Neurol Sci (2005) 26:156–160
DOI 10.1007/s10072-005-0453-2

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Olfactory screening test in mild cognitive impairment

Received: 12 December 2004 / Accepted in revised form: 16 June 2005

Abstract Mild cognitive impairment (MCI) is a transient status between physiologic ageing and dementia. Each year more than 12% of subjects with MCI develop Alzheimer's disease. This study evaluated the presence of an olfactory deficit in amnesic MCI (aMCI) patients. Twenty-nine patients diagnosed with aMCI and a homogeneous control group of 29 subjects were enrolled in the study. Olfactory function was assessed by the Sniffin' Sticks Screening Test (SSST) and the Mini Mental State Examination, the Clinical Dementia Rating, the Geriatric Depression Scale and the Mental Deterioration Battery were used to evaluate the neurocognitive status. aMCI patients showed a significant impairment of their olfactory identification compared to controls (SSST score: 8.3±2.1 *vs*. 10.8±0.9; $p<0.001$). These results suggest that olfactory tests should be part of the diagnostic armamentarium of pre-clinical dementia. A long-term follow up might confirm the olfactory identification function as an early and reliable marker in the diagnosis of pre-clinical dementia.

Key words Hyposmia • Mild cognitive impairment • Olfactory test

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Introduction

The social impact of neurodegenerative diseases is high: 5%–6% of the population over 65 years suffer from dementia and 50%–80% of it is represented by Alzheimer's disease [1–6]. Mild cognitive deficit is gaining more attention among neurologists and geriatrists. The term mild cognitive impairment (MCI) defines a transient condition that occurs along the progression from normal aging to dementia and comprises a broad clinical spectrum of pre-dementia stages. Standard MCI diagnostic criteria are the following: (1) subjective memory deficit, (2) pathologic performance in mnemonic testing in relation to age and level of schooling, (3) intact activities of daily living, (4) normal cognitive functions, (5) absence of dementia, and (6) lack of other diseases which impair or may alter memory [7–9].

Every year 12% of patients with MCI develop Alzheimer's disease, whereas the incidence of such progression falls to 1%–2% in controls of the same age [8]. Thus MCI patients are widely studied because an early diagnosis may guide towards a preventive treatment of Alzheimer's disease. Many studies have highlighted the close link of olfactory function with Alzheimer's disease [10–15]. The ability to identify different odours is altered in the early stages of Alzheimer's disease, while the olfactory threshold deteriorates later on [16, 17]. Olfactory identification is processed in the mesial structures of the temporal lobe and is more strictly involved in cognitive functions, whereas the olfactory threshold is mostly influenced by peripheral deficits of the sense of smell. A constant flow of cognitive and sensitive information from the associative areas is received by the entorhinal cortex and forwarded to the hippocampus. Here these data are processed and then transmitted back, through the entorhinal cortex, to the associative areas where ultimately they are codified as mnemonic traces. It has been shown that typical lesions of Alzheimer's disease (i.e., amyloid core and neurofibrillar tangles) are already detectable in the preclinical stages in central olfactory pathways [18]. Based on these anatomopathological findings it

has been hypothesised that an olfactory deficit could be present during preclinical phases and therefore used as an early diagnostic marker [19]. To assess olfactory function in aMCI patients we used an olfactory screening test: the Sniffin' Sticks test [20–22]. It was introduced in 1995 by Hummel and Kobal [20] and is composed of a screening test (SSST) and a complete test (SSET). The SSST has good sensitivity and specificity [21], it is easy to use and inexpensive. Although rarely employed in aMCI patients, this test is a useful and quick diagnostic tool in the evaluation of olfactory deficit.

