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The Relationship between Age-Related Macular Degeneration and Olfactory Function

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Key Words

Age-related macular degeneration · Olfactory functions · Sniffin' Sticks

Abstract

Background: Olfactory dysfunction is a common symptom of many neurodegenerative diseases, and age-related macular degeneration (AMD) is a late-onset neurodegenerative disease. **Objective:** Thus, the aim of this study was to investigate olfactory functions in patients with AMD. **Methods:** A total of 69 subjects with AMD and 69 age- and sex-matched healthy controls were enrolled. After a complete ophthalmic evaluation, the AMD patients were subclassified as early- and late-stage AMD. Psychophysical testing of olfactory function was performed using the validated Sniffin' Sticks test. **Results:** This study was carried out in 138 subjects, with a mean age of 74.3 ± 8.9 years (range 51–89). The current investigation showed the following two major findings: (1) patients with AMD had decreased olfactory abilities, especially in odor discrimination and odor identification, even at early stages compared to controls, whereas patients had decreased olfactory abilities in all subtasks of olfactory testings

in advanced stages of AMD disease, and (2) as the visual acuity of AMD patients decreased, the olfactory abilities of these patients worsened. **Conclusion:** This study demonstrated that AMD had significant negative effects on all orthonasal olfactory tasks, particularly in advanced stages. Similar to other neurodegenerative diseases, odor discrimination and identification seemed to be more affected than odor detection threshold tasks.

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Introduction

Olfactory dysfunction is a common symptom of many neurodegenerative diseases [1]. Impairment of olfaction may develop at the early stage of Alzheimer's disease (AD), Parkinson's disease (PD) and other synucleinopathies and mild cognitive impairment [2, 3]. Olfactory dysfunction in mild cognitive impairment is a precursor sign of its progression to dementia [4]. Smell dysfunction is one of the most common nonmotor signs of PD that may develop in 90% of cases. Impairment of olfaction is also a preclinical sign of PD [5]. Recently, olfactory dysfunction

was thought to be an early marker for the diagnosis of neurodegenerative diseases. The pathological changes in neurodegenerative diseases may involve the olfactory epithelium, olfactory bulb/tract and primary olfactory cortices. Damage to cholinergic, serotonergic and noradrenergic systems may also contribute to olfactory dysfunction [6].

Age-related macular degeneration (AMD) is a late-onset neurodegenerative disease that affects photoreceptors, retinal pigment epithelium, Bruch's membrane, and the choroid. It is the leading cause of irreversible blindness among the elderly in industrialized nations [7]. The pathogenesis of AMD is multifactorial and is thought to involve a complex interaction between genetic and other factors such as oxidative stress, hydrodynamic alterations, hemodynamic changes, inflammatory influences, and apoptotic factors [8]. AMD shares common similar pathways of pathogenesis and common risk factors (aging, smoking, oxidative stress, chronic inflammation, intra- and extracellular deposits) with neurodegenerative disorders. Olfactory involvement in AD and PD has been well studied and identified. However, to the best of our best knowledge, there have been no studies to date relating to olfactory involvement in AMD. We may expect olfactory dysfunction in AMD because of its many similarities with AD and PD. Thus, the aim of this study was to investigate the olfactory functions in patients with AMD.

Materials and Methods

Study Design

This prospective, cross-sectional comparative study was performed at the Ophthalmology and Neurology Departments of Gulhane Military Medical Academy Haydarpaşa Training Hospital. All investigations were performed in accordance with the Declaration of Helsinki on biomedical studies involving human subjects, and informed consent was obtained from all participants before the study began. This study was approved by the Clinical Research Ethics Committee of Haydarpaşa Numune Education and Research Hospital.

Subjects

A total of 69 subjects with AMD and 69 age- and sex-matched healthy controls were enrolled. All subjects underwent a complete ophthalmological examination, including logMAR best-corrected visual acuity, intraocular pressure measurement with a pneumatic tonometer, slit-lamp biomicroscopy, dilated fundus examination, fundus photography, and optical coherence tomography. After detailed ophthalmic examination, patients in the AMD group were subclassified as early AMD and late AMD according to the criteria described by the International Age-Related Maculopathy Epidemiologic Study Group [9]. For subjects with asymmetric AMD lesions in both eyes, AMD was defined according to the more affected eye.

