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Editorial

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Need for an Update for the Guideline for the Management of Mild Cognitive Impairment

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Attention is being paid to diagnosis and treatment of mild cognitive impairment (MCI) because early diagnosis and preventive management can slow down the progression of Alzheimer's disease. In particular, in the present era, the use of biomarkers for predicting conversion into dementia is permitted in medical practice. Therefore, authors aimed to propose additional considerations when updating guidelines for the management of MCI, including predictable biomarkers, revising treatment option after additional clinical trials for cholinesterase inhibitors, and detailed regimes for lifestyle interventions. After reviewing 3 patients with MCI by detailed evaluation, we realized that cholinesterase inhibitors were not recommended. In addition, regular exercise and cognitive training were only possible recommendations for patients according to current guidelines, although all 3 patients had evidence of β-amyloid accumulation and related neurodegeneration. Furthermore, caregivers for all 3 patients were worried whether patients could keep doing regular exercise and cognitive training by themselves and asked about the economic training system which monitors patients so that they can keep training. Therefore, we propose that guidelines for managing MCI need to be updated in the present era when the use of biomarkers for predicting conversion into dementia is permitted in medical practice.

Keywords: Mild Cognitive Impairment; Guideline; Cholinesterase Inhibitors; Amyloid

INTRODUCTION

Currently, it is widely accepted that β-amyloid (Aβ) and pathologic tau as the most representative neuropathology in Alzheimer's disease (AD) can accumulate from cognitively unimpaired stage and develop into mild cognitive impairment (MCI) and dementia through neurodegeneration over a couple of decades.[1] Accordingly, the importance of early diagnosis and preventive management to slow down the progression of AD has been emphasized.[2] Some studies have put their weight behind this emphasis on early diagnosis and prevention of dementia, showing that age-adjusted incidences of dementia have actually fallen in countries with changes in lifestyle-related risk factor profiles such as improved management of vascular risk factor and increased educational opportunities.[3,4] In addition, attention is being paid to

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diagnosis and treatment of MCI, which is usually considered as a pre-dementia and diagnosed when concern regarding a change in cognition, objective evidence of impairment in 1 or more cognitive domains, and preservation of independence in functional abilities without significant impairment in social or occupational functioning are confirmed.[5-8]

We aimed to study current management of MCI in real-world practice. MCI is an intermediate stage of AD spectrum. During this stage, intervention is desperately needed to suppress the progression to dementia. Therefore, we reviewed 3 patients who had been admitted for detailed investigation of their cognitive decline and diagnosed with MCI. Clinical practice for 3 patients and the most distinguished guidelines on MCI by both American Academy of Neurology (ANN) updated in 2018[9] and the Korean Dementia Association (KDA) updated in 2021[10] were then compared. Finally, we aimed to propose additional considerations when updating guidelines for managing MCI, including predictable biomarkers, revising treatment option after additional clinical trials for cholinesterase inhibitors, and detailed regimes for lifestyle interventions.