Material and methods

This study evaluated the presence of an olfactory deficit in aMCI patients. All subjects were recruited in the Alzheimer Evaluation Unit of the Department of Neurology and Otorhinolaryngology of the University of L'Aquila and La Sapienza of Rome. We selected 29 patients with aMCI, 19 females and 10 males between the age of 61 and 80 years with a mean age of 71.6±5.3. Diagnosis of MCI was made according to Petersen's criteria [7]. All patients suffered from subjective cognitive deficit for more than 6 months; the schooling level was greater than or equivalent to 3 years, Mini Mental State Examination (MMSE) score >24, Clinical Dementia Rating (CDR) score=0.5 and Geriatric Depression Scale (GDS) >6. In the control group of 29 subjects, 18 females and 11 males between the age of 57 and 82 years with a mean age of 68.8±5.4 were selected. Both samples were matched by age, gender and education status.

Cognitive deficits different from aMCI and olfactory dysfunctions were considered exclusion criteria: patients with neuropsychiatric disorders (Parkinson's disease, schizophrenia, multiple sclerosis and depression), head trauma (with loss of consciousness greater than 15 min), patients who underwent maxillofacial surgery, with pathologies of the nose and paranasal sinuses (rhinosinusitis and polyposis, allergic rhinitis), with chronic obstructive pulmonary disease, asthma, active hepatitis, cirrhosis, chronic renal failure, vitamin B12 deficiency, alcohol and drug abuse, cerebral vascular accidents, insulin-dependent diabetes mellitus, hypothyroidism and Cushing syndrome were not included in the study.

All patients had an accurate medical history and physical examination including a detailed neurological and otorhinolaryngological examinations. Medical history including upper respiratory tract infections, neoplasia, surgical procedures and concomitant medical conditions was carefully evaluated. In addition, patients were screened for potential exposure to chemical agents, use of alcohol, alimentary habits, pharmacological history and family history of allergies and dementia. All patients and controls were non-smokers.

Renal, liver and thyroid functions were assessed as well as vitamin B12 levels. Patients were also asked to quantify the degree of olfactory deficit (reduced sense of smell, altered odour discrimination) to evaluate their awareness. All patients underwent CT scan or MRI of the brain to assess the presence and degree of cerebral atrophy and causes of secondary dementia. The neuropsychological functions were evaluated using the MMSE [23] and the Mental Deterioration Battery (MDB) [24]. The MMSE is a quick, simple and reliable screening test to assess the cognitive functions and to monitor the course of the disease. The scoring range is between 0 and 30 points and adjusted according to the age and level of schooling. The MMSE score >24 was utilised as a cut-off to discriminate subjects with MCI and patients with early dementia. The test, however, detects only as a whole the cognitive impairments and therefore cannot be used to distinguish different pathological processes. The MDB is an extensive battery including a wide range of tests to quantify the subjects' performances not only in memory tasks but also in other cognitive abilities such as language, praxis, reasoning abilities, visuo-spatial abilities and attention. The role of MDB is to discriminate with a high degree of accuracy between demented patients and normal elderly subjects; it also provides qualitative information over the potential cognitive deficit. Further inclusion criteria were the diagnosis of "questionable demented" (score=0.5) according to the CDR. Depressive symptoms were rated using the GDS with a score >6 as the cut-off to discriminate patients with depression.

In both the control and aMCI groups olfactory evaluation was carried out with the SSST. The SSST is a rapid subjective olfactory assessment that utilises 12 common odours (orange, leather, cinnamon, peppermint, banana, lemon, liquorice, coffee, cloves, pineapple, rose and fish) presented in felt-tip pens (sticks). A few hours prior to the test food intake is limited only to water. The subject is asked to identify among 4 written names of different odours the one smelled on a specific single-odour stick [21]. Based on the final score, adjusted for age and sex, subjects are classified into three categories: normosmic (>12), hyposmic (≤10), and anosmic (≤6). As opposed to neuropsychological tests, the smell test is not influenced by the level of schooling. We also studied the degree of subjective awareness of the olfactory deficit in hyposmic and anosmic patients with aMCI. The study was conducted according to the guidelines on biomedical research involving human subjects (Declaration of Helsinki). Informed consent was obtained from each patient and normal subjects.

