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Research Paper: Profiling cognitive performance and sleep quality measures in patients with age-related macular degeneration

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ABSTRACT

Objective: This study is aimed at profiling cognitive functions in patients with age-related macular degeneration (AMD).

Method: This cross-sectional investigation enrolled 45 patients with AMD and 45 age- and sex-matched controls. The overall cognitive performance in AMD sufferers versus control subjects was assessed using the Persian version of Addenbrooke's Cognitive Examination battery (ACE-R). Subjects' sleep quality was also evaluated using the Pittsburgh Sleep Quality Index (PSQI). The mean global assessment and subscale scores were statistically compared between groups.

Results: The mean global scores for ACE-R in AMD and control groups (80.4±12.3 and 86 ± 9.6, respectively) were found to be statistically different (p=0.018). On the other hand, there was no significant difference (p=0.793) between the AMD and control groups in terms of PSQI scores (9.7±2.8 and 9.8±2.8, respectively).

Conclusion: AMD patients seem to have cognitively underperformed in memory and verbal fluency domains compared to the control group. Evidence on cognitive impairments in patients with AMD may possibly herald neurocognitive insufficiencies and have common pathological mechanisms with dementias.

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1. Background

Age-related macular degeneration (AMD) is a neurodegenerative retinal disorder resulting from the apoptotic cell death at retinal pigment epithelium (RPE) and adjacent photoreceptors level, leading to central vision loss. It is considered the leading cause of progressive central blindness among elderly patients in developed countries (1). The prevalence of AMD is known to be directly linked with age, affecting almost 2% and 25% of the population by the age 40 and 80 years, respectively. The condition is therefore regarded as an important social and economic burden in every society (2).

Since the retina is considered as an outpouching of the central nervous system, retinal degenerative changes have hypothetically been linked to neurodegenerative changes at the brain cortical level. This hypothesis has however not been systematically tested in the existing literature.

The overall cognitive functions encompass memory, language, orientation, judgment, reasoning, planning, problem-solving, and executive functions. Alzheimer's Disease (AD) which is the leading cause of dementia has affected over 35 million people worldwide (3). The incidence of AD steadily rises with age (4). The pre-Alzheimer's state can be categorized into three different phases including age-associated memory impairment, mild cognitive impairment, and depressive dementia (5-7). Early diagnosis of these three pre-Alzheimer's disease conditions, plays a key role in timely initiation of treatments and slowing down the process towards AD (6, 7).

AMD and AD constitute an important social problems of public health. Because of their irreversible nature, their great impact on vision and cognition, disability-induced functional and social impairment, and its financial burden for society, these two conditions have recently attracted great health care attention (8). AMD and cognitive impairment are both chronic neurodegenerative disorders affecting an increasing number of aging individuals. Similar pathophysiology of the two conditions and the common risk factors raise the hypothesis of their concurrence in some ways. Our study aims to evaluate cognitive functions in patients diagnosed with AMD.

2. Methods

This cross-sectional, case-control study enrolled 90 participants. Out of those, 45 subjects were in the case group already diagnosed with AMD, and others who had no sign of AMD were assigned to the control group. AMD was clinically diagnosed by a qualified ophthalmologist subspecializing in retinal disease. Apart from careful retinal examination, macular optical coherence tomography (OCT) assisted in confirming the diagnosis of some cases. Patients with macular atrophy or choroidal neovascularization were enrolled in the case group.

Patients suffering from any psychological/neurological illnesses or retinal diseases such as diabetic retinopathy, hypertensive retinopathy, high myopia (6 diopters of myopic refractive error), traumatic macular lesion, central serous chorioretinopathy, presumed ocular histoplasmosis, uncontrolled systemic condition (such as uncontrolled diabetes, uncontrolled systemic hypertension, renal failure, heart failure, active inflammatory disease, and history of malignancy, radiotherapy, or chemotherapy) were excluded.

All participants were concurrently evaluated for cognitive disorders by a clinical neuroscientist who was blind to the subject's group. Cognitive functions were profiled by means of the Persian version of Addenbrooke's cognitive examination (ACE-R) tool which is the extension of Mini-Mental State Examination (MMSE). The overall ACE-R score of 100, constitutes domain scores related to attention/orientation, memory, fluency, language, and visuospatial abilities. ACE-R's test reliability is considered favorable based on its internal consistency (Cronbach alpha coefficient = 0.8). This version introduced cut-off scores of 88 and 82, which were reported to have good sensitivity and specificity to identify dementia (0.94 and 0.79; 0.84 and 1.00, respectively) (9).