CASE REPORT

Patient information, clinical findings, and diagnostic assessment

Patient 1 was a 72-year-old housewife with 16 years of education. She first presented to the clinic because of her forgetfulness. Her memory problem was first noticed around 10 months ago by her daughter. It insidiously deteriorated, resulting her repeating the same sentences or questions. She also had complaints of word-finding difficulties. However, she had no problem remembering important appointments, finding her own ways, financing, or doing housework. She was taking daily ezetimibe 10 mg and rosuvastatin calcium 5.2 mg for dyslipidemia and choline alfoscerate 0.4 g due to forgetfulness. Her neurological examination was unremarkable. Detailed neuropsychological evaluation showed impairment in transient/sustained attention/concentration, verbal/visual memory, and some frontal/executive functions considering her age and education (**Table 1**). Right-left disorientation and ideomotor apraxia were suggested whereas confrontational naming and visuo-analytic/visuo-constructive functions were within normal ranges. In the Korean Mini Mental State Examination (K-MMSE), she scored 27 out of 30. Her Clinical Dementia Rating (CDR) global score and sum of boxes were 0.5 and 0.5, respectively. In the Korean Instrumental Activities of Daily Livings (K-IADL) questionnaires, she scored 0.11. Results of blood test such as complete blood counts, routine chemistry, electrolytes, serum venereal disease research laboratory (VDRL), thyroid function test, and Vitamin B12 were unremarkable, whereas her *apolipoprotein E (APOE) genotype was ε3/ε4*. Her cerebrospinal fluid showed no evidence of any inflammation. Her electroencephalogram was also unremarkable. Brain magnetic resonance imaging (MRI) (**Fig. 1A**) showed minimal global brain atrophy, hippocampal atrophy score of 1 on the right and 2 on the left based on the Scheltens' scale,[11] and grade 1 periventricular and grade 1 deep white matter hyperintensities based on the Fazekas scale.[12] F-18 Flutemetamol positron emission tomography computed tomography (PET CT) (**Fig. 1B**) showed abnormal accumulation of Aβ plaque in mainly bilateral frontal lobes, posterior cingulate gyri, precuneus, and left lateral temporal lobe. Consequently, a diagnosis of amnestic multiple-domain MCI accompanied by Aβ pathology and related neurodegeneration was established.

Patient 2 was a 70-year-old and 6-year educated woman who had become more forgetful over the last 5 months. She was originally a person who worked out and actively participated in

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Table 1. Results of neuropsychological evaluations for patients 1, 2, and 3

Tests	Patient 1	Patient 2	Patient 3
Attention			
Digit span: forward/backward	5 (−1.1)/3 (−1.3)	5 (−0.2)/3 (−0.4)	6 (−0.4)/4 (−0.4)
Language & related function			
K-BNT (/60)	48 (−0.4)	39 (−0.6)	38 (−2.7)
Right-left orientation	Abnormal	Abnormal	Normal
Calculation	Abnormal	Abnormal	Abnormal
Praxis	Abnormal	Normal	Abnormal
Visuospatial function			
Clock drawing test	1/1/1	1/1/1	1/1/0
RFCT copy (/36)	34 (0.1)	33 (0.6)	29 (−2.4)
Memory			
SVLT immediate recall/delayed recall	19 (−0.5)/3 (−1.7)	12 (−1.3)/0 (−2.3)	10 (−2.8)/0 (−3.2)
SVLT recognition true/false positive	11 (0.4)/4 (−2.8)	10 (0.1)/4 (−1.4)	9 (−1.1)/2 (−1.0)
RFCT immediate recall/delayed recall	7.5 (−1.6)/6.5 (−1.7)	6 (−0.9)/5 (−1.1)	4 (−2.3)/1.5 (−2.8)
RFCT recognition true/false positive	10 (0.0)/7 (−3.7)	4 (−2.6)/2 (0.1)	9 (−0.6)/4 (−1.7)
Frontal/Executive function			
Controlled Oral Word Association Test			
Animal/Supermarket	18 (0.3)/14 (−0.8)	8 (−1.5)/10 (−0.9)	9 (−1.9)/8 (−1.9)
‘ㄱ’/’ㅇ’/’ㅅ’	9 (−0.3)/12 (0.6)/16 (1.6)	3 (−0.9)/4 (−0.6)/6 (−0.1)	6 (−1.2)/5 (−1.4)/6 (−1.3)
Stroop test word/color	110/44 (−2.5)	112/41 (−1.5)	81/81 (−0.8)
K-TMT-e part B (sec)	41 (0.1)	130 (−1.1)	91 (−2.8)
General Index			
K-MMSE	27 (−1.1)	24 (−1.2)	24 (−3.7)
CDR global/Sum of boxes	0.5/0.5	0.5/1.5	0.5/1.5
Geriatric Depression Scale (/15)	5	8	0
K-IADL	0.11	0.4	0.36

Z-scores were inserted within parenthesis next to raw scores.
K-BNT: Korean version of the Boston Naming Test, RCFT: Rey Complex Figure Test, SVLT: Seoul Verbal Learning Test, K-TMT-e: Korean version of Trail Making Test for the elderly, K-MMSE: Korean version of the Mini-Mental State Examination, K-IADL: Korean version of the Instrumental Activities of Daily Livings.