Results

In the group of 29 aMCI patients 6 were normosmic (mean SSST score: 11.3, SD=0.52), 17 hyposmic (mean SSST score: 8.3, SD=1.00) and 6 anosmic (mean SSST score: 5.3, SD=0.82). Total mean SSST score was 8.3 (SD=2.1) and mean MMSE score was 26.1 (SD=1.3). In the control group of 29 subjects 19 were normosmic (mean SSST score: 11.4, SD=0.71) and 10 hyposmic (mean SSST score: 9.7, SD=0.71). The total mean SSST score was 10.8 (SD=0.9) and the mean MMSE score was 28.7 (SD=0.7). SSST and MMSE scores in both groups are summarised in Table 1. The mean SSST score was significantly lower in patients (8.3, SD=2.1) than in controls (10.8, SD=0.9) (Wilcoxon test: z=–4.4756, p<0.0001).

The aMCI patients were then further divided into 2 groups based upon MMSE scoring. The first group (score ≥26) of 15 patients included 4 normal, 10 hyposmic and 1 anosmic with a mean SSST score of 24.2 (SD=0.07). The second group of 14 patients (score <26) included 2 normal, 7 hyposmic and 5

Table 1 SSST and MMSE scores in normal subjects and in MCI patients. Data represent mean±SD

	Normal subjects (n=29)	aMCI patients (n=29)
Age, years	68.8±5.4	71.6±5.3
Score on SSST	10.8±0.9	8.3±2.1*
Score on MMSE	28.7±0.7	26.1±1.3

*Deficit of the olfactory function in aMCI patients compared with normal subjects (ζ=4.681, p<0.001)
aMCI, amnesic Mild Cognitive Impairment; *SSST*, Sniffin' Sticks Screening Test; *MMSE*, Mini-Mental State Examination

anosmic with a mean SSST score of 27.8 (SD=1.56). A Wilcoxon test was conducted to evaluate the significative difference of SSST scores between aMCI patients with MMSE score ≥26 and MCI patients with MMSE score <26. We found that MMSE scores ≥26 were related to higher SSST values as opposed to lower MMSE scores, which were correlated with lower SSST scores (z=–2.0723, p<0.0382).

Of the 29 aMCI patients, 23 were hypo-anosmic. Of these 23 patients only 3 patients had conscious impairments of their sense of smell (mean SSST score: 8.53±2.14, mean MMSE score: 26.16±1.36) while 20 patients were unaware and had shown lower olfactory test and MMSE scores (mean SSST score: 6.66±1.52, mean MMSE score: 25.6±1.0). Of the 29 controls, 10 were hyposmic and all of them were conscious of the impairment of their sense of smell.

We found a significative correlation between the SSST scores and MMSE scores in the 58 subjects (29 MCI patients and 29 controls) using the test of Spearman (r=0.54; p<0.0001).

In order to evaluate the diagnostic accuracy of the olfactory test the Receiver Operating Characteristic (ROC) analysis was applied. Using a cut-off of 10 for the SSST score we obtained a specificity of 72.41% and a sensitivity of 84.38% (Table 2, Fig. 1). The ROC analysis of the

Table 2 Measures of diagnostic accuracy of the SSST with a detailed report of sensitivity and specificity (ROC area 0.8427; 95% confidence interval: 0.744–0.941)

Cut-off point	Sensitivity, %	Specificity, %
(≥4)	100.00	0.00
(≥5)	100.00	3.45
(≥6)	100.00	10.34
(≥7)	100.00	20.69
(≥8)	100.00	34.48
(≥9)	96.88	51.72
(≥10)	84.38	72.41
(≥11)	62.50	82.76
(≥12)	25.00	96.55
(≥12)	0.00	100.00

