から考えると，身体活動量を測定することは対象者の健康状態を評価する上で有用な一指標であると考えることもできる。

身体活動量を定量的に測定するためには機器を用いた方法と質問紙を用いた方法の2つが主に使用されている。前者の中で用いられることの多い機器としてモーションセンサーである加速度計が挙げられる[15]。加速度計は，センサーを利用して体動によって生じた加速度を計測する機器で，前腕遠位部や腰部に取り付けることが多い。機器を数時間から数日にわたって装着することで生活全般における身体活動量を把握し，計測結果をグラフ化することでその頻度・強度・時間を簡便に示すこともできる。しかし歩行については精度高く評価できる反面，階段昇降や上肢中心の身体活動などは正しく評価できない欠点があるともされる[15]。後者の質問紙は多種多様な形式のものが存在するが，国際的に広く用いられているInternational Physical Activity Questionnaire Long version（IPAQ）や，高齢者を対象としたPhysical Activity Scale for the Elderly（PASE）などが本邦では多く用いられている。日本語版PASEはHagiwara et al.[16]によって作成され，過去1週間の仕事関連の活動，家庭内の活動，余暇活動の3要素それぞれの身体活動量を得点化できる。青田ら[17]によるとその利点は「①低強度の身体活動が項目として含まれている。②回答が短時間でおこなえる。③思い出しの期間が短い。④郵送法にも面接法にも利用が可能」であるとされている。

身体活動量の減少は特に高齢者において多く見られ[18]，慢性的ストレスなどの健康状態に関与していると思われる。我が国では高齢者を配偶者が，もしくは65歳以上の子らが介護することも多く見られる。このような高齢介護者の身体活動について横断的に調査し，その特性を把握することは重要な課題であると考える。以下に一般的介護者，および認知症介護者の身体活動に関する横断研究を紹介する。

一般的介護者を対象とした横断研究ではFredman et al.[19]が179名の介護者と670名の非介護者を対象に質問紙法を用いて余暇活動での身体活動状況と生活全般的な身体活動状況を調査している。結果，非介護者に比べて介護者の余暇活動での身体活動量は有意に少なく，生活全般的な身体活動量に差はなかったとしている。北村ら[20]は介護者10名に対し加速度センサーを搭載したライフコーダEXを用いて身体活動量を測定し，ZBIとWHO-QOLとの関連を調べている。結果，身体活動量とQOLとの間に正の相関が，介護負担感とQOLとの間に負の相関がみられたとしている。身体活動量と介護負担感との間には負の相関傾向がみられたが有意ではなかったとしている。また，仕事・趣味の有無により身体活動量に有意な差がみられたとも報告している。

認知症家族介護者を対象とした横断研究ではHirano et al.[21]がアルツハイマー型認知症者を介護する65歳以上の家族50名に対して調査を行っている。身体活動の評価にはphysical activity questionnaire for the elderly（PAQ）を用い，あわせてZBIを用いて介護負担感の評価を行った。PAQは家事活動，スポーツ活動，趣味活動の3項目から構成され，それぞれ得点化される。結果，PAQ全体の得点とZBIの間に有意な相関がみられ，PAQ3項目の中では趣味活動の得点のみがZBIと有意な相関関係にあった。結論として，身体活動，特に趣味活動の活動量を増加させる介入が介護負担感の軽減に有効である可能性に言及している。Chattillion et al.[22]は認知症者を介護する55歳以上の家族66名に対して

調査を行った。身体活動の評価には Rapid Assessment of Physical Activity questionnaire（RAPA）と Activity Restriction Scale（ARS）を用い，あわせて Role Overload Scale（ROS）を用いて介護負担を，そして血圧値を用いて健康状態の指標とした。ARS は日常生活での活動が制限されていることに対する自覚の程度を測定するものであり，5 件法 9 項目の質問から成る。血圧値には収縮期血圧と拡張期血圧の他，平均動脈圧も算出している。結果，日常生活の活動制限を多く自覚するグループで有意に平均動脈圧が高く，この傾向は収縮期血圧，拡張期血圧でもみられた。結論として，このような結果には活動制限の状況のみならず喜ばしい出来事（Pleasant Events）の有無なども関与するとしながらも，それらが心疾患発症の要因と成り得る血圧の昇降に関連していることを示唆した。Ho et al.[23] は上述の Chattillion らと同様 ARS を用いて日常生活に関する制限の自覚と，ストレスの指標として血液中の norepinephrine（NE），epinephrine（EPI）の値との関連を調べた。対象はアルツハイマー型認知症者を介護する 55 歳以上の家族 84 名であった。結果，まず活動制限の自覚と介護期間の間に関連がみられ，制限が大きい場合に介護期間と EPI の間に有意な相関がみられた。しかし制限が小さい場合の EPI，および制限の大小にかかわらず NE の値は介護期間との関連はみられなかった。