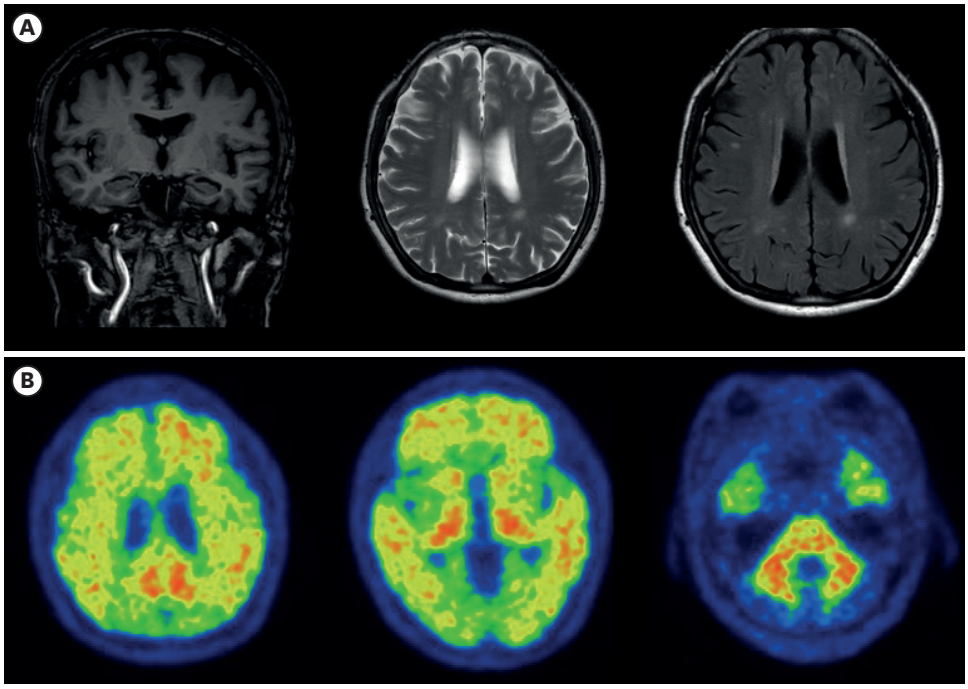

Fig. 1. Neuroimaging of Patient 1. Brain MRI showed (A) minimal global brain atrophy, hippocampal atrophy score of 1 on the right and 2 on the left based on the Scheltens' scale[11] and grade 1 periventricular and grade 1 deep white matter hyperintensities based on the Fazekas scale.[12] F-18 Flutemetamol positron emission tomography computed tomography showed (B) abnormal accumulation of β-amyloid plaque in mainly bilateral frontal lobes, posterior cingulate gyri, precuneus, and left lateral temporal lobe.