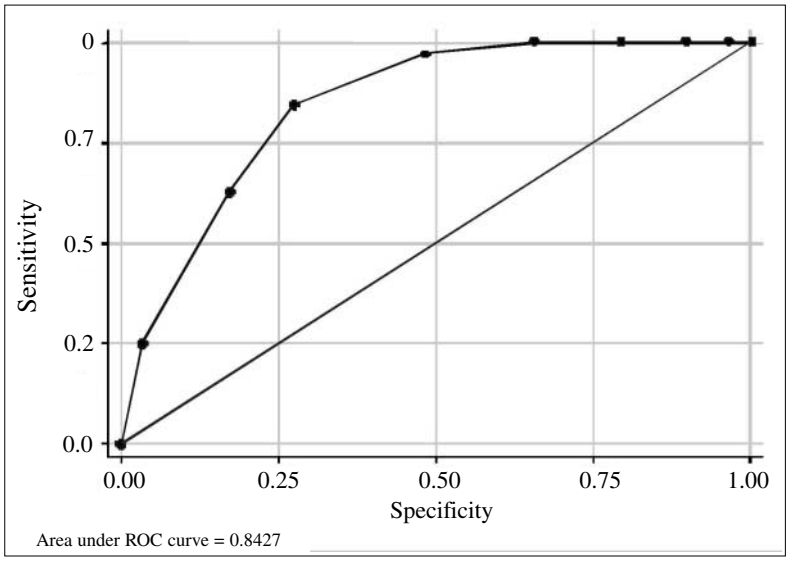

Fig. 1 Area under ROC curve indicates the discriminating ability of the olfactory screening test

SSST revealed a significant gap between aMCI patients and healthy control subjects (area under the ROC curve 0.8427, $p<0.001$)

The Mann-Whitney test (non-parametric comparison) was used to evaluate the statistical significance of the olfactory performance. We considered statistically significant a p value <0.01. The Mann-Whitney test showed a clear deficit of the olfactory identification function in aMCI patients compared to controls ($z=4.681$; $p<0.001$). Results were analysed using the computerised statistical package STATA version 8.

Discussion

Compared to previous reports [25, 26] employing different smell tests (University of Pennsylvania Smell Identification Test, Cross-Cultural Smell Identification Test) in this study the SSST has been used to assess the olfactory function in patients with aMCI. The SSST indicated that 19 out of 29 normal subjects were normosmic while only 6 out of 29 aMCI patients had normal olfactory function. This finding suggests that in aMCI patients a significant impairment of the olfactory identification function is present. Our data also show that a high number of aMCI patients are not aware of this deficit (20 over 23 aMCI hyposmic–anosmic). As pointed out by Devanand et al. [25], the relationship between olfactory deficit and lack of its awareness represents in MCI patients a greater risk of progression towards Alzheimer's disease: in this study [25] 77 aMCI patients were followed up; 19 were diagnosed with Alzheimer's disease by 2 years and 16 of 19 had low olfaction plus lack of awareness. This effect remained significant in Cox survival analyses after controlling age, sex, education and cognitive scores indicating that the results could not be explained by lack of attention or poor memory [25].

Because the sensitivity and specificity of the SSST is respectively 84.38% and 72.41% we suggest that the first screening level (SSST) may be followed by a complete smell test (SSET) to assess odour threshold, discrimination and identification, and the MMSE must always be associated to the MDB, CDR and GDS.

One and two-year follow up will be carried out with both neuropsychological and olfactometric assessments and those patients unaware of their olfactory deficit that will develop Alzheimer will be monitored.

In conclusion, the otorhinolaryngological evaluation and the SSST should be included in the diagnostic procedures of aMCI patients along with neuropsychological tests, ApoE and neuroimaging studies such as SPECT and MRI. Neuroimaging will help to identify early abnormalities of the entorhinal cortex and the hippocampus [27] in aMCI patients. Involvement of these brain areas could be revealed by a mild cognitive failure and by a selective deficit of olfactory identification. Further studies will verify the sensitivity and specificity of the olfactory test in the early diagnosis of Alzheimer's disease and indicate whether it may have a significant prognostic role in preclinical dementia. Longer follow-up periods and larger experimental groups are needed to reveal the neuroanatomical interpretation of the olfactory deficits in aMCI patients and the clinical utility of olfactory evaluation in the diagnostic procedures for Alzheimer's disease.

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