Given the impact of subjects' overall sleep quality on cognitive functions, patients' subjective sleep quality was also examined using the Pittsburgh Sleep Quality Index (PSQI). PSQI Consists of 19 items measuring several aspects of sleep including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep-aid medication, and daytime dysfunction. The global PSQI score is then calculated by summing up the seven component scores, providing an overall score ranging from 0 to 21, where lower scores suggest a better sleep quality. The mean score of these tests and the score of each domain

were compared between case and control groups by statistical analysis.

Each individual was fully informed of the purpose of the study and entitled to quit the study at any point on his/her own will. The study protocol was approved by the ethical committee of Shiraz University of Medical Sciences.

3. Results

All retinal and cognitive profiling assessments were done in a total of 90 subjects. Among case subjects, 35 and 10 patients were found to have wet- and dry-type AMD. The remaining 45 subjects were assigned to the control group. Demographic details of case and control group subjects are summarized in Table 1.

There was no statistically significant difference between the case and control groups in terms of age (p= 0.972). The global mean score of ACE-R in the case and control groups were 80.4 ± 12.3 and 86 ± 9.6, respectively, suggesting a statistically significant difference (p= 0.018).

The overall mean PSQI score in the case and control groups were 9.7 ±2.8 and 9.8 ± 2.8, respectively. This difference was however not found to be statistically significant (p= 0.793).

We also compared the domain-specific score upon cognitive profiling and PSQI assessment in both groups. In ACE-R, memory and verbal fluency were statistically different in these groups. None of PSQI subscale scores were significantly different in case and control groups. Results domain-specific scores of ACE-R and subscale scores of PSQI are demonstrated in Tables 2 and 3, respectively.

Table 1. Demographic data of AMD and healthy subjects enrolled in the study

Study group	Mean age	Male	Female	Total number
Case	68 ± 9.4	21	24	45
Control	68 ± 8.6	21	24	45

Table 2. Domain-specific scores of ACE-R in both study groups

Cognitive domain	Case	Control	Significance level
Orientation attention	14.8±2.4	15.1±2.2	0.681
Memory	21.7±3.1	23.7±2.1	0.001*
Verbal fluency	7.6±3.5	10.7±2.3	0.000*
Language	21.9±3.1	22±3	0.863
Visuospatial	14.3±1	14.5±1.2	0.572
Total score	80.4±12.3	86±9.6	0.018*

* P. value<0.05

Table 3. Subscale scores of PSQI in both study groups

PSQI subscale	Case	Control	Significance level
Sleep Duration	2.5±0.5	2.6±0.5	0.529
Sleep Latency	1.4±1	1.5±1	0.604
Sleep Efficiency	1.4±0.5	1.4±0.5	0.831
Sleep Disturbance	1.5±0.5	1.5±0.5	0.835
Sleep Quality	1±0.4	1±0.4	0.799
Sleep Medication	0.1±0.3	0.1±0.3	0.751
Daytime dysfunction	1.7±0.5	1.7±0.5	0.824
Total score	9.7±2.8	9.8±2.8	0.793

* P. value<0.05

4. Discussion

Approaches towards early detection of dementia symptoms and prodromal AD have been investigated since 2004 (10). Despite all such efforts, it seems that almost 40% of people with AD remain not timely diagnosed in the United States. The percentage of people with AD who are neither diagnosed nor treated is even higher in many other countries (6, 7).

AMD is an ocular disease potentially sharing some pathophysiological features with AD. At one point, AMD and AD are both categorized as neurodegenerative diseases. They not only share common risk factors but also some pathological underpinnings. Common risk factors between the two diseases comprise aging, obesity, atherosclerosis, hypertension, and smoking, of which almost all drive cellular aging (11). AMD and AD also share common histological and molecular features and pathogenic pathways; therefore, some authors have even called AMD the AD in the eye (12).

Some common or similar molecular constituents of AMD and AD include amyloid-β, vitronectin, apolipoprotein E, complement components, and inflammatory mediators which are found as equivalent in the drusens of AMD and senile plaques of AD (13).

