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Profile of memory impairment as a prognostic marker in amnestic mild cognitive impairment

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ABSTRACT

We aimed to evaluate whether recognition memory can be used to identify patients with amnestic mild cognitive impairment (aMCI) at greater risk for converting to dementia. We recruited 2172 aMCI patients. They were divided into two groups: aMCI with impaired recall but normal recognition (aMCI-IRNR) vs aMCI with impaired recall and impaired recognition (aMCI-IRIR). We compared demographic findings and neuropsychological performance and illustrated the difference in converting to dementia between the two groups. Study subjects consisted of 1022 (47.0%) patients with aMCI-IRNR and 1150 (53.0%) patients with aMCI-IRIR. In most neuropsychological tests except for digit span forward, patients with aMCI-IRIR were more impaired than patients with aMCI-IRNR even after adjustment of their age and sex. Cox analysis adjusting age and gender revealed that the risk of dementia conversion was higher in patients with aMCI-IRIR than in patients with aMCI-IRNR [hazard ratio (HR) = 1.400, 95% CI 1.009–1.943; $P = 0.044$]. This study showed that recognition memory can be used to identify patients with amnestic mild cognitive impairment (aMCI) at greater risk for converting to dementia.

1. Introduction

Amnestic mild cognitive impairment (aMCI) is a disorder that has been associated with risk for Alzheimer's disease (AD) [1]. By defining the subtype of aMCI, the clinician can make a reliable prediction regarding the outcome of the MCI syndrome. The most commonly used subtyping for aMCI is made as to whether memory is the only cognitive domain affected (aMCI single domain) or whether memory is impaired along with other cognitive domains (aMCI multiple domain). The rate of conversion to AD is greater in aMCI multiple domain than in aMCI single domain [2]. It has been suggested that aMCI multiple domain is a transitional state between aMCI single domain and AD [3]. Next, the profile of memory impairment may be a factor for the subtyping of MCI. One subtyping by the profile of memory impairment is based on verbal versus visual memory-predominant deficits. Previous studies have shown that aMCI patients with verbal memory deficits have higher progression rates to AD than those with visual memory deficits [4,5]. In addition, patients with aMCI with both verbal and visual memory deficits are more known to be classified as an aMCI multiple domain than those with either verbal or visual memory deficit [6] and most AD patients show combined verbal and visual memory deficits [7]. These findings suggest that aMCI with verbal memory deficits and aMCI with both verbal and visual memory deficits are more likely to be a precursor of AD than aMCI with visual memory deficits, and that aMCI with both verbal and visual memory deficits may be a more advanced subtype than aMCI with verbal memory deficits on the spectrum from MCI to AD [8]. Another possible subtyping by the profile of memory impairment is based on whether the recognition memory is preserved or not. A previous study revealed that some aMCI patients showed impaired recall and recognition memory impairment while others showed impaired recall but preserved recognition memory [9]. Whereas cortical atrophy in aMCI patients with preserved recognition was confined to frontal areas, the cortical gray matter loss in aMCI patients with impaired recall and recognition memory was distributed in the right medial temporal lobe and bilateral temporoparietal regions, a pattern of gray matter loss usually described in early AD. The result suggested that impairment of recognition memory may be a predictor for conversion to dementia in aMCI patients, and the longitudinal data showed that impaired visual recognition memory predicted AD in aMCI [10]. However, there have been no studies which included a large number of patients.

In our study, we aimed to compare the clinical characteristics of aMCI patients in a large cohort as to whether the recognition memory is preserved or not. In addition, we attempted to evaluate whether the recognition memory can be used to identify those at greater risk for converting to dementia.

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2. Methods

2.1. Patients

From November 2005 to February 2011, we recruited 2172 patients who had been newly diagnosed with aMCI from a nationwide multicenter study of dementia, the Clinical Research for Dementia of South Korea (CREDOS) study. A total of 31 university and general hospitals in South Korea participated in this study. The CREDOS cohort is dynamic and hospital-based. Participants can leave or be added over time. Participants are continually added when they are diagnosed with subjective memory impairment, mild cognitive impairment, mild cognitive impairment of a subcortical vascular type, Alzheimer's disease, and subcortical vascular dementia and agree that they are registered to the cohort, so new subjects are continually added. Subjects can also leave the cohort by stopping visiting the hospital or dying. Details of diagnostic evaluation of patients and inclusion/exclusion criteria were published previously [11]. The aMCI patients were diagnosed according to the criteria proposed by Petersen et al. [1].

This study was approved by the Institutional Review Boards of all participating hospitals, and written informed consent was obtained from patients and their caregivers after receiving a complete description of the study.