適度な身体活動が人々の健康に寄与することは周知の事実であろう。高齢者や介護者の身体活動に関する報告を俯瞰すると，その全体的な活動量はもちろんのこと，活動の質や内容に注目することが重要であるとわかる。一般的に高齢者でいうと退職や子育ての終了に伴う役割的活動の減少が，介護者でいうと社会参加や趣味に従事する時間の減少などの余暇活動の減少が多くみられる。対象者の身体活動上の問題点を正しく把握し，その問題点に向けた介入支援を行っていくことが重要であると考えられる。その際，前項でも述べたように，評価の中で機器やバイオマーカーを用いてより客観的にあらわすことで，その効果や有用性

表 1　認知症家族介護者に対して身体活動を用いて介入を行った RCT3 報告の比較

	①Hirano et al.(2011)	②King et al.(2002)	③Connell et al.(2009)
被介護者の認知症原因疾患	アルツハイマー病	特定の疾患なし	
対象者	65歳以上の家族 31名 （介入群17名，対照群14名）	女性配偶者 100名 （介入群51名，対照群49名）	50歳以上の女性家族 137名 （介入群74名，対照群63名）
身体活動プログラムの内容	3 METsの運動 30分/回	主に，速い歩行 30～40分/回	有酸素運動 30分/回
運動強度	中等度		低～中等度
頻度，期間	3回/週，12週間	4回/週，12か月	3回/週，6か月
実施場所	自宅		
対照群プログラム	なし	栄養教育	なし
介入効果	・介護負担感 ・疲労感 ・睡眠の質の改善	・総エネルギー消費 ・ストレス誘発性血圧反応 ・睡眠の質 ・抑うつ ・自覚ストレスの改善	・運動スコア ・自覚ストレス ・運動に対する自己効力感の改善

を広く発信することができると考える。

Ⅳ．認知症家族介護者への身体活動を用いた介入

ではこれまでに認知症家族介護者への身体活動を用いた介入にはどのようなものがあるか。本稿では Hirano et al.[24]（以下，①），King et al.[25]（以下，②），Connell et al.[26]（以下，③）の3つのRCTを紹介するとともに，その概要を表1に示す。

1. 対象者

②③では被介護者の認知症の原因疾患は限定せず，①のみアルツハイマー型認知症に限定して行っている。②③は女性介護者に限定しており，②では配偶者を，③では50歳以上を対象としている。①は男女の制限はなく65歳以上の介護者を対象としている。①②③の対象者数はそれぞれ31名（介入群17名，対照群14名），100名（介入群51名，対照群49名），137名（介入群74名，対照群63名）であった。

認知症は原因疾患によってその症状は少なからず異なり，それぞれの介護者が経験する労苦も異なるものと考えられる。より質の高いエビデンス構築のためには認知症原因疾患を限定したプロトコールが必要であるかもしれない。同様に女性・男性，配偶者・子らなどではその生活スタイルや認知症者との関係性が異なることも多いため，広くリクルートを行い，それぞれの階層で分析を行うことが理想であるかもしれない。

2. プログラム内容

①では介入群に対して3 METsの一般的な運動を週に3回，12週にわたって実施し，対照群に対しては特に介入を行わなかった。②では介入群に対して心拍数が最大心拍数の60～75%程度になる運動（多くの対象者は速い歩行を実施）を1回30～40分，週に4回，12か月にわたって実施し，対照群に対しては栄養教育を実施した。③では介入群に対して低強度（遅い歩行程度）～中強度（速い歩行程度）の有酸素運動を1回30分，少なくとも週に3回，6か月にわたって実施し，対照群に対しては特に介入を行わなかった。

上記プログラムの強度，頻度としては中強度，1回30分，週に3回程度の身体活動を実施しており，これは厚生労働省の健康づくりのための身体活動基準[14]「30分以上の運動を週に2回以上行う」「高齢者でも3METs以上の運動に取り組み，身体活動量の維持・向上を目指すことが望ましい」とほぼ一致した内容であった。種目に関しては本人の趣味・好みもあるため統一することは望ましくないかもしれないが，今後は強度，頻度を客観的な指標で一定としたRCTを行うことでより介入効果を強調できるものと考える。

3. 実施方法

①の実施場所は自宅であり，日々の歩数や運動の記録を介護者自身に記録させている。②の実施場所も自宅であり，導入時説明のほか，期間中に15回の電話による指導を行った。身体活動の記録は介護者自身が行い，月に1回研究実施者に郵送した。③の実施場所も自宅であり，期間中に訓練を受けた行動変容カウンセラーが14回の電話による指導を行った。

いずれの研究も身体活動の実施場所に自宅を設定している。これには病院や施設でプログラムを実施するとなると，その都度介護者に赴いていただくこととなり，そのこと自体が負担になりかねないとの配慮がうかがわれる。決まった時間に決まった場所で行うのではなく，介護者のペースで慣れ親しんだ環境におい

てプログラムを行うことが主流となっているものとうかがわれる。そしてその上で問題となる実施方法の適切さを担保するため，電話による細やかな指導や自記式記録様式の工夫などが必要であるといえる。

