Journal of the Neurological Sciences 355 (2015) 174–179

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Olfactory function and neuropsychological profile to differentiate dementia with Lewy bodies from Alzheimer's disease in patients with mild cognitive impairment: A 5-year follow-up study

Jung Han Yoon *, Min Kim, So Young Moon, Seok Woo Yong, Ji Man Hong

Department of Neurology, Ajou University School of Medicine, Suwon, South Korea

ARTICLE INFO

Article history:
Received 2 February 2015
Received in revised form 5 June 2015
Accepted 8 June 2015
Available online 10 June 2015

Keywords:
Olfaction
Cognition
Dementia with Lewy bodies
Alzheimer's disease
Mild cognitive impairment

ABSTRACT

Background: Mild cognitive impairment (MCI) is a well-known precursor of Alzheimer's disease (AD) but often also precedes dementia with Lewy bodies (DLB). The early differentiation of DLB from AD is important to delay disease progression. Olfactory dysfunction is a well-known early sign of both AD and Lewy body disorders, including Parkinson's disease (PD) and DLB. Thus, the aim of the present study was to determine whether olfactory and neuropsychological tests can aid in the differentiation of DLB from AD at the MCI stage.
Methods: The present study included 122 MCI patients who were monitored until they developed dementia or until their condition stabilized; the follow-up period averaged 4.9 years (range: 3.9–6.2 years). Baseline olfactory function as measured with the Cross-Cultural Smell Identification (CCSI) test and neuropsychological data were compared.
Results: During the follow-up period, 32 subjects developed probable AD (MCI-AD), 18 had probable DLB (MCI-DLB), 45 did not convert to dementia (MCI-stable), and eight developed a non-AD/DLB dementia. The mean CCSI score (95% confidence interval [CI]) in patients with MCI-DLB (4.6; 95% CI: 4.0–5.3) was significantly lower than that of MCI-AD patients (6.4; 95% CI: 6.0–6.7, $p < 0.001$) and MCI-stable patients (7.3; 95% CI: 6.9–7.8, $p < 0.001$). The area under the curve of the receiver operating characteristic to discriminate MCI-DLB from MCI-AD using CCSI scores was (0.84; 95% CI: 0.72–0.97). Frontal-executive function and visuospatial ability was worse in patients with MCI-DLB, while verbal recognition memory impairment was greater in those with MCI-AD.
Conclusion: Olfactory and neuropsychological tests can help predict conversion to DLB or AD in patients with MCI.

1. Introduction

Mild cognitive impairment (MCI) is a transitional state between normal aging and dementia and its diagnosis aids in the detection and treatment of different types of dementia, especially AD, in the earlier stages. Generally, amnestic MCI is a risk factor for conversion to AD, and numerous studies have shown that specific patterns of neuroimaging data, cerebrospinal fluid (CSF) markers, and neuropsychological testing in MCI patients can predict the progression to AD [1]. Although a significant amount of attention has been given to early-stage AD, very little is known about the pre-dementia MCI stage of dementia with Lewy bodies (DLB). Several recent reports have shown that MCI precedes the classic manifestation of symptoms that are required for a DLB diagnosis [2–6]. These findings highlight the importance of identifying MCI patients with a high risk of progression to DLB and differentiating them from those at a risk of AD to enable early treatment or to delay disease progression [7].

A clinical diagnosis of DLB in the early stages, and even in the later stages, can be difficult because not all patients display all of the core clinical features, and some features overlap with those of AD to some extent [8–11]. In the earliest stages of DLB when the symptoms are mild, making a diagnosis can be difficult due to the low sensitivity of the current clinical diagnostic criteria [12]. Additionally, mild parkinsonian signs are frequently seen in patients with MCI [10]. As a result, DLB tends to be either underdiagnosed or misdiagnosed as AD [13]. To improve the accuracy of the DLB diagnosis, various imaging methods such as brain perfusion SPECT, cardiac MIBG and electroencephalogram [11,14,15], have been suggested, but simple markers are also needed to assist with the accurate identification of DLB in its early stages.