The amyloid-β which is a neuronal cell membrane glycoprotein has two main variants i.e. amyloid-β 40 and 42. Such soluble variants of amyloid-β which are commonly regarded as the predictors of AD (14), tend to accumulate in the senile plaques (15). Amyloid-β also accumulates in the drusen (16) which is more pronounced at the edge of geographic atrophies in AMD and increased with further degeneration (17). The accumulation of amyloid-β 42 oligomers triggers chronic inflammation, potentially leading to blood-retinal barrier dysfunction (18). On the other hand, amyloid β interacts with retinal pigment epithelial (RPE) cells and response by secretion of angiogenic markers namely the vascular endothelial growth factor and pigment epithelium-derived factor (19).

The process of oxidative stress and consecutive immunological mechanisms are other common pathways in the pathogenesis of AMD and AD (20-22). Hypoxia at the brain and retinal level is another crucial player contributing to oxidative stress. Two of the most energy-consuming tissues are the brain and retina (23). Similar to the choroidal blood flow is decreased in AMD (24), cerebral atherosclerosis drives cognitive changes and ultimately leads to AD (25). According to Roher et al., cerebral blood flow is 20% less in patients with AD than the age-matched controls (26).

The oxidative stress-derived amyloid-β build-up seems to play a central role both in AMD and AD (27). According to Murakami et al., transgenic mice lacking superoxide dismutase 1 were more prone to develop AD. Likewise, patients with AD have lower levels of superoxide dismutase 1 (28). On the other hand, superoxide dismutase 1 plays a major role in the pathogenesis of AMD (22, 29). Mice deficient in superoxide dismutase 1 develop the typical pathology of AMD as they age (30).

Vitronectin which is abundantly found in drusens is an acute phase reactant with toxic effects on neuroblastoma cells and retinal pigment epithelium (31). Vitronectin acts through adhesion to the Bruch's membrane. When bound to the Bruch's membrane, it inhibits the transmission of metabolites between the choriocapillaris and retinal pigment epithelium, leading to damage in the retinal pigment epithelium (32). Vitronectin is also found to play a part in AD (33). Microglial cells in senile plaques of AD are known to express receptors strongly positive for vitronectin (34). Recent studies have proposed this as a contributor to the formation of amyloid oligomers and fibrils(31).

Other than the above mediators, an abnormal lipid profile is suggested as a potential risk factor for neurodegenerative disorders. Indeed, hypercholesterolemia, increased low-density lipoprotein, and overexpression of apolipoprotein B are documented as independent risk factors for AD (35). The strongest genetic risk factor for AD is an apolipoprotein E variant known as E4 (36). Apolipoprotein E, B, and cholesterol accumulation in drusens, basal deposits, and Bruch's membrane have been shown through immunostaining studies (37). Evidence has shown that transgenic aged mice which express human apolipoprotein E4 are at notable risk for AD. Interestingly, when these mice aged over 1 year and were fed with a high-fat diet, they developed the pathological features of AMD. Meanwhile, administration of anti-amyloid-β antibodies was found to lessen the pathologic process (38).

From an immunological perspective, complement activation is over-triggered in AD on amyloid-β and neurofibrillary tangles (39). Similarly, diverse complement proteins and immune complexes are found in AMD drusens (40-42). Specifically, C5,

C5b9, and C3 fragments are observed in drusens. Amyloid-β can lead to uncontrolled complement activation by its ability to block C3b from inactivation (18). As such, the complement factor H gene, which is the inhibitor of C3, was found to be strongly associated with AMD (43).

In agreement with these findings, a large screening survey demonstrated that drusens in the retina of patients affected by dry AMD were more numerous than in the retina of patients affected by wet AMD and the elderly controls. A possible explanation of this finding is that drusens could be a reflection of the degree of β-amyloid accumulation in the central nervous system, potentially disclosed by both visual deficit and cognitive impairment (44).

The possible hypothesis of AMD and AD coincidence may gain strength based on the similar mechanisms involved in both conditions as neurodegenerative processes. Further studies have attempted to demonstrate and justify this relationship by investigating the characteristics of the two disease conditions.

