.7% and a high specificity of 95.5%[13] when compared with the other screening tests, such as the 8-item scale, which has a sensitivity of 94.9% and a specificity of 59.1%, the 2 in 3-item recall (51.3% and 87.3%), the 1 in 3-item recall (83.3% and 53.6%), and the clock drawing test (CDT) (39.0% and 96.9%).[13] Since the Mini-Cog test has the highest specificity, when compared with other tests, it has the highest ability to exclude dementia when the test is negative.

Herein we aim to investigate the ability to detect cognitive impairment in patients with AMD in comparison to age-matched controls using the Mini-Cog test.

Methods

Two hundred and twenty-nine patients older than 55 years visiting the retina clinic at the Kentucky Lions Eye Center at the University of Louisville were included in the study. This study was approved and monitored by the institutional review board of the University of Louisville. Each individual was fully informed of the purpose of the study. An informed written consent was obtained for each patient. This was a single center study which reflected our own experience in putting forward a practical way of screening the patients for cognitive impairment.

The patients were categorized into a control group (subjects without clinical evidence of AMD), which included 91 patients, dry AMD group (82 patients), and an exudative AMD group (56 patients). The control group included patients who were seen at the University of Louisville ophthalmology clinic for reasons other than AMD, including cataract evaluation, annual dilated eye examination, epiretinal membranes, floaters, and intraocular pressure monitoring. Patients suffering from any retinal diseases, such as diabetic retinopathy, hypertensive retinopathy, angioid streaks, high myopia (>6 diopters of myopic refractive error), central serous chorioretinopathy, presumed ocular histoplasmosis, were excluded from this study. Patients with significant uncontrolled systemic condition, such as uncontrolled diabetes, uncontrolled systemic hypertension, renal failure, heart failure, and active inflammatory disease were excluded. Age-related macular degeneration subtypes were diagnosed and classified based on clinical and angiographic findings including the presence or absence of choroidal subretinal neovascularization, and the presence of geographical atrophy. Patients in the control group had no clinical evidence of macular degeneration.

All patients underwent a simple 3-minute test (Mini-Cog test); the Mini-Cog test is composed of 2 tests at the same pack: the 3-item recall and the CDT.[13] Figure 1 showing a scheme of the test.

In the three-item recall test, the patient is given three words and is asked to recall the words immediately and at the end of the test. This part of the test is designed to examine the immediate-term and short-term memory. The other part of the test is used to examine time orientation; at this point of the test, the patient is asked to draw a clock and show the current time on it.[8,12]

Scoring methods mainly rely on the three-item recall test; if the patient did not recall any of the items given by the examiner then the test is considered positive for cognitive impairment, in this case, the patient is given a mark of zero. If the patient was successful in recalling all three items then the test is considered negative for dementia. The tests gray zone lies in those patients recalling one or two words of three words. In this case, we check on CDT; if the CDT was normal then the patient is considered not demented. But, if the CDT is abnormal then the test is considered positive for dementia screening.[12,13]

In this study, the Mini–Cog test scores for the 3 subgroups (control group, exudative AMD group, dry AMD group) were divided further into 2 subgroups; the first subgroup was of those patients who tested negative for dementia, the patients had either achieved a 3/3 or 1 to 2 in the 3-item recall test provided CDT was normal. The second subgroup was of those patients who tested positive for dementia, the patients who needed further evaluation for cognitive impairment; they achieved either a score of 0 or 1 to 2 in the 3-item recall test provided CDT was abnormal.[12]

For statistical analysis purposes, patients with normal CDT were given an arbitrary +2 added score. The passing score of the test is 3/5 (patients achieving 1 of 3 in the 3-item recall test, with a normal CDT [+2]). And the failing score of the test is 2/5 (patients achieving 2 of 3 in the 3-item recall test, with an abnormal CDT [+0]).