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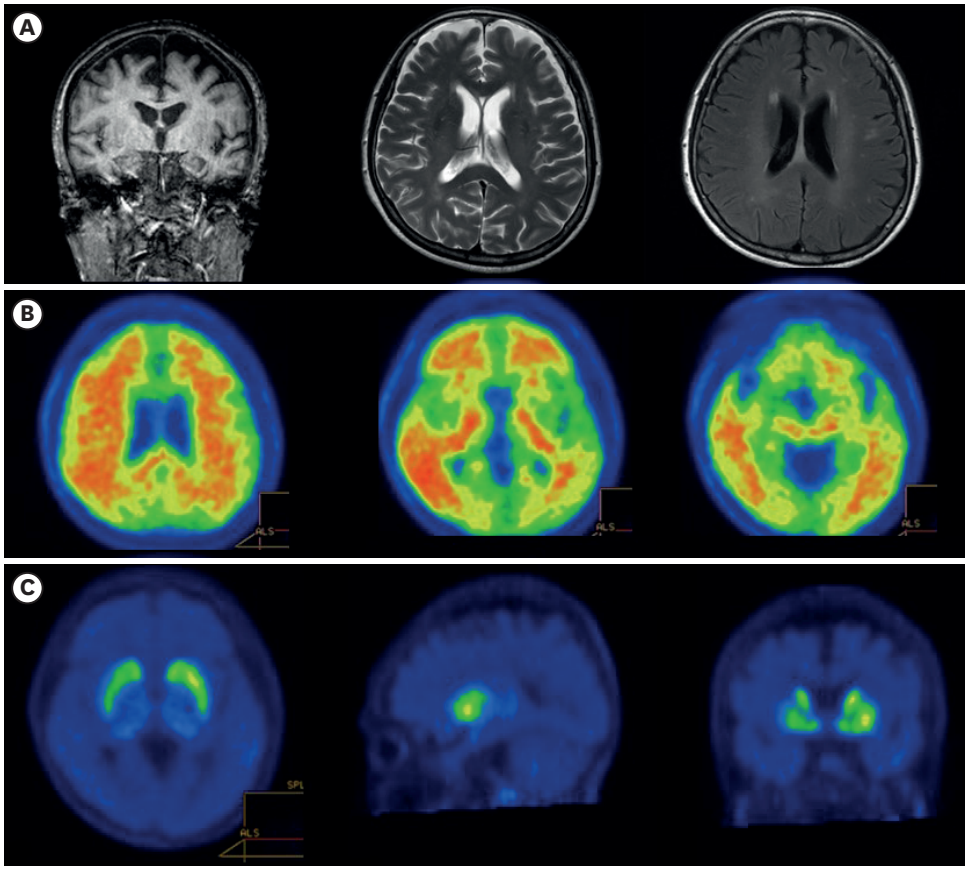

Fig. 2. Neuroimaging of Patient 2. Brain magnetic resonance imaging showed (A) left temporal atrophy, hippocampal atrophy score of 0 on the right and 1 on the left based on the Scheltens' scale[11] and grade 0 periventricular and grade 1 deep white matter hyperintensities based on the Fazekas scale.[12] F-18 Flutemetamol positron emission tomography computed tomography showed (B) abnormal extensive accumulation of β-amyloid plaque in the brain, including the frontal, temporoparietal cortex, and striatum. Subsequent 18F FP-CIT positron emission tomography showed (C) abnormal decreased FP-CIT uptakes in both basal ganglia on delayed phase.

social activities. However, since the coronavirus disease 2019 pandemic made all of these activities unavailable, she became depressed and helpless that she even lost 20 kg over the last 2–3 years, although her routine health check-up was unremarkable. She had been taking anti-depressants and anxiolytics for 5 months, but stopped those 2 months prior to the visit to the clinic due to complaints of visual hallucination such as seeing her dead grandmother. Her progressive memory loss started 3 years ago when she began forgetting close people' names and some words, which made her to hesitate, be less talkative, and spaced out. However, she had no problem remembering important appointments, finding her own ways, financing, or doing housework. She was on medication for the management of hypertension, diabetes, dyslipidemia, and burning sensation of tongue including sarpogrelate 0.1 g, metformin 0.5 g, amlodipine 2.5 mg, atrovastatin 10 mg, lafutidine 10 mg, and clonazepam 0.5 mg. Her neurological examination revealed masked face, rigidity, and bradykinesia in her extremities. Detailed neuropsychological evaluation showed impairment in verbal/visual memory and some frontal/executive functions such as semantic generative naming and inhibitory control considering her age and education (**Table 1**). In the K-MMSE, she scored 27 out of 30. Her CDR global score and sum of boxes were 0.5 and 1.5, respectively. In the K-IADL questionnaires, she scored 0.40. Results of blood test such as complete blood counts, routine chemistry, electrolytes, serum VDRL, thyroid function test, and Vitamin B12 were unremarkable, whereas

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her *apolipoprotein E (APOE) genotype was ε3/ε4*. Her cerebrospinal fluid showed no evidence of any inflammation. Her electroencephalogram was also unremarkable. Brain MRI (**Fig. 2A**) showed left temporal atrophy, hippocampal atrophy score of 0 on the right and 1 on the left based on the Scheltens' scale,[11] and grade 0 periventricular and grade 1 deep white matter hyperintensities based on the Fazekas scale.[12] F-18 Flutemetamol PET CT (**Fig. 2B**) showed abnormal extensive accumulation of Aβ plaque in the brain, including frontal, temporoparietal cortex, and striatum. Subsequent 18F FP-CIT PET (**Fig. 2C**) showed abnormal decreased FP-CIT uptakes in both basal ganglia on delayed phase. Consequently, a diagnosis of amnestic multiple-domain MCI accompanied by Aβ and related neurodegeneration as well as probable α-synuclein pathology was established.