4. 介入効果

①においては介入群でZBIスコア，疲労感，睡眠の質の有意な改善がみられたのに対し，対照群ではそのような変化がみられなかったとしている。②においては対照群と比べ介入群では総エネルギー消費，ストレス誘発性血圧反応，睡眠の質の有意な改善がみられたとしており，両群ともにではあるが，抑うつや自覚ストレスなどの有意な改善もみられたとしている。③においては対照群と比べ介入群では週当たりの運動時間などの運動スコア，自覚ストレス，運動に対する自己効力感の有意な改善がみられたとしている。

疲労，睡眠，抑うつやストレスなどに対しては一定の効果が示されているが，その効果が主観的介護負担の改善にまで波及している報告は一部であった。これには介護者のみへの介入であるがゆえ，認知症者本人への効果が得られず，介護そのものの負担に大きな変わりがなかったものと考えられる。しかし認知症者に対する介護者の態度，介護者自身の心理的状態が認知症者の症状の悪化・改善につながるとの報告[27]もあることから，介護者の健康状態の改善が認知症者へ良い影響を及ぼすことも充分に考えられる。今後，より質の高いRCTを蓄積することが必要であると考える。

V．おわりに

2015年1月27日，厚生労働省は認知症施策推進総合戦略（新オレンジプラン）を公表した。認知症高齢者等にやさしい地域づくりに向けて我が国初めての国家戦略に位置付けられ，その7つの柱の一つとして「認知症の人の介護者への支援」が明記された。本稿では支援の一方策としての身体活動に注目したが，認知症カフェや認知症初期集中支援チームの設置推進などの直接的な支援についても課題は多く残る。いずれにせよ認知症者本人への支援のみでは不充分であることは明らかであり，家族，そして家族を支える周囲の人々への介入が必要となっているのであろう。

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Prediction of Outcomes in Mild Cognitive Impairment by Using ^{18}F-FDG-PET: A Multicenter Study

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Abstract.
Background: ^{18}F-FDG-PET is defined as a biomarker of neuronal injury according to the revised National Institute on Aging–Alzheimer's Association criteria.
Objective: The objective of this multicenter prospective cohort study was to examine the value of ^{18}F-FDG-PET in predicting the development of Alzheimer's disease (AD) in patients with mild cognitive impairment (MCI).
Methods: In total, 114 patients with MCI at 9 participating institutions underwent clinical and neuropsychological examinations, MRI, and ^{18}F-FDG-PET at baseline. The cases were visually classified into predefined dementia patterns by three experts. An automated analysis for ^{18}F-FDG-PET was also performed to calculate the PET score. Subjects were followed periodically for 3 years, and progression to dementia was evaluated.

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Results: In 47% of the patients with MCI, progression of symptoms justified the clinical diagnosis of "probable AD". The PET visual interpretation predicted conversion to AD during 3-year follow-up with an overall diagnostic accuracy of 68%. Overall diagnostic accuracy of the PET score was better than that of PET visual interpretation at all follow-up intervals, and the optimized PET score threshold revealed the best performance at the 2-year follow-up interval with an overall diagnostic accuracy of 83%, a sensitivity of 70%, and a specificity of 90%. Multivariate logistic regression analysis identified the PET score as the most significant predictive factor distinguishing AD converters from non-converters.

Conclusion: The PET score is the most statistically significant predictive factor for conversion from MCI to AD, and the diagnostic performance of the PET score is more promising for rapid converters over 2 years.

Keywords: Alzheimer's disease, cerebral glucose metabolism, ^{18}F-FDG-PET, mild cognitive impairment, prospective study

INTRODUCTION

Although an effective treatment for Alzheimer's disease (AD) has not been established, it is possible to delay the progression of symptoms with pharmacological and non-pharmacological treatments. Since pathological changes, such as senile plaques, arise more than 20 years before the manifestation of AD symptomatology, early diagnosis is required for early intervention.

Mild cognitive impairment (MCI) is a diagnostic entity used to describe abnormalities of memory function that do not fulfill the criteria for dementia [1]. MCI includes prodromal AD and other causes of dementia, as well as a form of cognitive impairment that does not progress to dementia and can disappear. Recent progress in basic research on AD and advances in *in vivo* biomarkers have led to a substantial revision of the diagnostic criteria for AD [2] to capture the full spectrum of the disease and to detect its earliest stages [3]. The revised National Institute on Aging–Alzheimer's Association criteria [4–6] suggest that accuracy in diagnosing AD can be improved with information provided by structural and biological evidence of AD pathology. Such information, if discernible at the MCI stage, may allow for differentiation of early AD from MCI owing to other causes [6].