Statistical Analysis

Statistical analysis was carried out using SPSS software (Version 17.0; SPSS Inc, Chicago, IL). The data have been categorized in three Groups; control, exudative AMD group, and dry AMD group. Scores of Mini–Cog test were distributed according to subgroups;

Pt.Name:_____

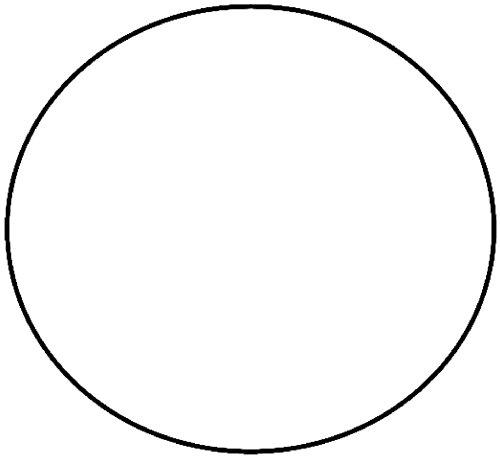
DOB:_____

Date:_____

Instructions

Inside the circle draws the hours of a clock as if a child would draw them

Place the hands of the clock to represent the time "forty five minutes past ten o'clock"



The MINI-COG

1. Instruct the patient to listen carefully and repeat the following

APPLE	**WATCH**	**PENNY**
MANZANA	**RELOJ**	**PESETA**

2. Administer the Clock Drawing Test

3. Ask the patient to repeat the three words given previously

_____ _____ _____

Scoring

Number of correct items recalled _____ [if 3 then negative screen. STOP]

If answer is 1-2

Is CDT Abnormal? No Yes

If No, then negative screen

If Yes, then screen positive for cognitive impairment

Fig. 1. Mini-cognitive score test chart.[12]

multivariate analysis was performed using the one-way analysis of variance analysis. The mean of the age and gender in the three subgroups were compared using the same test. Confirmation of the results was tested using the Scheffe test, Tukey B test and the 2-sided Dunnett test, provided that $P < 0.05$ was significant for the 1-way analysis of variance test.

Results

Patients in all groups did not differ in age, gender, and in the prevalence of systemic diseases. Table 1 summarized the results. Two hundred and twenty-nine patients were included in the study. The average overall age was age 76 ± 9 years (range, 56–98 years), 47% were men, and 53% were women. The total mean of Mini–Cog test score ± standard deviation was 4.06 ± 1.44.

The control group contained 91 patients, 55% of them were women; the mean Mini-Cog score ± standard deviation was 4.63 ± 0.9 with a 95% confidence interval of 4.45 to 4.8.

The exudative AMD group included 56 patients, 57% of them were women; the mean Mini-Cog score ± standard deviation was 3.95 ±0.7 (95% confidence interval, 3.51–4.39).

The dry AMD group included 82 patients, 49% were women; the mean Mini-Cog score ± standard deviation was 3.5 ± 0.5 (95% confidence interval, 3.15–3.85).

The percentage of volunteers having a positive Mini–Cog test; people achieving <2 score with an abnormal CDT were 6.6% for control, 20.9% for the exudative AMD group, and 25.6% for the dry AMD group. Figure 2 shows the differences in Mini–Cog test mean scores between the 3 groups.

There was no statistically significant difference between the AMD groups however; the AMD groups had significantly lower Mini–Cog test results than the control group.

Discussion

Cognitive impairment is a group of diseases, ranging from mild cognitive impairment, which is an early stage of Alzheimer disease, to the definitive Alzheimer disease.[8] Alzheimer disease is by far the most common cause of dementia in the United States, accounting for over 70% of dementia cases in individuals over 70 years of age.[14] Estimates from the Alzheimer Association in 2011 indicate that over 5.4 million people in the United States have

Table 1. Comparison of Mini-Cog test results in different study groups.