Patient 3 was a 66-year-old man who was admitted for detailed evaluation of cognitive function after abnormal cognitive test results were found at a public health center. He complained progressive cognitive decline over last 2 years such as forgetting recent events and getting lost while driving even looking at the navigation. He also mentioned that his speech and behavior slowed down and his facial expression disappeared. Furthermore, he had urinary incontinence. The caregiver, his wife, indicated that he had become more forgetful last year and even had difficulties with his former accounting management in the church. He forgot where he had put the donated money and mistakenly deposited the church funds into his account. His wife also said that his mood swings got worse. He could not understand the question occasionally. The patient's medical history showed no illness. However, his brother has similar symptoms of forgetting words. After retirement as a high school art teacher, he was living with his spouse and farming in front of his house. He was on no medication. His neurological examination was unremarkable. Detailed neuropsychological evaluation showed impairment in place orientation, praxis, verbal/visual memory, confrontational naming, semantic/phonemic generative naming, and visuo-analytic/visuo-constructive functions considering his age and education (**Table 1**). In the K-MMSE, he scored 24 out of 30. His CDR global score and sum of boxes were 0.5 and 1.5, respectively. In the K-IADL questionnaires, he scored 0.36. Results of blood test such as complete blood counts, routine chemistry, electrolytes, serum VDRL, thyroid function test, and Vitamin B12 were unremarkable, whereas his *apolipoprotein E (APOE) genotype was ε3/ε4*. His cerebrospinal fluid showed no evidence of any inflammation. His electroencephalogram was also unremarkable. Brain MRI (**Fig. 3A**) showed left frontoparietal atrophy, hippocampal atrophy score of 1 on the right and 2 on the left based on the Scheltens' scale,[11] and grade 0 periventricular and grade 1 deep white matter hyperintensities based on the Fazekas scale.[12] F-18 Flutemetamol PET CT (**Fig. 3B**) showed abnormal accumulation of Aβ plaque in the frontal, temporoparietal cortex, and striatum. However, 18F FP-CIT PET (**Fig. 3C**) showed normal FP-CIT uptakes in both basal ganglia on delayed phase. Consequently, a diagnosis of amnestic multiple-domain MCI accompanied by Aβ pathology and related neurodegeneration was established.

Application of clinical practice guidelines for MCI to patients' management

Based on diagnostic assessment, all 3 patients were diagnosed as neurodegenerative MCI particularly relating to AD, whereas Patient 2 was also accompanied by probably α-synuclein pathology. Regarding treatment plans for the 3 patients, the guideline on MCI by ANN updated in 2018 was complied.[9] To reflect the medical environment of South Korea, clinical practice guideline for dementia by the KDA updated in 2021 was also applied.[10] According to recommendations for management of MCI by these guidelines, the first steps during management are weaning patients from medications that can contribute to cognitive