^{18}F-FDG-PET is defined as a biomarker of neuronal injury according to the revised criteria. Studies with ^{18}F-FDG-PET have reported better diagnostic performance than other modalities in distinguishing AD-converters from non-converters in amnestic MCI patients [7–14]. Most studies have shown that the presence of AD-like hypometabolism in the posterior associative and/or posterior cingulate cortex of patients with MCI is predictive of conversion to AD within 1–3 years. However, with the exception of a few studies [11–14], the studies were conducted in relatively small groups of subjects, and follow-up times were not uniform. In this study, we report data from clinical and ^{18}F-FDG-PET assessments within a multicenter prospective cohort study of subjects with amnestic MCI (Study on Diagnosis of Early Alzheimer's Disease-Japan: SEAD-Japan). The objective of this study was to investigate the diagnostic value of ^{18}F-FDG-PET findings suggesting AD-like hypometabolism in predicting MCI conversion to AD, based on a multicenter prospective study.

METHODS

Participating subjects

Subjects with amnestic MCI were recruited between January 2006 and March 2007 and followed up annually for 3 years. Subjects were recruited from memory clinics of 9 centers specializing in AD and other dementias across Japan (Supplementary Table 1). All subjects were living independently in the community at the time of their baseline evaluation. This study was approved by the Ethics Committee at every participating institution. Each subject signed an informed consent form after the nature of the procedures had been fully explained.

All patients were free of significant underlying medical, neurological, or psychiatric illnesses. Patients were initially assessed using a neuropsychological test battery, including the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-cognitive component-Japanese version (ADAS-J cog), Clinical Dementia Rating (CDR), Geriatric Depression Scale (GDS), Everyday Memory Check List (EMCL), and Logical Memory Subset of the Wechsler Memory Scale Revised (WMS-R LM). In accordance with the inclusion criteria, MCI patients were aged between 50 and 80 years, with an MMSE score $\geq$24, a GDS score $\leq$10, a WMS-R LM I score $\leq$13, a LM II part A and part B score (maximum = 50) $\leq$8, and a CDR memory box score equal to 0.5. Patients with formal education for less than 6 years were excluded.

^{18}F-FDG-PET

Prior to baseline ^{18}F-FDG PET scanning, all subjects fasted for at least 4 h. Intravenous administration of ^{18}F-FDG (254 ± 107 MBq) was followed by a resting period of 40–60 min in a dimly-lit and quiet room, where participants were instructed to keep their eyes open. A static scan for 10.3 ± 5.5 min was performed in 2D or 3D mode after the resting period. Attenuation was corrected by a transmission scan with segmentation for dedicated PET and by a CT scan for PET/CT. Supplementary Table 2 lists the PET and PET/CT devices and reconstruction conditions.

The ^{18}F-FDG PET images were processed with the 3-dimensional stereotactic surface projections (3D-SSP) technique to generate z-score maps, using iSSP software version 3.5 (Nihon Medi-Physics Co. Ltd., Tokyo, Japan). The normal database used for generating the z-score maps was constructed based on 50 normal subjects (31 males and 19 females, average age = 57.6 y), with 10 normal subjects each from 5 participating institutions. The healthy subjects for the normal database had no memory complaint and no history of neurologic or psychiatric disorders. The results of their neurologic examination and brain imaging examinations (MR imaging or CT) were normal, and their cognitive function was judged to be normal by experienced neurologists (MMSE score, 25–30).

PET image interpretation

Three experts, blinded to clinical information, independently assessed the reconstructed PET images, referring to the 3D-SSP z-score map and correlating with MRI to classify the images into different dementia patterns of P1-P3, P1+, and N1-N3 [15]. When evaluations of the three raters did not completely match, the cases were discussed, and a consensus reading was agreed upon.

PET score

We calculated the AD t-sum, as described in previous publications [16, 17], by using the procedure implemented as module PALZ in the PMOD software package (version 3.2; PMOD Technologies, Zurich, Switzerland). The AD t-sum indicates the severity of the metabolic decrease in those brain areas that are typically affected by AD (multimodal association cortices mostly located in the temporal and parietal lobes), including an adjustment for an age effect.

In the present study, the AD t-sum was converted into the PET score by reference to its upper limit of normal, as determined previously [16], and log transformation to approach a normal distribution of values, according to the following equation [18]: PET score = $\log_2\{(\text{AD t-sum}/11{,}089)+1\}$.

MRI

All the subjects were scanned with a 1.5 T or 3T MRI system. A T1-weighted fast field echo sequence was used. Supplementary Table 3 lists the MRI devices and reconstruction conditions. T1-weighted 3-dimensional sagittal sections of the brains were acquired and analyzed on a PC using a voxel-based specific regional analysis system for Alzheimer's disease (VSRAD® advance, Eisai Co, Ltd, Tokyo, Japan), which was developed based on the voxel-based morphometry method and is now freely available [19–23]. First, equalization of voxel sizes and linear and nonlinear transformations were performed. Next, images of gray matter, white matter, and cerebrospinal fluid were separated, and the gray matter images were standardized and smoothed onto templates by using DARTEL (Wellcome Department of Imaging Neuroscience, London, UK). By using the z-score analysis method, comparative statistical analysis of the voxels was performed for the healthy control database. The database for the healthy controls contained data from 40 men and 40 women, each aged 54–86 (mean 70.2 ± 7.3) years. In this study, the averaged positive z-score in the target volume of interest (VOI) for the medial temporal structure, including the entorhinal cortex, head to tail of the hippocampus, and amygdala was used for further analyses.