Rhinological examination, including nasal endoscopy and neurological examination, was also performed on all subjects. Exclusion criteria included the following: history of ocular diseases such as glaucoma, uveitis, optic neuropathy, and acquired or hereditary retinal diseases, history of upper respiratory infections within the previous 3 weeks, taste and smell disorders, sinonasal disorders (nasal polyps, chronic rhinosinusitis, congestion, allergic rhinitis), asthma, malignancy, head trauma, neurological and psychiatric disorders (AD, PD, epilepsy, schizophrenia, history of stroke), metabolic and endocrine disorders (diabetes mellitus, hypogonadism), or current history of smoking more than 5 cigarettes per day.

Orthonasal Olfactory Testing

Psychophysical testing of olfactory function was performed using with Sniffin' Sticks test, where odorants were presented in commercially available felt-tip pens (Sniffin' Sticks; Burghart, Wedel, Germany) [10, 11]. This test was validated widely in Europe and also in our population [12, 13]. For odor presentation the cap of the pen was removed by the experimenter for approximately 3 s, and the tip of the pen was placed approximately 1–2 cm in front of the nostrils. The test consists of one threshold and two suprathreshold subtests, namely a test for thresholds of n-butanol, a test for odor discrimination (16 triplets with 2 different odors) and one for odor identification (16 common odors, presented in a 4-alternative, forced-choice procedure). The maximum TDI (threshold, discrimination and identification) score of each subtest was 16, resulting in a maximum composite score of 48 [14]. The normal values for the TDI composite score are >30.3, with a cutoff between anosmia and hyposmia at 16.5 [12].

Statistical Analysis

Data analyses were performed using SPSS 21.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, Ill., USA). The normal distribution of the considered variables was first evaluated using the Shapiro-Wilk test. Data are presented as the mean $\pm$ standard deviation for continuous variables and number of cases for categorical variables. Independent samples t test was used to compare the means between AMD and control groups. The differences between the groups (control, early AMD and late AMD) were analyzed by analysis of variance (ANOVA) or χ^2 test, as appropriate. Tukey's post hoc tests were also performed to identify the differences among the groups. The visual acuity of the more affected eye was used for statistical analysis. To explore olfactory function in relation to the continuous variables measured in this study, data were submitted to a multivariate ANOVA using the general linear model. Pearson's correlation coefficient was performed to evaluate the correlation between the visual acuity of patients with AMD and olfactory testing. A p value <0.05 was considered to be statistically significant.

Results

This study was carried out in 138 subjects, with a mean age of 74.3 ± 8.9 years (range 51–89). The subjects were divided into two groups: 69 patients with AMD and 69 age- and sex-matched healthy controls. Table 1 gives the descriptive statistics of each of the variables of the groups.

Table 1. Descriptive statistics of results from olfactory testing and measurement of visual acuity according to grouping: patients with AMD and controls

Characteristics	AMD group (n = 69)	Control group (n = 69)	p value
Age, years	74.6±9.1	74±8.8	0.7
Gender (M/F)	32/37	32/37	
Odor threshold score	9.4±2.4	10.1±1.7	0.03
Odor discrimination score	11.3±2.3	12.8±1.5	<0.001
Odor identification score	8.7±2.6	11.9±1.8	<0.001
TDI score	29.3±6.9	34.8±4.2	<0.001
Visual acuity (logMAR)	1.0±0.5	0.1±0.12	<0.001

p value: independent samples t test.

Table 2. Descriptive statistics of results from olfactory testing and measurement of visual acuity after staging AMD

Characteristics	Early-stage AMD (n = 25)	Advanced-stage AMD (n = 44)	Control group (n = 69)	p value
Age, years	71.4±9.8	76.5±8.3	74±8.8	0.69 ¹
Gender (M/F)	16/9	16/28	32/37	0.08 ²
Odor threshold score	9.9±2.7	9.1±2.3	10.1±1.7	0.02 ¹
Odor discrimination score	11.5±2.3	11.1±2.3	12.8±1.5	<0.001 ¹
Odor identification score	8.9±2.7	8.5±2.5	11.9±1.8	<0.001 ¹
TDI score	30.4±7.4	28.7±6.7	34.8±4.2	<0.001 ¹
Visual acuity (logMAR)	0.73±0.5	1.2±0.45	0.1±0.12	<0.001 ¹

¹ ANOVA with Tukey's post hoc test. ² χ^2 test.

