Olfactory dysfunction in mild cognitive impairment and early stage of Alzheimer disease.

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Abstract

Background: There is a rapidly increasing prevalence of dementia which requires simple and reliable tests to help diagnose the disease especially at an earlier stage. In our study, we aimed to evaluate the predictive value of testing olfactory functions for diagnosing the mild cognitive impairment (MCI) and the early stage of Alzheimer Disease (AD) and to explore the correlations of olfactory functions with neuropsychological battery.

Materials and methods: In current study the participants were separated in three distinct groups. The control group consisted of 19 healthy volunteering participants, the MCI group included 18 subjects and the AD group consisted of 11 selected subjects. Sniffin Sticks Test Battery (SSTB) was performed to assess the olfactory functions. For cognitive evaluation, Mini Mental State Examination (MMSE), Clock Drawing test (CDT), three words three shapes (TWTS), enhanced cued recall test (ECRT) and Geriatric Depression Scale (GDS) was performed.

Results: The scores for identifying and differentiating olfaction were significantly varied across the groups. Subjects in the MCI group performed better than the early AD group and healthy group performed better than the MCI group. Olfactory dysfunction also correlated with the cognitive decline which has been revealed in neuropsychological tests in the early AD group.

Conclusion: We concluded that the Sniffin Sticks test has significant diagnostic and screening feature for MCI and early AD.

Keywords: Alzheimer disease, Mild cognitive impairment, Sniffin Sticks battery.

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Introduction

The growth in ageing population in recent years has resulted in increasing prevalence of dementia. Alzheimer Disease (AD) is the most common cause of dementia [1] particularly, among the aged population. The most accurate way to diagnose AD is to analyze histopathological changes showing amyloid plaques and neurofibrillary bundles. However, in practice, the diagnosis is often based on clinical history, neuropsychological evaluation and imaging. Pathological changes that lead to AD and its affect on cognition would have been occurred, resulting in mild cognitive impairment (MCI), years before the diagnosis of AD [2]. Clinically, MCI is defined as impairment in cognitive areas in someone with formal education. Generally, this slightly impacts daily life but it may progress to the stage of dementia undetected and undiagnosed. Mild cognitive impairment is divided into three types which the amnestic type is the most closely related and the one with a risk of 10-15% of progression to AD [3-5].

Changes of degeneration in AD which are seen in the entorhinal, hippocampal and subicular complexes are known to start early whilst the patient is showing signs of MCI [6]. Neurofibrillary tangles and amyloid-beta depositions are cited in these areas as well as within the olfactory neuron epithelium [7,8]. Smell interpretation originates in the olfactory bulbus, following through the olfactory tract and then to the olfactory cortical areas. These cortical areas consist of the piriform cortex, amygdala and the entorhinal cortex and also information enters to the subcortical areas (ventral striatum and ventromedial hypothalamus). In addition there is protrusion into the secondary olfactory areas such as the hippocampus and the orbitofrontal cortex [9].

Clinical studies have found a significant association between olfactory impairment and subsequent cognitive decline. A large scale study on the relationship between olfactory identification ability and general cognitive functioning (as measured by Mini Mental State Examination (MMSE) indicated that olfactory dysfunction
at baseline was significantly predictive of future cognitive impairment after 5 years [10]. Olfactory dysfunction has been reliably demonstrated in AD and MCI [11-15]. Odor identification performance has been shown to predict cognitive decline those with increased genetic risk for AD based on their apolipoprotein E genotype and MCI [16]. There are also animal studies which showed the pathological depositions, related to the neurodegenerative disease, in the olfactory system. Wesson et al. have demonstrated amyloid-beta deposition (Abeta) throughout the olfactory system in mice with AD model and have also found the deposition within the olfactory bulb earlier than deposition within any other brain region which supports the significant association of olfactory dysfunction with the risk of future AD and AD neuropathology burden in the brain [17]. Cassano et al. have showed severe deficits in odor-based memory, without gross changes in general odor-ability in the triple-transgenic murine model of Alzheimer's disease. Aβ and tau immunoreactivity was not observed in the primary processing regions for odor (the olfactory bulb), whereas marked immunostaining was present in the piriform, entorhinal, and orbitofrontal cortex, as well as in the hippocampus [18]. The results of complex pathophysiological changes all come to the conclusion of impaired olfaction in AD which guides our hypothesis that screening olfaction can be a biomarker to detect AD particularly at an earlier stage. Thus, the overall goal of this study, was to demonstrate the olfactory dysfunction in MCI and early AD and evaluate the predictive value of olfactory tests for screening and diagnosing MCI and early stage of AD.