Follow-up

Patients were observed at 1-year intervals for 3 years. The CDR, MMSE, EMCL, and WMS-R-LM were re-administered at each visit. Repeat ^{18}F-FDG-PET and MRI scans were optional. The ADAS-J cog was also administered as an option in selected centers. Conversion to dementia was established when the CDR became ≥ 1.0. No further follow-up of patients after reaching CDR ≥ 1.0 was requested. AD was diagnosed in a given center when a patient fulfilled both CDR ≥ 1.0 and the National Institute of Neurological and Communicative Disorders–Alzheimer's Disease and Related Disorders Association's (NINCDS-ADRDA) "probable AD" criteria. The diagnosis of other causes was based on established clinical criteria for each disease, including vascular dementia (VaD) [23], dementia with Lewy bodies (DLB) [25], frontotemporal dementia (FTD) [26], and Creutzfeldt–Jacob disease [27].

Researchers (YW and YA) of the study group, who were highly experienced in evaluating dementia, finalized the clinical outcome of each case based on the submitted case report form. They were blinded as to the PET results.

Logistic regression analysis

Multivariate logistic regression analyses were used to assess whether baseline ^{18}F-FDG-PET was predictive of longitudinal clinical outcome. We estimated the odds of AD converters versus non-converters as a function of age, gender, education level, WMS-R-LM II, and PET score. Results were considered significant at $p<0.05$. Statistical analyses were performed using SPSS (version 14.0; SPSS Inc., Chicago, IL) for Windows (Microsoft).

RESULTS

Baseline characteristics and neuropsychologic reevaluation

In total, 114 patients (64 women and 50 men; mean age, 70.8 ± 7.5) were included in the study. The mean education level was 11.5 ± 3.0 years. Of these 114 patients, 23 withdrew from the study, including 5 with no follow-up, 5 with only 1 visit, and 13 with 2 visits without conversion to dementia. Because of the uncertainty concerning their cognitive status over time, these 23 patients were excluded from the outcome analyses. Of the remaining 91 subjects, 44 patients progressed to dementia, 41 developed AD, and 3 developed non-AD dementia (FTD, DLB, and VaD) (Fig. 1). The patterns of PET images for those 3 patients were as follows: FTD patient, P2; DLB and VaD patients, P1. Since AD was the primary outcome of the study, the patients with non-AD dementia were excluded from further analyses and were not considered in the denominator for the analysis of prediction accuracy. The cumulative conversion rate over 3 years was 47%.

Demographic and neuropsychological data at the initial visit in patients who developed AD (AD-converters) and those who did not (non-converters) are shown in Table 1. At baseline, the two groups differed in the MMSE, ADAS-J cog, WMS-R-LM, and GDS scores. There was no difference observed in age, educational level, or gender distribution between these two groups.

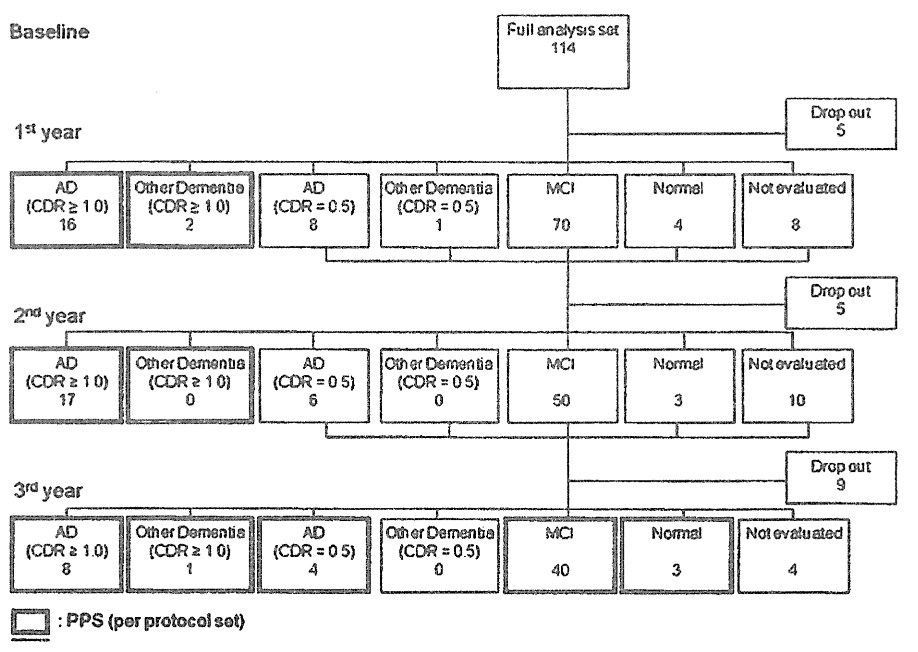

Fig. 1. Schematic summary of clinical outcomes in all MCI cases. Originally, 114 patients with MCI were included. A total of 23 patients dropped out during the 3 years. Our final sample size for the analyses of PET images was 88 patients (excluding 3 patients who converted to other dementias).

