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Conversion pattern and predictive factor of mild cognitive impairment in elderly Koreans

Sung-Mi Shim[a,b], Jihyun Song[a], Jong-Hoon Kim[b], Jae-Pil Jeon[a,*]

[a] Division of Brain Diseases, Center for Biomedical Sciences, Korea National Institute of Health, 187 Osongsaengmyung-2-ro, Osong-eup, Cheongju-si, Chungcheongbuk-do, Republic of Korea
[b] Department of Biotechnology, College of Life Sciences and Biotechnology, Korea University, 5-1 Anam-Dong, Seongbuk-Gu, Seoul, Republic of Korea

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ABSTRACT

Objective: We aimed to understand conversion characteristics of mild cognitive impairment (MCI) in elderly Koreans.
Methods: We analyzed clinical data of 760 individuals who participated in a two-year follow-up study. Neuropsychological assessments and clinical examination were conducted in the follow-ups. Logistic regression model was used to estimate predictive risk factors of MCI conversion.
Result: The participants at baseline ($n = 760$) represented 462 cognitively normal individuals (60.8%), 286 individuals with MCI (37.6%), and 12 individuals with dementia (1.6%). Among the cognitively normal individuals ($n = 462$), 108 (23.4%) progressed to MCI during the two-year follow-up period, including 92 with amnestic mild cognitive impairment (aMCI; 19.9%) and 16 with non-amnestic mild cognitive impairment (non-aMCI; 3.5%). Interestingly, 3.7% of participants with aMCI converted to non-aMCI, while 45.5% of participants with non-aMCI converted to aMCI. Moreover, a higher proportion of non-aMCI (27.3%) reverted to a cognitively normal state, compared to aMCI participants (18.6%), indicating that non-amnestic cognitive impairment is more unstable than amnestic cognitive impairment, and probably converges toward aMCI. Additionally, we found that weight loss was associated with incident MCI and future MCI. Weight loss was negatively correlated with Clinical Dementia Rating ($p = 0.005$), and significantly associated with a higher risk of MCI conversion from a cognitively normal state (OR = 1.10, 95% CI: 1.00–1.21, $p = 0.042$).
Conclusion: This study supports that non-amnestic MCI is prone to converge toward amnestic MCI, and the elderly people with weight loss are at risk for developing cognitive decline.

1. Introduction

Dementia is the progressive deterioration of cognitive function that increasingly interferes with daily activity in elderly people (Alzheimer's Association, 2015). The most common cause of dementia is Alzheimer's disease (AD), accounting for approximately 70% of cases. AD develops sequentially from a preclinical stage and mild cognitive impairment (MCI) (Sperling et al., 2011). MCI is a transitional risk phase between a cognitively normal state and AD. It is known that MCI prevalence ranges from 3% to 42%, and approximately 13% to 54% of patients with MCI convert to dementia (Ward, Arrighi, Michels, & Cedarbaum, 2012). In addition, MCI occasionally reverts to normal cognition with a reversion rate ranging from 2% to 53% (Roberts & Knopman, 2013). The MCI phase is a relatively erratic phase that is key for the intervention of a progressive cognitive decline and AD (Vega & Newhouse, 2014). Therefore, the preclinical phase and MCI have received attention as target stages for the development of successful predictors and biomarkers for the early diagnosis of AD.

In many epidemiological studies, changes in body mass index (BMI) or weight have been implicated in dementia, including AD and cognitive impairment (Albanese et al., 2013; Besser et al., 2014; Cronk, Johnson, & Burns, 2010; Emmerzaal, Kiliaan, & Gustafson, 2015; Gu et al., 2014; Johnson, Wilkins, & Morris, 2006). For example, it was reported that involuntary weight loss was a sign of AD, likely due to a hypermetabolic state, increased physical activity, and a lower energy intake (Sergi, De Rui, Coin, Inelmen, & Manzato, 2013). Longitudinal studies have shown that AD patients' body weight rapidly decreased starting from a year before diagnosis (Johnson et al., 2006). Individuals who converted from MCI to dementia experienced significantly greater weight loss at a

* Corresponding author at: 187 Osongsaengmyung-2-ro, Osong-eup, Cheongju-si, Chungcheongbuk-do 363-951, Korea. Fax: +82 43 719 8602.
E-mail address: jaepiljeon@hanmail.net (J.-P. Jeon).

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two-year follow-up (Sobow, Fendler, & Magierski, 2014). Participants with MCI significantly lost weight six years before diagnosis (Gao et al., 2011). Hence, weight loss may be a predictive factor of cognitive decline in the preclinical stage as well as of the onset of MCI or AD.

Here, we investigated the conversion rates of MCI and its risk factors using epidemiological data from a cohort study of Korean elderly people. We showed that the conversion rate from normal cognition to MCI was 23.4%, and non-amnestic cognitive impairment was more unstable than amnestic cognitive impairment. In addition, weight loss was significantly associated with a higher risk of MCI conversion from a cognitively normal state, suggesting that it is a potential risk predictor of incident MCI.