	Total (N = 229)	Control (N = 91)	Wet AMD (N = 56)	Dry AMD (N = 82)	*P*
Age (age range, years)	76 ± 8 (56–98)	75 ± 8 (60–95)	76 ± 8 (64–95)	77 ± 9 (56–98)	0.524
95% CI of age					
Lower	—	73.81	73.86	75.03	
Upper	—	77.36	78.86	79.12	
Gender Female (%)	53	55	57	49	0.644
Mini–Cog	4.06 ± 1.44	4.63 ± 0.85	3.95 ± 1.65	3.5 ± 1.59	0.0001
Mini–Cog score 2 or less (%)	—	6.6	21.4	25.61	
Mini–Cog score 3 or more (%)	—	93.4	78.6	74.4	
95% CI of Mini-Cog					
Lower	—	4.45	3.51	3.15	
Upper	—	4.8	4.39	3.85	
P for the Schaffe test on the mean of Mini-Cog test scores					
Control/wet AMD group					0.014
Control/dry AMD group					0.0001
Wet AMD/dry AMD group					0.169
P using the dunnett *t*-test (two-sided test)					
Dry AMD/control group					0.0001
Wet AMD/control group					0.007

CI, confidence interval.

Alzheimer disease, including 5.2 million people aged 65 years or older.[14]

Early detection of Alzheimer disease has been under-investigation since 2004, namely positron emission tomography with 11 C-labeled Pittsburgh Compound-B (PiB),[15] it is a noninvasive method which will provide an opportunity to diagnose Alzheimer disease early but it is still expensive.

Age-related macular degeneration and Alzheimer disease not only share epidemiologic but also some molecular finding as summarized by Kyoko Ohno-Matsui review.[16] For example, both characteristic senile plaque of Alzheimer disease and hallmark drusen of AMD share common active components, the most important one is B-amyloid (AB), both components contain AB(1–40) and AB(1–42).[17,18] B-amyloid seems to play an important role in the chronic inflammation that occurs in both AMD and Alzheimer disease.[19–22] Double immune-labeling experiments confirm that amyloid vesicles within drusen are both C3b-immunopositive and AB-immunopositive.[17] Complement factor H, an inhibitor of the alternative pathway of the complement system, is also known to be deposited along the surface of amyloid vesicles.[23–25] Age-related macular degeneration-associated complement factor H allele was found at an increasing rate in patients with Alzheimer disease and is considered a risk factor for the development of Alzheimer disease in patients with AMD.[26] Moreover, high concentrations of C3 and C4b have been recorded in the serum of patients with Alzheimer disease, and the major attack complex of the complement has been demonstrated in the senile plaques of brains with Alzheimer disease, indicating that overactivation of the complement system has neurotoxic consequences.[27] Dysfunctional mitochondria release oxidizing free radicals that cause considerable oxidative stress in the brains of patients with Alzheimer disease and the retinal pigment epithelium of patients with AMD.[28–32]

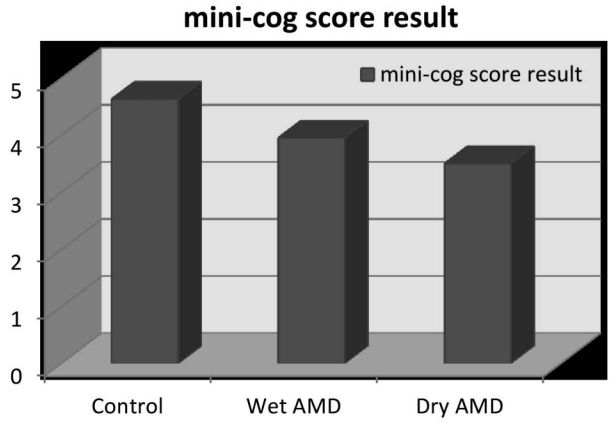


Fig. 2. Shows the differences in Mini–Cog test scores between the three groups.