Table 1
Demographic and neuropsychological data at baseline

	AD converter ($n = 41$) Mean (SD)	Non-converter ($n = 47$) Mean (SD)
Age	71.2 (6.5)	70.5 (6.7)
Education (year)	12.1 (3.2)	11.8 (3.0)
WMS-R-LMI**	6.3 (3.3)	9.4 (3.2)
WMS-R-LMII**	1.7 (2.2)	4.1 (2.9)
MMSE*	25.6 (1.7)	26.9 (2.0)
ADAS*	10.6 (5.0)	7.6 (4.3)
GDS*	4.9 (2.2)	3.4 (2.0)

WMS-R-LM, Wechsler Memory Scale–Revised Logical Memory; MMSE, Mini-Mental State Examination; ADAS, Alzheimer's Disease Assessment Scale; GDS, Geriatric Depression Scale. * $P < 0.005$, ** $P < 0.001$.

PET image interpretation

As the result of image interpretation, P1 and P1+ patterns were observed in 69.9% and 8.0%, respectively, and the other patterns were observed in 22.1%, including the P2 pattern in 4.4%, of all the amnestic MCI patients (Fig. 2). In this study, all P1+ cases showed a P1 pattern with occipital hypometabolism. Therefore, we combined the P1 pattern and P1+ pattern as an AD/DLB pattern for calculating the diagnostic performance.

Silverman's classification in the central image interpretation completely matched in 53% of cases, and two or more complete matches from three raters were achieved in 91% of cases. Since the P1 pattern accounted for about 70% of cases in the image interpretation, the frequency distribution of the Silverman's classification was significantly biased. A significant deviation in the distribution increases the probability of accidental match, making it difficult to correctly evaluate the degree of agreement.

The image interpretation based on the classification of PET images predicted conversion to AD during 3-year follow-up with an overall diagnostic accuracy of 68%, a sensitivity of 98%, and a specificity of 41% for the full analysis data set of the 88 subjects in this study.

The diagnostic parameters for each follow-up interval are summarized in Table 2.

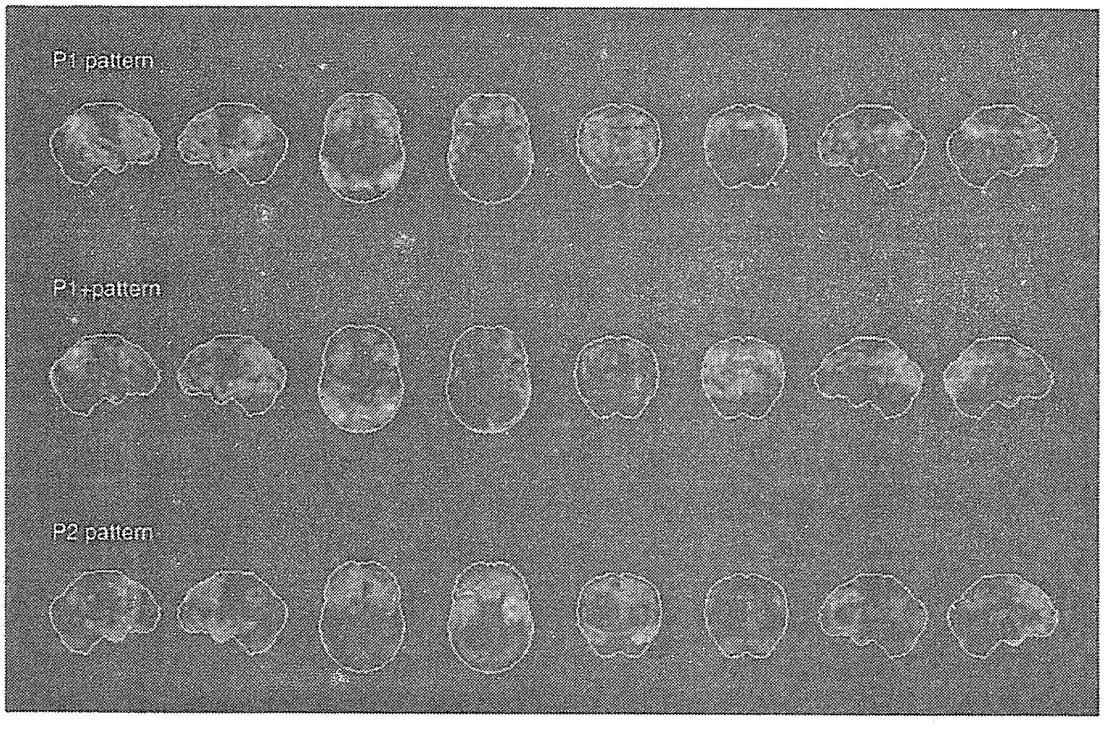

Fig. 2. 3D-SSP z-score maps showing hypometabolism in the progressive pattern groups (P1 pattern group, P1+ pattern group, and P2 pattern group) in comparison with the normal database are shown. From left to right, 3D-SSP maps are shown on the right lateral, left lateral, superior, inferior, anterior, posterior, and right and left middle views of a standardized brain image.