2. Methods

This study included elderly Korean participants who were recruited for a general population-based geriatric cohort study. Its study design, sampling, concept, and consent are described elsewhere (Han, Jo, Kim, Jo, & Park, 2009). Briefly, the screening study in an initial recruitment phase aimed to enroll study subjects who completed surveys using an interviewer-administered questionnaire and some neuropsychological tests, including the Korean Mini-Mental State Examination (K-MMSE) (Kang, Na, & Han, 1997), and the Beck Depression Inventory (BDI), but no clinical laboratory tests or blood samplings were administered. Next, following the screening study, the first main study (baseline) included the clinical diagnosis of dementia and MCI subtypes using several expanded neuropsychological assessments including the Korean version of the Consortium to Establish a Registry for Alzheime's Disease (CERAD-K) (Lee et al., 1999, 2002), the MMSE in the CERAD-K battery (MMSE-KC) (Lee et al., 2002), the Clinical Dementia Rating (CDR), the Korean version of Geriatric Depression Scale, Barthel Activities of Daily Living (ADL) and Korean Instrumental Activities of Daily Living (IADL). At this stage, clinical laboratory data and blood-derived biological samples (e.g. blood DNA, serum, or plasma) were collected from study participants; thus, the first main study was considered the baseline study.

2.1. Participants

A total of 2767 elderly Korean people over 60 years of age were enrolled in the initial recruitment phase for the Ansan geriatric cohort study from 2002. The first main study (baseline, from September 2003 to March 2006) and the first follow-up (1st FU, from April 2006 to January 2008) study were conducted approximately every 2–3 years. The baseline study included 1391 individuals of which 841 were evaluated at the 1st FU phase (Supplemental Fig. 1). Among the individuals who had participated in both baseline and 1st FU, a total of 760 individuals were selected for the MCI conversion analysis, excluding individuals who have some missing clinical and laboratory data.

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2.2. Diagnosis

Cognitive function and memory impairment of participants were assessed using the CERAD-K neuropsychological battery and CDR. Dementia was defined according to the diagnostic features of dementia given in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). The subtypes of MCI were diagnosed by the Petersen criteria (Petersen et al., 1999).

2.3. Statistical analysis

Two-tailed Student's *t*-test or ANOVA was performed to compare clinical characteristics of normal non-converters and MCI converters, and then adjusted by Bonferroni corrections for multiple comparisons. Simple correlations were determined using Pearson's correlation coefficient. The odds ratios (OR) were estimated using the logistic regression model adjusted by age, gender, and education. All analyses were performed using IBM SPSS Statistics 20, and statistical significance was considered to be at the $p < 0.05$ level.

3. Results

3.1. Prevalence of MCI and dementia

In the recruitment phase, a total of 2693 participants were diagnosed as being cognitively normal (75.9%, $n = 2044$), with MCI (14.3%, $n = 384$), or dementia (9.8%, $n = 265$) using the K-MMSE (Table 1). In the first main study (baseline), study participants ($n = 1338$) were diagnosed as cognitively normal (53.9%, $n = 721$), with any MCI subtype (42.2%, $n = 564$), or dementia (4.0%, $n = 53$). Compared with the screening study, the baseline study represented a higher percentage of participants with MCI. In fact, these participant were individuals with amnestic MCI (aMCI; 36.4%) and non-amnestic MCI (non-aMCI; 5.8%); thus, this group contained a much higher number of individuals with aMCI than with non-aMCI (over 6 times). Of the aMCI subtypes, the proportion of single-domain aMCI (18.8% of total participants) was comparable to that of multiple-domain aMCI (17.6% of total participants). The 1st FU study also contained a similar proportion of participants with MCI (46.1%, $n = 382$) and dementia (2.2%, $n = 18$). As in the baseline study, higher proportions of aMCI subtypes, including single- (24.1%) and multiple-domain (16.8%) aMCI, remained in the 1st FU

Table 1
Prevalence of MCI and dementia in the study participants.

Phases	Recruitment ($n = 2693$[a])		Baseline ($n = 1338$[b])		First follow-up ($n = 829$[c])	
	Cases (n)	Prevalence (%)	Cases (n)	Prevalence (%)	Cases (n)	Prevalence (%)
Cognitively Normal	2044	75.9	721	53.9	429	51.7
Mild Cognitive Impairment	384	14.3	564	42.2	382	46.1
aMCI single domain			251	18.8	200	24.1
aMCI multi domain			235	17.6	139	16.8
Non-aMCI single domain			68	5.1	42	5.1
Non-aMCI multi domain			10	0.7	1	0.1
Dementia	265	9.8	53	4.0	18	2.2

Note: aMCI, amnestic mild cognitive impairment

[a] 2767 participants were recruited in the initial recruitment phase, but neuropsychological data were missing for 74 individuals who refused examination. Therefore, the prevalence rate was estimated on the basis of diagnostic data for 2693 individuals. In the recruitment phase, clinical subtypes of MCI were not determined.

[b] 1391 individuals participated in the baseline study, but neuropsychological data were missing for 53 individuals who refused the examination.

[c] 841 individuals participated in the first follow-up, but neuropsychological data were missing for 12 individuals who refused the examination.