Impairments in olfactory function are a well-known symptom of LB disorders such as Parkinson's disease (PD) and DLB, and may aid in the differentiation of these disorders from other parkinsonian syndromes including corticobasal degeneration, progressive supranuclear palsy, and multiple systemic atrophy, which all are associated with preserved or mildly impaired olfaction [16,17]. Olfactory dysfunction is also associated with AD in the preclinical stage, although this dysfunction is

* Corresponding author at: Department of Neurology, Ajou University School of Medicine, 5 San, Woncheon-dong, Yongtong-gu, Suwon-si, Kyunggi-do 442-749, South Korea.
E-mail address: jhyoon@gmail.com (J.H. Yoon).

http://dx.doi.org/10.1016/j.jns.2015.06.013
0022-510X/

Table 1
Baseline demographic characteristics of MCI-AD, MCI-DLB, and MCI-stable patients.

Characteristics	MCI-AD (n = 32)	MCI-DLB (n = 18)	MCI-stable (n = 45)	p-Value
Age (years)	71.2 (5.0)	69.8 (6.4)	69.2 (6.2)	NS
Gender (number of males, %)	14 (43.7%)	8 (44.4%)	22 (48.8%)	NS
Education duration (years)	7.8 (3.5)	8.2 (3.8)	8.5 (3.6)	NS
K-MMSE	24.7 (2.8)	25.0 (2.4)	25.7 (2.0)	NS
CDR	0.5 (0.0)	0.5 (0.0)	0.5 (0.0)	NS
CDR-SB	1.7 (0.3)	1.6 (0.3)	1.4 (0.7)	NS
UPDRS, motor	1.3 (1.6)	4.4 (2.5)[a,b]	1.4 (1.6)	<0.05
History of RBD	2 (6.2%)	12 (66.7%)[a,b]	4 (8.9%)	<0.05

Values are expressed as mean (standard deviation) or number (percentage). MCI, mild cognitive impairment; DLB, dementia with Lewy bodies; AD, Alzheimer's disease; K-MMSE, Korean version of the Mini-Mental State Examination; CDR, Clinical Dementia Rating Scale; CDR-SB, sum of the box score of CDR; UPDRS, Unified PD Rating Scale; RBD, REM sleep behavior disorder. Significant differences between [a]MCI-DLB and MCI-AD and [b]MCI-DLB and MCI-stable.

more likely to be due to problems identifying odors than detecting them [18,19]. While several studies have shown that DLB patients have a diminished ability to identify smells, as compared to patients with AD [20,21], it remains unclear whether this is evident at the MCI stage because no clear definition of the presymptomatic neuropathological precursors of DLB exists as yet. Therefore, the present study aimed to assess whether the Cross-Cultural Smell Identification (CCSI) test and comprehensive neuropsychological tests can differentiate DLB from AD at the MCI stage.

2. Patients and methods

2.1. Subjects

The present study initially recruited 328 participants who were selected from a prospective study on the usefulness of olfaction tests in patients with cognitive impairments that was carried out in outpatient memory clinics. Of the 328 participants, 99 had AD, 39 had vascular dementia, 24 had DLB, 24 had subjective cognitive impairments, and 142 had MCI. All patients underwent a baseline neurological examination, comprehensive neuropsychological assessments, a routine blood analysis, and a brain magnetic resonance imaging (MRI) scan. From this cohort, 122 patients with MCI were selected. The exclusion criteria consisted of the following: (1) focal brain lesions, diffuse white matter hyperintensities, or multiple lacunae in the basal ganglia evident on an MRI scan, (2) clinical diagnostic criteria compatible with PD, including at least two of the four cardinal features (bradykinesia, rigidity, tremor, and postural instability), (3) past use of drugs that could cause parkinsonism (antipsychotics, gastrointestinal motility enhancers, anti-epileptics, or L-type calcium channel blockers), and/or (4) a history of head trauma, nasal fracture, rhinitis, sinusitis, nasal polyps, or a recent history of a common cold. Possible medical comorbidities were also excluded by laboratory tests including a thyroid function test, assessments of vitamin B12 and folic acid levels, and the Venereal Disease Research Laboratory VDRL test for syphilis. Smell identification was assessed using the CCSI test, a widely used test of odor identification involving a scratch-and-sniff test of 12 microencapsulated odorants with a forced choice of four alternatives per item; a high score indicates a good olfactory performance [22].