Table 2
Diagnostic parameters

Variable	Follow-up intervals (y)	AUC (95% CI)	Cutoff	SEN	SPE	ACC	PPV	NPV
PET visual interpretation	1	–	–	1.00	0.22	0.35	0.21	1.00
	2	–	–	0.97	0.32	0.56	0.45	0.95
	3	–	–	0.98	0.41	0.68	0.60	0.95
PET score	1	0.708 (0.569–0.846)	1.03	0.69	0.75	0.74	0.34	0.93
	2	0.809 (0.714–0.905)	1.03	0.70	0.90	0.83	0.79	0.84
	3	0.747 (0.641–0.852)	1.03	0.61	0.91	0.77	0.86	0.73
VSRAD z-score	1	0.679 (0.533–0.825)	1.47	0.75	0.57	0.60	0.26	0.92
	2	0.684 (0.570–0.799)	1.44	0.69	0.64	0.66	0.51	0.79
	3	0.658 (0.543–0.774)	1.44	0.64	0.64	0.64	0.60	0.68

AUC, area under the curve; SEN, sensitivity; SPE, specificity; ACC, accuracy; PPV, positive predictive value; NPV, negative predictive value.

PET score

The PET scores at baseline were 1.26 ± 0.69 for the AD converters and 0.70 ± 0.44 for the non-converters, respectively ($p < 0.001$). It was hypothesized that subjects who had a PET score at baseline above 1.0 had a significantly increased risk for progression. The statistics for predicting progression during 3-year follow-up were sensitivity, 61%; specificity, 79%; and accuracy, 70%. When mean PET scores were calculated according to conversion time, converters in the 1st and 2nd year showed a significantly higher PET score compared to that of non-converters. In contrast, converters in the 3rd year showed no difference in the mean PET score compared to non-converters (Fig. 3). The diagnostic accuracy during the 2-year follow-up was more promising, with an overall diagnostic accuracy of 76%, a sensitivity of 70%, and a specificity of 80%.

Area under the curve of ROC analysis for the PET score was greatest for 2-year follow-up. The ROC-derived PET score thresholds obtained using Youden index [28] yielded an adjusted accuracy of 83%, with 70% sensitivity and 90% specificity at a threshold value of PET score = 1.03 during 2-year follow-up. The diagnostic parameters for each follow-up interval are summarized in Table 2.

MRI

Because four cases at one institution were examined exceptionally with a 3T MRI system, those four were excluded from further analysis.

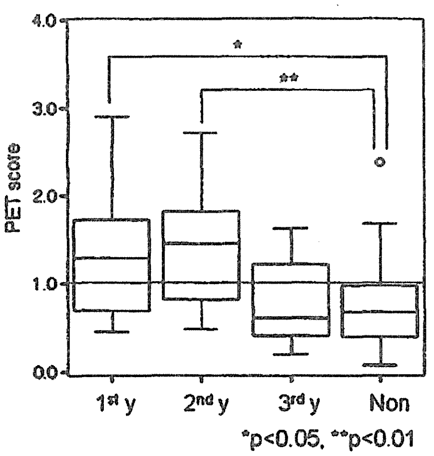

Fig. 3. Box plot of baseline PET scores (interquartile and full range) for converters according to conversion time. MCI patients progressing to AD in the 1st and 2nd year have significantly higher scores than non-converters ($p < 0.05$ and $p < 0.01$ in Tukey multiple comparisons). 1st y = 1st year converter, 2nd y = 2nd year converter, 3rd y = 3rd year converter, and Non = non-converter.

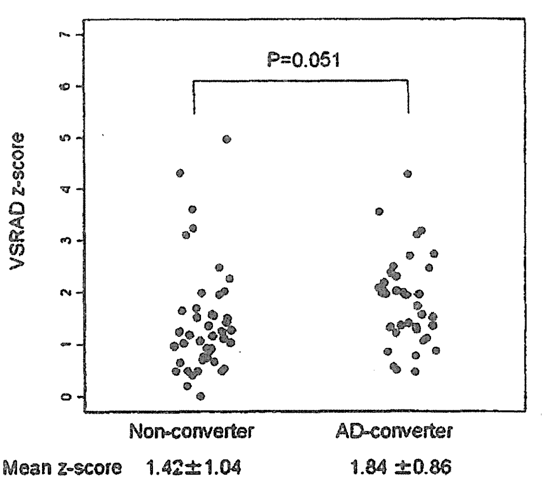

Fig. 4. Comparison between AD converters and non-converters on VSRAD z-scores in the target VOI for the left medial temporal structures. There was no significant difference between the two groups ($p = 0.051$). VSRAD, voxel-based specific regional analysis system for Alzheimer's disease.