Table 3. p values according to the results of Tukey's post hoc test for the comparison of the study groups in terms of olfactory testing and visual acuity

	I–II	I–III	II–III
Odor threshold score	0.2	0.9	0.02
Odor discrimination score	0.7	0.02	<0.001
Odor identification score	0.8	<0.001	<0.001
TDI score	0.5	0.004	<0.001
Visual acuity (logMAR)	<0.001	<0.001	<0.001

Group I: early-stage AMD; group II: late-stage AMD; group III: controls.

As shown in table 1 the differences in terms of odor threshold, odor discrimination, odor identification, and TDI scores between the control and AMD groups were significant. The scores of olfactory testing of the AMD group were lower than those in the control group. Also, as expected, a significant decrease was detected in the AMD group in terms of visual acuity compared to controls.

After an ophthalmic evaluation, the AMD subjects were further classified as early and late AMD. Statistical analysis was performed between these groups – early AMD, late AMD and control groups. Tables 2 and 3 give the descriptive statistics of this analysis. There was no significant difference between the groups in terms of age and gender ($p = 0.69$ and $p = 0.08$, respectively). There were significant differences between the study groups in terms

of all the subtasks of olfactory testing and visual acuity. When post hoc tests were performed, it was detected that the late AMD group had significantly lower scores in odor threshold testing compared to the control group ($p = 0.02$). However, we did not find a significant difference either between the early AMD and control groups or between the early and late AMD groups in terms of odor threshold scores ($p = 0.9$ and $p = 0.2$, respectively).

When the post hoc tests were performed for odor discrimination, odor identification and TDI scores, we found that both the early and late AMD groups had significantly lower scores compared to controls ($p = 0.02$ and $p < 0.001$, respectively, for odor discrimination; $p < 0.001$ and $p < 0.001$, respectively, for odor identification; $p = 0.004$ and $p < 0.001$, respectively, for TDI). However, no difference was detected between the early and late AMD groups in terms of odor discrimination, identification and TDI scores ($p = 0.7$, $p = 0.8$ and $p = 0.5$, respectively).

Moreover, a multivariate analysis was performed for evaluating the effects of independent variables (age and logMAR) on dependent variables (Sniffin' Sticks subtests). Both age and logMAR scores had a significant effect on olfactory scores ($p = 0.002$ and $p < 0.001$, respectively). Also, the correlation analyses were performed with Pearson's test and we found a negative correlation between visual acuity and olfactory testing of the following: odor threshold, odor discrimination, odor identification, and TDI scores ($p < 0.01$, $r = -0.32$; $p < 0.001$, $r = -0.46$; $p < 0.001$, $r = -0.6$ and $p < 0.001$, $r = -0.5$, respectively; fig. 1).

Discussion

The current investigation showed the following two major findings: (1) patients with AMD had decreased olfactory abilities, especially in odor discrimination and odor identification, even at early stages compared to controls, whereas AMD patients had decreased olfactory abilities in all subtasks of olfactory testing in advanced stages of AMD disease, and (2) as the visual acuity of AMD patients decreased, the olfactory abilities of these patients worsened.

To the best of our knowledge, this study was the first regarding the association between olfactory dysfunction and AMD. There are several possible mechanisms for the association between AMD and olfactory impairment. Olfactory dysfunction is known to be a common and early symptom of many neurodegenerative diseases, particularly PD and AD [1]. AMD shares common similar path-

Fig. 1. Visual acuity scores (logMAR) had a significant correlation with the sum score of olfactory testing (TDI) in patients with AMD. Scatter plot graph modeling (black – controls; red – early-stage AMD; green – late-stage AMD; color in online version only).

ological risk factors with PD and AD, including aging, smoking, oxidative stress, chronic inflammation, and intra- and extracellular deposits. The results of recent studies on the diseases of aging such as AMD, PD, AD, and atherosclerosis demonstrated that they have a common feature – the buildup of extracellular deposits (containing many shared molecular constituents) that contribute to their pathogenesis and progression. An association is explained with the local activation of proinflammatory pathways, thereby leading to the concurrent deposition of activated complement components, acute phase reactants, immune modulators, and other inflammatory mediators in these degenerative diseases [15–18].