The retina gives the advantage of direct visualization of drusen (retinal amyloid) either by fundoscopy or spectral domain optical coherence tomography. Koronyo-Hamaouiet et al[33] found retinal AB plaques using curcumin, a safe plaque-labeling fluorochrome, in postmortem eyes from patients with Alzheimer disease.

Simple screening of the patients with AMD, using various cognitive screening tests, can potentially be an easy method for early detection of mild cognitive problems.

The importance of screening for Alzheimer disease has been recently recognized. Alzheimer disease is not a singular homogeneous disease, but rather it represents a final common pathway. It is argued that there are three pre-Alzheimer disease pathways. The first is age-associated memory impairment, the second is mild cognitive impairment, and lastly depressive dementia.[8,34,35] It is shown that for these three pre-Alzheimer disease spectrum conditions, intervention must occur before final conversion to Alzheimer disease, intervention after conversion to diagnostic Alzheimer disease is regarded as too late.[34,35] Whenever a disorder follows a long-term multiphasic course with intermediate points, first intervention must occur at preconversion phases.[35] The purpose of this small study was to investigate the ability to detect cognitive impairment in patients with AMD using the Mini-Cog test in a retina clinic setting. Unlike other large-scale studies, which investigated the relationship between Alzheimer disease and AMD, this is the first time screening for cognitive impairment (and not full dementia) is investigated in relation to AMD.

Only 60% of people with Alzheimer disease in the United States are diagnosed. Percentages of people with Alzheimer disease who are neither diagnosed nor treated are even higher in many other countries.[34,35] Cognitive impairment and Alzheimer disease have been associated with a lower life satisfaction, and recent studies have shown that cognitive impairment was associated with twice the odds of fatal incident stroke.[36] Impaired vision in addition to cognitive impairment reduces the quality of life of the elderly considerably.[37] It translates into a huge economic burden because of the expensive services required to be provided to these patients.[38,39] A study by Day et al[38] shows that there is an overall vast increase in Medicare's payments per beneficiary in treating these patients.

The association between AMD and cognitive impairment has been suggested by many studies.[6,40–42] To the best of our knowledge, there are no studies to show the subjective usefulness of simple cognitive tests on patients with AMD or to compare it with age-matched controls. This study demonstrated that the use of Mini-Cog tests on patients with AMD may assist in the early detection of cognitive abnormalities, as patients with a positive test should be subjected to further tests to determine dementia.

Our study has some inherent limitations, the samples were not corrected for smoking and atherosclerosis.[11] We did not correct the groups for hypertension, diabetes, and depression as it was identified as a risk factor for dementia but has been proven as unrelated to cognitive impairment.[43,44] Recently, cataract and moderate-to-severe diabetes have been suggested as a risk factor for cognitive impairment in the Singapore Malay study.[44] However, no other study has reached a similar conclusion. Further large-scale studies may be needed to confirm our findings. It is to be noted that this study did not determine Alzheimer disease, which requires an appropriate level of imaging and other tests to diagnose, but rather demonstrated the usefulness of a screening test for cognitive impairment. A positive test result will certainly demand further workup.

In summary, Mini-Cog testing may be easily performed in an ophthalmology outpatient clinic setting, and may be useful for early screening for cognitive impairment in patients with AMD. There are many reasons well outlined in literature to suggest the use of the Mini–Cog test:

1. It is easy to perform—a technician can do it.
2. It is not time consuming—takes less than 3 minutes to conduct.
3. It is inexpensive.
4. It can be easily performed by illiterate patients or patients from different ethnicity. Language is no a barrier to conduct the test.

We suggest considering using the test by an ophthalmologist or a retina specialist based on the results of this study that suggested that patients with AMD were more likely to be screened as positive for cognitive impairment in comparison to controls. The ophthalmologist may serve an important role of directing the positively screened patients with AMD to further investigation, early dementia diagnosis, and care.

Key words: cognitive impairment, age-related macular degeneration, mini-cognitive screen test.

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