Materials and Methods

This study is a prospective study including a total of 48 participants. Nineteen volunteered healthy participants were selected and 29 patients who attended the dementia clinic at Ankara Research and Training Hospital were selected for the study. The study was approved by the Human Research Ethics Committees of the associated institutions and participants were provided with informed consent before the assessment.

The participants were separated in three distinct groups. The control group consisted of 19 healthy volunteering participants, above 50 years of age with an education level of at least 5 years, with no complaints of cognitive or functional decline and who did not meet the criteria for either MCI and/or dementia. MMSE score [19,20] for the control group was 30 and at the neuropsychological tests they have performed better than 1.5 standard deviations below the mean of their age group according to the published data. The MCI group including 18 subjects was also above 50 years of age with an education level of at least 5 years who has reported a decline in their cognitive ability particularly at memory. Subjects in the MCI group were assessed by the Peterson MCI criteria [21] which were particularly amnestic MCI and scored 26 or above in MMSE, with a score of 0.5 in Global Clinical Dementia Rating Scale [22]. The AD group which consisted of 11 selected subjects was also above 50 years of age and with an education level of at least 5 years with an MMSE score of 24 or below. These patients were diagnosed with probable AD by the standards of the Association for Neurological Disorders and Stroke, Alzheimer Disease and Related Disorders (NINCSD-ADRDA) [23] and were assessed to have a score of 1 in Clinical Dementia Rating Scale.

Full and comprehensive data on the patients were collected to cover detailed medical history, personal information and educational background. Participants were asked to go through various laboratory tests (complete blood count, sedimentation rate, liver and kidney function tests, level of thyroid stimulating hormone and vitamin B12) including nasal examination and cranial Magnetic Resonance Imaging. Participants with a diagnosis of past traumatic brain injury, stroke, on-going psychiatric illness, nasal surgery, liver or kidney failures, chronic obstructive lung disease, diabetes, thyroid disease, alcohol or tobacco dependency and epilepsy were excluded from the study.

MMSE, Enhanced cued recall test (ECRT) [24], three words, three shapes test (TWTS) [25,26] and clock drawing test (CDT) [27] were also carried out to assess patients for cognitive ability. The tests were sensitive and specific to help identify participants with mild cognitive impairment, and those with AD from the elderly who had no dementia. Geriatric Depression Scale (GDS) [28,29] was also used to distinguish depression in the elderly which closely resembles dementia.

‘Sniffin Sticks’ battery test (SSBT) was applied to all of the participants to evaluate odor identification and odor discrimination. This is a test to detect nasal chemo sensory performance based on pen like odor dispensing devices. The assessment for odor discrimination, 16 triplets of pens were presented, with 2 containing the same odorant and 1 containing the target odorant. The subjects’ task was to identify the sample that had a different smell. To prevent visual detection of the target pen, subjects were blindfolded. Subjects were only allowed to sample the odor once. Presentation of triplets was separated by at least 30 s. The test result was a sum score of correctly identified pens. Odor identification was assessed by means of 16 common odors. Using a multiple forced-choice paradigm, identification of individual odors was performed from a list of 4 verbal descriptors each. Each odorant was presented by the experimenter and there was an interval of at least 30 s to prevent olfactory desensitization. Subjects were free to sample the odors as often as necessary to make a decision. The test result was a sum score of the correctly identified odors [30,31].

Statistical Methods

All data were expressed as the mean ± SD (Standard Deviation). All statistical analyses were carried out by SPSS (version 11.5) and the Pearson correlation factor was used.
to calculate correlation between the neuropsychological test results and the smell assessment scores. To compare variables between groups one way Anova and Duncan test has been used. Multivariates analyse and Discriminate has been used to discriminate tests between groups.