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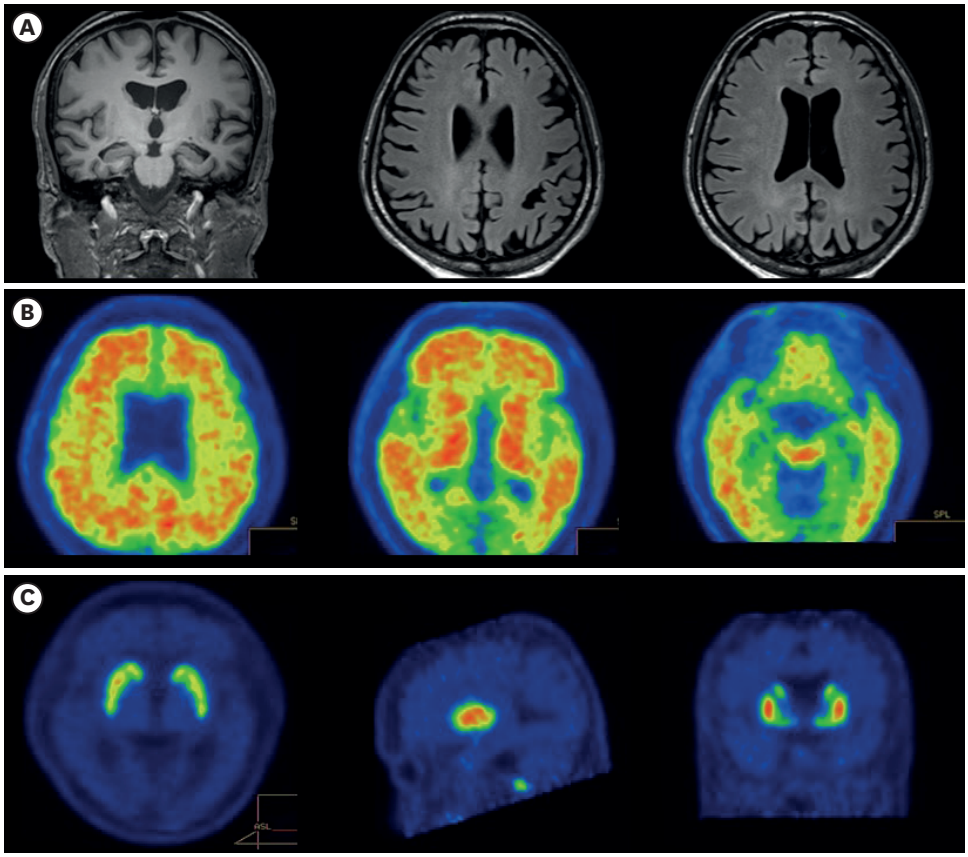

Fig. 3. Neuroimaging of Patient 3. Brain magnetic resonance imaging (A) showed left frontoparietal atrophy, hippocampal atrophy score of 1 on the right and 2 on the left based on the Scheltens' scale[11] and grade 0 periventricular and grade 1 deep white matter hyperintensities based on the Fazekas scale.[12] F-18 Flutemetamol positron emission tomography computed tomography showed (B) abnormal accumulation of β-amyloid plaque in the frontal, temporoparietal cortex, and striatum. However, 18F FP-CIT positron emission tomography showed (C) normal FP-CIT uptakes in both basal ganglia on delayed phase.

impairment (where feasible and medically appropriate) and treating modifiable risk factors that may contribute to MCI (Level B). Regarding pharmacologic treatments, there are no approved medications for treating MCI. High-quality and long-term studies identifying the improvement of cognition or delay of progression in the MCI by pharmacologic or dietary agents are currently unavailable. Because cholinesterase inhibitors lack efficacy with common side effects, clinicians are recommended not to offer cholinesterase inhibitors (Level B). If offering, they must first explain the less of evidence (Level A) and rather recommend clinical trials to patients who are interested in using such inhibitors. Additionally, clinicians should recommend regular exercise (Level B) with possible cognitive interventions (Level C). Regarding the quality of life of patients, behavioral/psychiatric symptoms in MCI could be treated with both pharmacologic and non-pharmacologic approaches when indicated (Level B). Finally, clinicians should monitor cognitive status of patients with MCI over time (Level B).

Although all 3 patients had evidence of Aβ accumulation and related neurodegeneration well-known to be a predictor for conversion of MCI to dementia,[1] cholinesterase inhibitors were not recommended according to the guidelines. In addition, for all 3 patients, regular exercise and cognitive training were recommended. However, caregivers for all 3 patients were worried about whether patients could keep doing regular exercise and cognitive training

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by themselves and asked about the economic training system that could monitor patients so that they could keep training. Especially, Patients 1 and 3 were living in fishing and farming villages far away from the clinic. For Patient 2, relieving her depression might help alleviate her cognitive decline. However, because she was assumed that she had α-synuclein pathology, particularly the possibility of dementia with Lewy bodies, she should be thoroughly monitored when anti-depressants or anxiolytics are considered.

