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Characteristics of mild cognitive impairment tending to convert into Alzheimer's disease or dementia with Lewy bodies: A follow-up study in a memory clinic

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ABSTRACT

Aim: To determine characteristics of MCI that can predict whether patients will go on to develop AD or DLB.
Methods: Ninety-three patients diagnosed with MCI underwent neuropsychological and neuroimaging examinations, and were followed-up for a mean of 44.9 ± 19.3 months. They were divided into four MCI subtypes (amnestic/non-amnestic MCI, single/multiple domain) according to neuropsychological findings, and into three other MCI categories (AD-type PET, DLB-type PET, and unknown-type PET) based on ^{18}F-fluorodeoxyglucose PET findings. Patients who were eventually diagnosed with AD, DLB, other dementia, or remained MCI were analyzed in relation to the groups to which they had initially been allocated at the MCI stage.
Results: Clinical diagnosis after follow-up determined AD in 21 patients (22.6%), DLB in 12 patients (12.9%), other dementia in 2 patients (2.2%), and non-converter in 58 patients (62.3%). Amnestic single-domain MCI and AD-type PET tended to convert into AD. Amnestic multiple-domain MCI and DLB-type PET tended to convert into DLB. A few patients with AD-type PET later developed DLB, and some with DLB-type PET later developed AD.
Conclusions: Predicting which type of dementia a person with MCI will later develop might be possible based on early assessment with clinical symptoms in conjunction with neuropsychological and ^{18}F-fluorodeoxyglucose PET findings.

1. Introduction

A diagnosis of dementia is made when cognitive impairment affects the social activity of an individual [1]. Recently, however, a need for early diagnosis has been growing. In Alzheimer's disease (AD), disturbances in recent memory can appear in the early stages [2,3]. In contrast, in dementia with Lewy bodies (DLB), the second most common type of dementia after AD, memory disturbance may not be distinct, but clinical symptoms such as cognitive fluctuation, visual hallucination, and parkinsonism can appear in the early stages [4]. The prodromal phase of dementia is viewed as the state in which cognitive impairment occurs, but diagnostic criteria for dementia are not satisfied.

Among concepts that explain the prodromal phase of dementia, mild cognitive impairment (MCI) proposed by Petersen et al. [5] may be the most commonly used. MCI is divided into amnestic MCI (aMCI) or non-amnestic MCI (naMCI) depending on the presence or absence of memory disturbance. aMCI and naMCI are each further divided into single-domain or multiple-domain types depending on how many cognitive domains are affected [6]. Among these four subtypes, aMCI and multiple-domain naMCI are considered the most likely to later develop (convert) into AD and DLB, respectively [7]. However, a recent follow-up study of MCI patients [8] reported slightly different results; single-domain aMCI was most likely to convert into AD and single-domain naMCI was most likely to convert into DLB.

^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) of the brain has been widely used in diagnosing dementia. AD can be characterized by glucose hypometabolism in the parietotemporal region and in the area extending from the posterior cingulate gyrus to the precuneus [9]. Glucose hypometabolism in this latter region has also been shown in patients with MCI that later converted into AD (MCI due to AD) [10,11]. In DLB, while some patterns of glucose hypometabolism resemble those of AD [4], ^{18}F-FDG PET has shown that glucose hypometabolism in the primary visual cortex (PVC) is a characteristic that can be used to distinguish it from AD [12]. Our research has indicated that glucose hypometabolism in the

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PVC can even be observed in patients with MCI that later converted into DLB (MCI due to DLB) [13].

Moreover, Graff et al. indicated the importance of cingulate island sign (CIS) which distinguishes AD from DLB on ^{18}F-FDG PET images [14]. However, in our knowledge, there is no report on CIS in patients with MCI.

In their 15-year follow-up study, Petersen et al. [5] reported that MCI converted into AD or another dementia at an annual average rate of 12%, and that about 80% of MCI patients were diagnosed with dementia within 6 years. According to a meta-analysis of 19 longitudinal studies, the percentage of MCI patients who later develop dementia is 10% per year [15]. Thus, we can expect people with MCI to later develop some type of dementia, and being able to predict which one at the earliest possible time will be helpful for patient therapy and quality of life. As a potential means for early diagnosis, here we looked for MCI characteristics associated with later conversion into AD or DLB. We classified MCI patients based on neuropsychological and ^{18}F-FDG PET examinations, and examined the relationship between these classifications and the clinical diagnoses after the follow-up.

2. Methods

2.1. Subjects

223 patients visited memory clinic between 2006 and 2012. Among them we selected patients who were aged >60 years, and were diagnosed with MCI, which was defined as having a Functional Assessment Staging Tool (FAST) score ≤ 3, a Clinical Dementia Rating (CDR) ≤ 0.5, and a Mini-Mental State Examination (MMSE) score ≥ 24. The exclusion criteria were those aged <60 years at baseline, whose observation periods were less than a year, and those who exhibited severe cerebrovascular change (the Fazekas scale ≥2). The total of 93 patients were selected for the present study. All patients met the Petersen et al. [5] criteria for MCI. The presence or absence of Neuropsychiatric Inventory-4 (NPI-4) symptoms (hallucination, delusion, depression, and apathy), parkinsonism, and probable REM sleep behavior disorder (RBD) was evaluated. Evaluation of parkinsonism was performed using the Unified Parkinson's Disease Rating Scale (UPDRS) part III [16]. Neuropsychological and neuroimaging examinations were carried out within 1 month of the first visit, and patients were followed up for a mean period of 44.9 ± 19.3 months. Table 1 outlines patient demographics, MMSE scores, and clinical symptoms. The study was carried out at the Juntendo Tokyo Koto Geriatric Medical Center, with approval from the Ethics Committee. Informed consent was obtained from each patient.