**Results**

A total of 48 volunteered participants were selected for the study where 19 were in the healthy control group, 18 were diagnosed with MCI and 11, with early stage of AD. The summary of group characteristics and test scores of MMSE, CDT, GDS, SSTB are shown in Table 1. All participants were above 50 years of age and there were 27 (56.25%) male and 21 female participant (43.75%). The mean age of the participants were respectively 60.20 ± 1.8 years for the control group, 68.11 ± 1.78 years for the MCI group and 75.36 ± 6.51 years for the early AD group. The level of education for all subjects was between 5 years and 15 years. The 73.7% of the subjects included in the control group had an education level above 8 years. The 22.3% of the subjects who were diagnosed with MCI and 27.3% diagnosed with probable early AD had an education level above 8 years.

There was a significant difference between the MMSE mean scores of the groups. The mean scores of the CDT of the control and the MCI group were comparable. Yet in AD group CDT mean score was significantly lower than the control and the MCI group scores. The GDS mean scores between the groups were insignificant and also the mean score of the test within the groups were below the cut off score to diagnose depression in subjects. In TWTS test in the parameters described in Table 2 the MCI group performed significantly higher scores than the early AD group and the healthy group significantly performed higher scores than the MCI group. In ECRT test scores of Table 3, the shape copying, acquisition of word, recognition accuracy of shape and word were comparable between the healthy and the MCI group but were significantly lower in

<table>
<thead>
<tr>
<th>Table 1. Summary of group characteristics and test scores.</th>
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<tbody>
<tr>
<td><strong>CONTROL (n: 19)</strong></td>
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<td>---------------------</td>
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<tr>
<td><strong>Age</strong> (in years)(mean)</td>
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<tr>
<td><strong>Gender (M/F) (n)</strong></td>
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<tr>
<td><strong>MMSE(mean scores)</strong></td>
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<td><strong>GDS (mean scores)</strong></td>
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<td><strong>Clock Drawing (mean scores)</strong></td>
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<td><strong>Olfactory identification (mean scores)</strong></td>
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<td><strong>Olfactory Discrimination (mean scores)</strong></td>
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<tr>
<td><strong>Education (years)</strong></td>
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<tr>
<td><strong>Mean education (years)</strong></td>
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</tbody>
</table>

*a, b, c* There were significant difference between groups (Control group>MCI group>AD group) in MMT, Clock drawing, olfactory identification and olfactory discrimination scores (P<0.05)

*a, b, c* There were no significant difference between the control group and MCI group, but there were significant difference between the control group and AD group and MCI group and AD group in GDS scores

<table>
<thead>
<tr>
<th>Table 2. Scores of the TWTS battery within the groups</th>
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<tbody>
<tr>
<td><strong>Control</strong></td>
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<tr>
<td><strong>Shape copying</strong></td>
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<tr>
<td><strong>Word copying</strong></td>
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<tr>
<td><strong>Incidental recall of shape</strong></td>
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<tr>
<td><strong>Incidental recall of word</strong></td>
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<tr>
<td><strong>Acquisition of shape</strong></td>
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<td><strong>Acquisition of word</strong></td>
</tr>
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<td><strong>Trial number</strong></td>
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<tr>
<td><strong>Delayed recall of shape</strong></td>
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<tr>
<td><strong>Delayed recall of word</strong></td>
</tr>
<tr>
<td><strong>Recognition accuracy of shape</strong></td>
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<tr>
<td><strong>Recognition accuracy of word</strong></td>
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</tbody>
</table>

*a, b, c* there is significant difference between the groups (P<0.05)

*a, b, c* there is not significant difference between the control group and the MCI group, there is significant difference in the AD group compared to the control and MCI group (P<0.05)

*a, b, c* there is not significant difference between the control group and the MCI group, no significant difference between the MCI and the AD group, there is significant difference between the control and the AD group (P<0.05)
Olfactory dysfunction in mild cognitive impairment and early stage of Alzheimer disease.

The AD group when compared with the MCI and healthy groups. In addition in ECRT there was a significant difference at the scores of first, second, third, total free recall and total recall scores between the groups. The MCI group performed higher scores than the early AD group and the healthy group performed higher scores than the MCI group. There was not a significant difference at the scores of first, second and total cued recall between the groups.