DISCUSSION

After reviewing 3 patients and clinical guidelines for the management of MCI, we came to realize that regular exercise and cognitive training were only possible recommendations for patients by clinicians, although all 3 patients were diagnosed with MCI accompanied by well-known predictors for conversion of MCI to dementia after detailed evaluations.[1] However, while we were reviewing the 3 patients, we realized that the clinical diagnostic criteria of MCI should be updated, particularly in the present era when the use of biomarkers such as amyloid PET and plasma Aβ oligomerization assay[13] is permitted in medical practice and research. In addition, exercise and cognitive training should be recommended. However, in the real world, patients and their caregivers feel embarrassed and burdened by such implementation. Therefore, guidelines for the management of MCI should be updated, including revising treatment options after additional clinical trials for cholinesterase inhibitors and detailed regimes for lifestyle interventions.

First, in the present era when the use of biomarkers is permitted in medical practice and research, there are some important ambiguities when diagnostic criteria of MCI are applied in the real-world clinical practice. In particular, there are several problems when performing and interpreting IADL questionnaires. These IADL questionnaires are surveys scored 1 up to 5 points for each item and instructed to be answered by caregivers. Therefore, results are quite subjective. They might have various degrees of reliability depending on caregivers' concerns, characteristics, or how much caregivers witness the patient's daily living. All 3 patients in this study had clear symptoms and objective evidence of impairment in one or more cognitive domains. Furthermore, their neuroimaging such as amyloid PET and brain MRI showed positive results of many possibilities which might lead to conversion the dementia. However, cholinesterase inhibitors could not be recommended because they seemed to be still independent in functional abilities without significant impairment in social or occupational functioning.[14] As the importance of early intervention has recently been emphasized, it should be considered to apply treatment differently by dividing detailed categories according to the status of biomarkers among MCI patients rather than depending on caregivers' report based on IADL questionnaires.[1547] In the near future, we expect to use various biomarkers such as blood Aβ42/Aβ40 ratio, phosphorylated tau at threonine 181 (pTau181), and neurofilament light instead of subjective questionnaires to discriminate disease status of patient in clinical practice and research.[13]

Second, the evidence supporting guidelines for the prescription of cholinesterase inhibitors should be outdated considering the present era. The study which made donepezil not available in MCI was published in 2005. It showed that the rate of progression to AD after 3 years was not lower among patients treated with donepezil than that in MCI patients given placebo.[18] Taken into consideration that reports about the concept of MCI began to be published in early 21 century[19-23] and that trial had been actually conducted between March

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1999 and January 2004, characteristics of patients with the MCI between those who had been recruited for the trial and those in the present era with evidence of risk factors for conversion might be quite different. Furthermore, according to another study published in 2018,[24] which reanalyzed the previous donepezil study,[18] removal of false positive MCI diagnoses might unmask beneficial effects of donepezil. The false positive MCI could be characterized by normal Aβ and tau biomarkers,[25] normal PET amyloid burden,[26] normal cortical thickness measures,[27] a low rate of progression to AD,[25] and a high rate of reversion to "cognitively normal" within a few years.[25] Experts might suggest their opinions on the use of cholinesterase inhibitors in amyloid positive MCI patients. However, guidelines must be made based on evidence. Therefore, the effect of cholinesterase inhibitors in amyloid positive MCI patients must be proven through well-designed placebo controlled randomized clinical trials.

Finally, practical regimes for exercise and cognitive training are necessary. They should be included in the clinical guidelines to relieve patients' and their caregivers' burden with implementation of exercise or cognitive training. Multi-domain lifestyle interventions with detailed practical regimes have already been studied through the global network[28,29] so that investigation can be carried out by applying those to MCI including non-face-to-face treatment using digital therapeutics.

In conclusion, guidelines for the management of MCI should be updated based on evidence.

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