Table 1
Demographics, MMSE scores, and clinical symptoms in 93 patients.
Values are expressed as mean ± standard deviation or number of patients (percentage). MMSE, Mini-Mental State Examination; RBD, REM sleep behavior disorder.

	MCI (N = 93)
Demographics	
Age at baseline (y)	74.3 ± 6.4
Sex (male/female)	45/48
Follow-up period (m)	44.9 ± 19.3
Duration of education (y)	12.7 ± 2.8
MMSE score at baseline	26.5 ± 2.1
Clinical symptoms at baseline	
Hallucination (visual hallucination)	5(5.4%)
Delusion	6(6.5%)
Depression	10(10.8%)
Apathy	17(18.3%)
Parkinsonism	15(16.1%)
Probable RBD	13(14.0%)

2.2. Classification by neuropsychological examination

All patients underwent neuropsychological examinations (MMSE, the Wechsler Adult Intelligence Scale [WAIS]-III, and the Wechsler Memory Scale-Revised [WMS-R]). Based on the WAIS-III and WMS-R, patients were divided into four groups [6], as has been previously described [17]. Briefly, if general memory on the WMS-R was less than verbal IQ on the WAIS-III, patients were considered to have a memory disturbance, and were allocated to the aMCI group. If the opposite were true, patients were considered to have a non-memory disturbance, and were allocated to the naMCI group. Furthermore, among aMCI, those whose scores were ≥90 (the normal range) on all four WAIS-III indices (verbal comprehension, perceptual organization, working memory, and processing speed) were considered to have single-domain aMCI (aMCI-s), those whose scores were <90 on any of the four indices were considered to have multiple-domain aMCI (aMCI-m). Among naMCI, those whose scores were <90 on one of the four indices were considered to have single-domain naMCI (naMCI-s), and those with scores <90 on two or more indices were considered to have multiple-domain anMCI (naMCI-m).

2.3. Classification by ^{18}F-FDG PET examination

All patients underwent magnetic resonance imaging (MRI; 1.5 T scanner, MAGNETOM Symphony, Siemens, Munich, Germany) and ^{18}F-FDG PET (GE Healthcare, Chalfont St. Giles, UK). The T1-weighted MR images were evaluated for brain atrophy using the Scheltens medial temporal lobe atrophy (MTA) scale, with grades from 0 to 4 [18]. All patients were rated as grades 0–2 (left 0.4 ± 0.5, right 0.4 ± 0.5), and exhibited normal to mild atrophy. Periventricular hyperintensity and deep and subcortical white matter hyperintensity were evaluated on the T2-weighted images using the Fazekas scale from 0 to 3 [19]. All patients were rated as grades 0–1, suggesting normal cerebrovascular change for their ages. To determine where the regional cerebral metabolic rate of glucose (CMRglc) was less than normal, first, three-dimensional stereotactic surface projection (3D-SSP) analysis was used to compare glucose metabolism for each patient with an age-matched normative database [20,21]. Decreases in CMRglc were expressed as Z-scores and superimposed on a 3D-SSP map [22]. The Z-score in each region was analyzed by stereotactic extraction estimation (SEE). Specifically, we used SEE to calculate the extent ratio and severity for each region indicated by a Z-score > 0. We examined Brodmann areas (BA) that corresponded to the regions of interest (ROI); BA 7, 39, and 40 (parietal/precuneus area; PAR/PRE), BA 23 and 31 (posterior cingulate gyrus; PCG), and BA 17 (primary visual cortex; PVC). Following our previously described method [23], within each ROI we summed the product of each pair of extent ratios and severities. We classified the patients into AD-type (AD-type PET) and DLB-type (DLB-type PET) groups based on the patterns of CMRglc decrease. The AD-type PET group exhibited decreased CMRglc in the PCG but not in the PVC, while the DLB-type PET group exhibited decreased CMRglc in the PVC regardless of the CMRglc levels in the PCG. Patients that did not meet these criteria were categorized as unknown-type (unknown-type PET) group.

2.4. Classification by clinical diagnosis after follow-up

Patients who had progressed to probable AD or probable DLB by the follow-up examination were allocated to AD and DLB groups, respectively. Here, the clinical diagnosis of probable AD was based on the diagnostic criteria of the National Institute on Aging and the Alzheimer's Association workgroup (NIA-AA) [24], while the diagnosis of probable DLB was based on the criteria adopted at the third International Workshop on DLB [4]. Patients who did not meet either of these criteria, but did meet criteria for dementia (FAST score > 3, CDR > 0.5, and MMSE score < 24), were allocated to the “other dementia” group, while those who did not were allocated to the non-converter group.