There was a significant difference in olfactory identification and discrimination scores between the groups (Table 1). Olfactory test results showed significant correlation with the neuropsychological tests only in the AD group. With TWTS, as scores for shape copying which shows visuospatial and copying ability, decreased in the early AD, olfactory discrimination score deteriorated. Also, with ECRT, as first, second and third free recall scores which show instant, recent and remote memory functions, decreased, olfactory discrimination score worsened. In ECRT, as total recall scores decreased, olfactory identification score deteriorated. Figure 1 shows the multivariate analysis and discrimination of the tests between groups. The best discriminating tests across the groups were as follows: Total recall and third free recall parts in the ECRT and word recognition part of the TWTS test and eventually olfactory identification.

**Discussion**

It is found that there are significant neurochemical changes particularly at cholinergic system in some age related neurodegenerative diseases. These changes are likely present prior to the onset of neuropathology and cognitive and motor phenotypes are associated with diseases like AD and PD. This implies that some such changes may prime the organism or lower the threshold for adverse influences from neural insults, mutations and other deleterious factors and could be, in fact, a critical substrate for the so-called 'preclinical' stages of these diseases. Importantly, such neurochemical changes may be region specific, preferentially involving, for example, limbic structures early in the aging process like in AD [32]. AD is neuropathologically classified in accordance with the Braak and Braak staging criteria. According to this, in the early stages the neurofibrillary tangles are first seen in the entorhinal cortex [33], an area of the brain that is important in the processing of olfactory information [34]. There are also different studies that have found a strong association between tau pathology in olfactory system, Braak staging of AD pathology and cognitive decline [35]. Furthermore it is found that acetylcholine is intimately involved in the modulation of olfactory function such as increasing contrast and synchronization of odor induced activity from the olfactory bulb to the piriform cortex and facilitating attention, odor learning, memory and cortical plasticity [36]. Anosmia is correlated with wide spread changes in gray matter within olfaction related structures, including the piriform cortex, insular cortex, orbitofrontal cortex, medial prefrontal cortex, hippocampus, parahippocampal gyrus, supramarginal gyrus, nucleus accumbens, subcallosal gyrus and the medial and dorsolateral prefrontal cortices [37]. These anatomical regions are

**Table 3.** Scores of the ECRT battery within the groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shape copying</td>
<td>14.68 ± 0.58 (SD)</td>
<td>13.94 ± 1.34 (SD)</td>
<td>11.73 ± 3.19 (SD)</td>
</tr>
<tr>
<td>Word copying</td>
<td>15.00 ± 0.00 (SD)</td>
<td>14.59 ± 1.20 (SD)</td>
<td>13.27 ± 3.19 (SD)</td>
</tr>
<tr>
<td>Incidental recall of shape</td>
<td>14.00 ± 1.76 (SD)</td>
<td>9.00 ± 5.53 (SD)</td>
<td>3.00 ± 4.21 (SD)</td>
</tr>
<tr>
<td>Incidental recall of word</td>
<td>12.84 ± 4.48 (SD)</td>
<td>8.28 ± 6.13 (SD)</td>
<td>3.36 ± 5.10 (SD)</td>
</tr>
<tr>
<td>Acquisition of shape</td>
<td>14.74 ± 0.45 (SD)</td>
<td>11.06 ± 3.55 (SD)</td>
<td>5.82 ± 4.66 (SD)</td>
</tr>
<tr>
<td>Acquisition of word</td>
<td>14.95 ± 0.22 (SD)</td>
<td>13.11 ± 3.77 (SD)</td>
<td>6.45 ± 6.02 (SD)</td>
</tr>
<tr>
<td>Trial number</td>
<td>1.32 ± 0.82 (SD)</td>
<td>2.72 ± 1.77 (SD)</td>
<td>4.00 ± 1.61 (SD)</td>
</tr>
<tr>
<td>Delayed recall of shape</td>
<td>14.74 ± 0.45 (SD)</td>
<td>10.17 ± 4.57 (SD)</td>
<td>3.00 ± 4.62 (SD)</td>
</tr>
<tr>
<td>Delayed recall of word</td>
<td>14.95 ± 0.22 (SD)</td>
<td>6.89 ± 5.74 (SD)</td>
<td>1.64 ± 3.66 (SD)</td>
</tr>
<tr>
<td>Recognition accuracy of shape</td>
<td>15.00 ± 0.00 (SD)</td>
<td>14.17 ± 3.53 (SD)</td>
<td>9.27 ± 6.38 (SD)</td>
</tr>
<tr>
<td>Recognition accuracy of word</td>
<td>15.00 ± 0.00 (SD)</td>
<td>12.22 ± 3.52 (SD)</td>
<td>8.18 ± 7.16 (SD)</td>
</tr>
</tbody>
</table>