Subjects were diagnosed with MCI if their performance in at least one of five cognitive domains on the Seoul Neuropsychological Screening Battery (SNSB) was abnormal [23,24]. The SNSB evaluates attention, language, praxis, visuoconstructive function, verbal and visual memory, and frontal/executive function. Quantifiable tests on the SNSB include the digit span (forward and backward) test, Korean version of the Boston Naming Test (K-BNT), 20 Rey Complex Figure Test (RCFT; copying, immediate, and 20-min delayed recall and recognition), Seoul Verbal Learning Test (SVLT; three learning-free recall trials of 12 words, a 20-min delayed recall trial for the same 12 words, and a recognition test), phonemic and semantic controlled oral word association test (COWAT), go-no-go test and contrasting program, and Stroop tests (word and color reading of 112 items during a 2-min period). The scores on these quantifiable cognitive tests were classified as abnormal if they were below the 16th percentile for age-, sex-, and education-matched normal subjects (based on a pool of 447 subjects). All patients had scores above the 16th percentile, as compared to age- and education-matched normal subjects on the Korean version of the Mini-Mental State Examination (K-MMSE) and did not exhibit any evidence of difficulties with day-to-day life, as judged clinically by an Activities of Daily Living (ADL) scale [25]. The present study was approved by the local ethical committee at Ajou University Hospital and written informed consent was obtained from all participants.

2.2. Clinical follow-up

Subjects with MCI were followed-up at least twice per year. DLB was diagnosed using the 2005 revised criteria [12] and AD was diagnosed using the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) [26]. During follow-up, patients with stable cognitive function were classified as MCI-stable, patients with probable AD were classified as MCI-AD, and patients with probable DLB were classified as MCI-DLB. Five patients with DLB underwent cardiac [^{123}I]-MIBG scintigraphy and all five showed decreased MIBG uptake on the delayed image. Nine MCI patients with DLB underwent [^{18}F]-fluoropropyl-CIT positron emission tomography (PET) scans and all showed decreased dopamine transporter uptake in the posterior putamen. Subjects were considered to have fluctuating cognition if a caregiver gave positive answers to one or both questions regarding fluctuating confusion or impaired consciousness from the Clinical Assessment of Fluctuation Scale [27]. Visual hallucinations were defined as repetitive involuntary images of people, animals, or objects that were experienced as real during the waking state but for which there was no objective reality using the caregiver-based structured interview of the Neuropsychiatric Inventory [28,29].

2.3. Statistical analysis

Group differences were analyzed using the Kruskal–Wallis test or one way analysis of variance (ANOVA) for categorical and continuous variables, respectively, and these tests were followed by post hoc comparisons. A univariate analysis of covariance (ANCOVA) with age at neuropsychological evaluation, gender, and years of education as the factors was conducted to compare the raw scores of each neuropsychological

Table 2
Core DLB features present during the MCI stages of AD and DLB.

Core features	MCI-AD (n = 32)	MCI-DLB (n = 18)	p
Parkinsonism	4/32 (12.5%)	14/18 (77.7%)	<0.05
Visual hallucination	2/32 (6.2%)	7/18 (38.9%)	<0.05
Cognitive fluctuation	1/32 (3.1%)	4/18 (22.2%)	0.032

Values are expressed as number (percentage). MCI, mild cognitive impairment; DLB, dementia with Lewy bodies; AD, Alzheimer's disease.