The neuropathological changes that cause these neurodegenerative diseases might also affect the olfactory epithelium, olfactory bulb/tract, primary olfactory cortices, and their secondary targets by increasing the accumulation of pathological proteins, oxidative stress and neuroinflammation [1]. Oxidative stress plays an important role in neurodegeneration, and cases of increased oxidative damage within the olfactory neuroepithelium of patients with AD have been reported [19]. Hawkes et al. [20] examined the functional and morphological aspects of olfaction in motor neuron disease. The pathological results showed marked accumulation of lipofuscin in olfactory neurons compared to controls. Lipofuscin refers to a diverse group of autofluorescent lipid and protein aggregates which is derived from the imbalance between the production of damaged cellular components and degradation. Its presence in increased amounts is associated with oxidative tis-

sue damage. Lipofuscin granules can contain toxic compounds such as N-retinyl-N-retinylidene ethanolamine (A2E) which can lead to cellular dysfunction [21]. Lipofuscin also plays an important role in AMD pathogenesis. Lipofuscin accumulates in the retinal pigment epithelium cells and is reported to photochemically generate reactive oxygen species, including singlet oxygen, hydrogen peroxide and superoxide anions that may increase oxidative damage in the retinal pigment epithelium [8].

Nitric oxide (NO) is an important cellular signaling molecule that acts as a neuromodulator. However, excess NO is able to form other reactive intermediates, including nitrite and peroxynitrite, which can cause neurodegeneration by increasing oxidative and nitrosative stress [22]. Murdaugh et al. [23] reported that 3-nitrotyrosine (a neurochemical marker of peroxynitrite) and nitrated A2E levels increase in human Bruch's membrane with age. Yang et al. [24] examined the age-related changes in 3-nitrotyrosine in the olfactory bulb of mice. They found increased 3-nitrotyrosine expression in mitral and tufted cells in the olfactory bulb of aged mice. Taken together, these findings suggest that nitrosative stress in Bruch's membrane and olfactory bulb may play a potential role in the pathogenesis of AMD and olfactory dysfunction.

A meta-analysis study about the effect of AD and PD on olfaction indicated that AD and PD patients are more impaired in odor identification and discrimination than in odor threshold tasks. PD patients are more impaired in detection thresholds than AD patients, suggesting that PD patients are more impaired in low-level perceptual olfaction tasks, whereas AD patients are more impaired in higher-order olfactory tasks involving specific cognitive processes [25]. Our results resemble those of the meta-analysis study.

Since sensory problems may affect an older person's ability to carry out routine activities that define social roles and quality of life, olfactory impairment is more important for AMD patients. AMD patients have significantly

more difficulty when shopping, managing money, preparing meals, performing light housework, and using the telephone than community adults of similar age. Diminished vision is also associated with increases in hip fractures, falls, depression, physician visits, hospitalizations, and mortality [26]. The sense of smell plays an important role in human daily life, for example, by alerting us against and attracting us toward odorous items, influencing food intake, and affecting interpersonal relations. Impairment of olfactory ability, therefore, leads to disturbances in important areas, mainly in food enjoyment and in detecting harmful food, smoke and environmental hazards. Olfactory impairment is also associated with depressive symptoms and poorer quality of life [27]. Combined visual and smell disorder may cause more impairment of life quality.

Conclusion

This study demonstrated that AMD had significant negative effects on all orthonasal olfactory tasks, particularly in advanced stages. Similar to other neurodegenerative diseases, odor discrimination and identification seemed to be more affected than odor detection threshold tasks.

Potential limitations of our study should be mentioned. First, it was a case-control study with a small number of subjects. Second, we used only psychophysical tests for assessing the olfactory system. Electrophysiological and imaging procedures could be used for assessment. Further studies, with a large number of subjects, are needed to understand the relationship between visual and olfactory impairment in older patients.

Disclosure Statement

The authors have no conflicts of interest to declare.

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