a,b,c there is significant difference between the groups (P<0.05)
also selectively involved in neurodegenerative diseases such as Frontotemporal dementia, semantic dementia and corticobasal degeneration. Therefore olfactory impairment is also associated with these disorders [38]. Related to the neurochemical and neuropathological changes going on in AD, tests to check for a possible dysfunction in olfaction could be used to diagnose the early phase of the disease like MCI [39-43]. Fusetti et al. have found olfactory impairment in amnestic MCI patients whom 31% developed AD. These patients had lower olfaction scores than the patients who did not develop AD. In addition odor discrimination and identification performance correlated with the performance on neuropsychological tests which resembles our study [44]. It has been suggested that olfactory discrimination and identification are more closely associated with higher cognitive functions while olfactory threshold is strongly related to sensory capability [45]. Furthermore Schab noted that olfactory identification may represent semantic memory function and also some researchers suggest that is primarily predictive of memory decline [42,46].

In our study we have performed odor identification and discrimination and have found significant changes at the scores of the participants diagnosed with early phase of AD and MCI when compared with the healthy subjects. The MCI group significantly performed worse at odor identification and discrimination in SSBT compared with the healthy subjects but performed better than the AD group. In addition the neuropsychological tests used in our study to diagnose MCI and AD, also showed significant results to discriminate MCI from the healthy subjects. MMSE, TWTS and ECRP test scores showed significant decrease in cognitive functions between the groups. MCI group performed better than the early AD group and healthy group performed better than the MCI group. The scores of incidental recall and delayed recall of shape and word which represent episodic memory were significantly different between the groups which the MCI group performed better than the early AD group and the healthy group performed better than the MCI group. It is known that spontaneous retrieval and delayed recall of information over time were the components of memory, most affected in AD [25]. Importantly there was a significant correlation of the neuropsychological tests with the SSBT in the AD group. Results of the tests implicated that when there is deterioration in instant, recent and remote memory functions, visuospatial and copying skills, scores of olfactory identification and discrimination showed significant impairment. This supports the pathophysiological changes in AD and its correlation with the olfactory dysfunction. We have also found that the best discriminating tests across the groups were total recall and third free recall parts in the ECRT and word recognition part of the TWTS test and eventually olfactory identification. Sohrabi et al. have also used SSBT to predict cognitive decline. They have found significant correlation between olfactory discrimination and decline in cognitive functions which also supports the usage of the battery in screening dementia[46]. In studies by Devenand et al. they have shown that subjects diagnosed with MCI were found to have unsuccessful olfaction scores but if they were not aware of the abnormality in olfaction, risk of developing AD was higher [47]. In our study, the subjects either in healthy or in the MCI group were unaware that they had a smell deficit. These subjects continue to be monitored and any progression to AD will be assessed in the future [48].

Our study had some limitations that should be considered. First the number of the participants in the groups were low and the subjects were divided into MCI and early stage of AD based on neuropsychological measures. However the tests we have used have high sensitivity to detect cognitive dysfunction and with this study we have observed significant association between olfaction and cognitive decline among the groups. In addition the mean age increased at the MCI and the AD group compared with the healthy subjects.

There is surely a decrease in olfactory functions with age but the complex pathological changes differ at olfactory system or related cortical areas in neurodegenerative diseases [49]. Furthermore olfactory deficits can be different in several neurodegenerative diseases. Rahayel et al. have found that Parkinson disease patients are more impaired on low level perceptual olfactory tasks whereas AD patients are more strongly impaired on higher order olfactory tasks involving specific cognitive processes [50].

In conclusion, olfactory tests are easy, practical and reliable to use and to administer on any patient, irrespective of gender and educational background. There is an association between olfactory impairment and ongoing cognitive decline accompanying neurodegenerative diseases. In this study it has been found that screening olfaction can be used as a biomarker to detect early stage of AD.

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References


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