2.2. Neuropsychological tests and classification of aMCI

All patients and controls underwent neuropsychological tests using a standardized neuropsychological battery, called the Seoul Neuropsychological Screening Battery (SNSB) [12]. This battery contained tests for attention, language, praxis, the four symptoms of Gerstmann syndrome, visuoconstructive function, verbal and visual memory, and frontal/executive function. Among these, scorable tests included the digit span test (forward and backward), the Korean version of the Boston Naming Test (K-BNT), the Rey–Osterrieth Complex Figure Test (RCFT; copying, immediate and 20-minute delayed recall, and recognition), the Seoul Verbal Learning Test (SVLT; three free recall trials of 12 words, and a 20-minute delayed recall trial of the same 12 items, and a recognition test), the phonemic and semantic Controlled Oral Word Association Test (COWAT), and the Stroop Test (word and color reading of 112 items for 2 min). Age-, sex-, and education-specific norms for each test, based on 447 normal subjects, were available. The scores on these scorable cognitive tests were classified as abnormal when they were below the 16th percentile of the norms for the age-, sex-, and education-matched normal subjects.

On the basis of the profile of memory impairment, patients were divided into two groups: aMCI with impaired recall but normal recognition (aMCI-IRNR) vs aMCI with impaired recall and impaired recognition (aMCI-IRIR). Then, patients with aMCI-IRIR were grouped into patients with impaired recall and impaired recognition in both SLVT and RCFT vs patients with impaired recall and impaired recognition in SLVT or RCFT.

2.3. Assessment of white matter changes

Three neurologists trained in rating ischemic white matter changes, and who had been blinded to clinical and functional data, rated the white matter changes on the T2 axial and/or FLAIR images. The CREDOS rating scales were developed by the CREDOS study central committee, with modifications from Fazekas' [13] and Scheltens' [14] scales. Each longest-diameter white matter change around the lateral ventricles (capping or banding on the periventricular areas) or deep in white matter (especially the centrum semiovale) were evaluated separately. Periventricular white matter changes were rated as P1 (<5 mm), P2 (≥5 mm, <10 mm), or P3 (≥10 mm) and the deep white matter changes were rated as D1 (<10 mm), D2 (≥10 mm, <25 mm), or D3 (≥25 mm). The results were combined to give a final ischemia score of mild, moderate, or severe. The combinations of D1 with P1 (D1P1) and D1 with P2 (D1P2) were classified as "mild." The combinations D2P1, D3P1, D2P2, D3P2, D1P3, and D2P3 were classified as "moderate," while D3P3 was classified as "severe". As previously mentioned, D3P3 was used as the imaging criteria for subcortical vascular dementia diagnoses. The inter-rater reliability for ratings of periventricular, deep, or total white matter changes was excellent ($\kappa = 0.726$–0.905).

2.4. Follow-up

Of the 2172 MCI patients, 533 (24.5%) patients completed at least one follow-up visit with the same interview and neuropsychological tests for the baseline evaluation from November 2005 to February 2011. There was no significant difference in their age, sex, education, and scores of baseline MMSE between patients who performed at least one follow-up neuropsychological test and those who did not. The diagnosis of dementia was based on criteria from the Diagnostic and Statistical Manual of Mental Disorders (4th edition) and required clinical evidence of cognitive deficits confirmed by neuropsychological tests, as well as evidence of impairment in social or occupational functions confirmed by activities of daily living scales.

2.5. Data analysis and statistics

First, we compared patient demographic findings between aMCI-IRNR and aMCI-IRIR. Pearson's chi-square (χ^2) test was used to examine trends in categorical data and the independent *t*-test was used for continuous variables. Age and gender were included as covariates for analyses of covariance (ANCOVA), in comparison of baseline neuropsychological test performances between two groups. Second, we compared patient demographic findings between two subgroups of aMCI-IRIR. Pearson's chi-square (χ^2) test was used to examine trends in categorical data and the independent *t*-test was used for continuous variables. Age was included as covariates for ANCOVA, in comparison of baseline neuropsychological test performances between two groups. Third, Cox proportional hazard models were used to illustrate the difference in converting to dementia between aMCI-IRNR and aMCI-IRIR, after controlling for age and gender. Time to the event was defined as the time from study entry to the follow-up visit at which a first-time diagnosis of dementia was made. Subjects that did not convert to dementia were treated as censored observations from the time of their final follow-up evaluation. Finally, Cox proportional hazard models were used to illustrate the difference in converting to dementia between two subgroups of aMCI-IRIR, after controlling for age. $P < 0.05$ was considered significant. All statistical analyses were performed using SPSS version 20.0 (Chicago, IL, USA).

3. Results

3.1. Characteristics of the patients

Study subjects consisted of 1022 (47.0%) patients with aMCI-IRNR and 1150 (53.0%) patients with aMCI-IRIR (Fig. 1). Patients with aMCI-IRIR were older (years, 70.6 ± 7.6 vs 69.5 ± 8.1, $P = 0.001$) and included more men (37.7% vs 32.3%, $P = 0.009$) than patients with aMCI-IRNR. Proportions of patients with hypertension or diabetes mellitus were not different between two groups (Table 1).

Among 1150 patients with aMCI-IRIR, 852 patients showed impaired recall and impaired recognition in SLVT or RCFT whereas 298 patients revealed impaired recall and impaired recognition in both SLVT and RCFT. Patients with impaired recall and impaired recognition in both SLVT and RCFT were older than patients with impaired recall and impaired recognition in SLVT or RCFT (Table 2).

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