Macula pigments (MP) constitute lutein (L), zeaxanthin (Z), and meso-zeaxanthin (MZ) (at a 1:1:1 ratio) (45). A study on MP in patients with mild to moderate AD exhibits significantly less MP, poorer vision, and a higher occurrence of AMD when compared to control subjects (46). On the other hand, supplementation with the macular carotenoids (MZ, Z, and L) not only augments MP in terms of clinically meaningful improvements in visual function but also benefits AD patients' performance in a range of cognitive tests (47, 48). Plasma concentrations of L and Z were also lower in AD compared to controls. Studies have proposed an inverse relationship between L concentrations and the severity of dementia (49, 50).

Along these lines, other studies suggest that older adults with higher macular pigment optical density (MPOD) outperform those with lower MPOD in various indices of cognitive performance (51). These observations perhaps support the view that vision and cognition are not easily separable.

The notions supporting the effect of lutein in cognitive function include: 1) Lutein is the predominant carotenoid in human cerebral tissue (52, 53); 2) Macular pigment density is related to brain lutein concentrations (54); 3) Macular pigment density is related to cognitive function in adults (51, 55); and 4) Lutein supplementation in adults improves cognitive function (48). It is believed that carotenoids improve communication through cell-to-cell channels, modulate the dynamic instability of microtubules, and prevent degradation of synaptic vesicle proteins (56, 57).

Another mechanism that possibly explains the relationship between visual impairment and cognitive function may include degenerative changes in the optic nerve and retina. Electrophysiological studies of patients with AD have shown spoiled visual pathways when compared with those without AD (58). The visual sensory system is essential for optimal cognitive function, hence affecting performance on neurocognitive evaluations (59).

In addition to the above immunological and chemical similarities in the pathogenesis of AD and AMD, use-dependent synaptic plasticity is another key mechanism to consider. The environment affects neural processing and synaptic organization, thereby causing neurological processes to become more efficient, adaptive, and plastic (60, 61). People with decreased vision have difficulty doing visually-intensive cognitive activities. Accordingly, older adults with loss of vision have reduced levels of leisure-time activities (62, 63). Visual impairment influences the level and quality of interactive experiences of older adults, and deteriorates development and maintaining relationships and participation in activities that may improve their physical, mental, and psychosocial well-being (64). Vision impairment affects cognitive performance by decreasing participation in stimulating activities and leads to reduced cognitive reserve (33, 65). Furthermore, the lack of activity by inducing depression and social isolation may exacerbate cognitive decline (66).

The number of studies to directly examine the association between AMD and cognitive function in the general population are scarce. In the Cardiovascular Health Study, 2088 participants were enrolled. Findings revealed that participants with a score in the lowest quartile on the DSST (digit symbol substitution test) were more likely to have early AMD than subjects obtaining higher scores (67). The 'atherosclerosis risk in communities' study which enrolled 9286 participants reported an association between cognitive impairment and the incidence of early AMD (68). In addition, the 'Blue Mountains Study' which evaluated 3509 patients using the mini-mental status examination (MMSE) concluded late AMD is associated with a low-normal score (24–27) on the MMSE (69). In the 'Singapore

Malay Eye Study' which was performed on 1179 patients, no relationship was observed between low scores of cognitive tests and late AMD (70).

There are various studies on the relationship between proper sleep quality and cognitive performance. Meanwhile, to our knowledge, no study has so far put together sleep, cognitive performance, and AMD. The present investigation is perhaps among preliminary attempts on evaluating multiple domains of cognition and sleep in AMD sufferers. Meanwhile, the small sample size and lack of further neurological tests or neuro-imaging modalities have been the potential limitations in this study.

Based on our findings, patients with AMD, especially those with the dry-type, were shown to be at greater risk for impairment distinct cognitive domains (memory and verbal fluency). Our results, in line with some previous studies, confirm the significance of neurocognitive screening tests for AD in patients who have AMD and also in AMD sufferers demonstrating signs of dementia.

Despite the cognitive assessment scores, no significant impairment was detected in scores of sleep quality questionnaire in our study.

5. Conclusion

The association of AMD and AD may have informed clinicians, namely ophthalmologists, about the potential concern for cognitive impairments and progression towards AD in patients diagnosed with AMD. This would signify the necessity of timely neurocognitive screenings and individualized cognitive rehabilitation planning in AMD patients to prevent or slow the inevitable march into the cognitive fog.

Prospective cohort studies at larger scale populations using neuroimaging and more comprehensive neurocognitive tests would be helpful to further address related clinical questions on this topic.

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