For the AD converters and non-converters, the bilateral mean z-scores in the target VOI for the medial temporal structures at baseline were 1.84 ± 0.75 and 1.57 ± 1.01, respectively ($p = 0.191$); the right side mean z-scores were 1.80 ± 0.93 and 1.66 ± 1.13, respectively ($p = 0.543$); and the left side mean z-scores were 1.84 ± 0.86 and 1.42 ± 1.04, respectively ($p = 0.051$). Thus, the AD converters showed a tendency toward higher mean z-score in the target VOI for the left medial temporal structures but did not reach significance (Fig. 4).

Area under the curve of ROC analysis for VSRAD z-score was greatest for 2-year follow-up (Table 2). The ROC-derived thresholds using Youden index [28] for VSRAD mean z-score yielded an adjusted accuracy of 66%, with 69% sensitivity, and 64% specificity at a threshold value of VSRAD z-score = 1.44 during 2-year follow-up.

Logistic regression analysis

Multivariate logistic regression analysis identified PET score and WMS-R-LM II as predictors distinguishing AD converters from non-converters over 2 years. When age, gender, education level, WMS-R-LM II, and PET score were submitted to the forced entry procedure, AD conversion was associated significantly with the PET score ($p < 0.0001$; odds ratio, 28.25; 95% confidence interval [CI], 6.02–132.6) and WMS-R-LM II ($p = 0.001$; odds ratio, 0.61; 95% CI, 0.46–0.81) (Table 3). The combination of PET score and WMS-R-LM II distinguished AD converters from non-converters with 84.8% accuracy, 72.7% sensitivity, and 91.5% specificity.

DISCUSSION

In this study, 41 (47%) of 88 MCI patients progressed to AD. The annual conversion rate was 15.7% during the 3-year follow-up. These results are consistent with reports from other groups, indicating that, annually, 12% to 15% of amnestic MCI patients progress to AD [1].

Group comparisons based on classification of the PET image interpretations demonstrated heterogeneity in ^{18}F-FDG-PET among subjects with amnestic MCI (Fig. 2). Although the progressive pattern included the P1 pattern (69.9%), the P1+ pattern (8.0%), and the P2 pattern (4.4%), 41 (93.2%) of 44 converters were AD converters with 3 converting to DLB, FTD, and VaD.

The frequency of the P1+ pattern in the absence of DLB was relatively high. We reported that 28% of patients with AD had reduced blood flow in the occipital lobe [29]. Additionally, in our prospective SPECT study to examine the value of ^{123}I-N-Isopropyl-4-Iodoamphetamine cerebral blood flow SPECT with regard to early diagnosis of AD in patients with MCI, the frequency of the DLB pattern was 18.7% of all patients with amnestic MCI [30]. We assumed that older patients in general tend to have reduced blood flow or glucose metabolism in the occipital lobe, including those with AD. This is a topic for a future study.

Because we considered that differentiating between AD and DLB based on reduced blood flow or glucose metabolism in the occipital lobe was difficult and that PET scores do not distinguish DLB from AD, we applied pooling of the P1 pattern with the P1+ pattern in this study in the same way as in our previous SPECT study [30]. Although we analyzed the data for the P1 pattern only, the results were almost the same as those when pooling P1 with P1+(data not shown). Therefore, we believe that combining the P1 pattern with the P1+ pattern as an AD/DLB pattern to investigate the role of ^{18}F-FDG-PET in predicting conversion to AD is not problematic. The clinical significance of the heterogeneity in ^{18}F-FDG-PET should be further evaluated.

The diagnostic performance of ^{18}F-FDG-PET was calculated based on the clinical outcomes after 3 years of follow-up. The PET image interpretation showed a high sensitivity for detection of AD-converters, but its specificity was relatively low. Low specificity

Table 3
Results of multivariate logistic regression analyses for predictors of AD conversion

Variable	Coefficient (B)	SE	Wald	df	p value	Odds ratios	95% CI	
Age	0.019	0.063	0.092	1	0.761	1.019	0.901	1.153
Gender	−0.958	0.743	1.662	1	0.197	0.384	0.089	1.646
Education level	0.041	0.114	0.129	1	0.720	1.042	0.833	1.303
WMS-R-LMII	−0.502	0.146	11.887	1	0.001	0.605	0.455	0.805
PET score	3.341	0.789	17.942	1	<0.0001	28.252	6.021	132.572
Constant	−4.051	4.994	0.658	1	0.417	0.017		

df, degree of freedom; CI, confidence interval; WMS-R-LM, Wechsler Memory Scale–Revised Logical Memory.

indicated that some non-converters showed AD/DLB-like hypometabolism on ^{18}F-FDG-PET images. These results were not in line with previous reports [7–11] where higher specificity and diagnostic accuracy were reported. The true reason for low specificity in spite of a longer follow-up compared to previous reports is unclear. One possible explanation is the difference in the characteristics of registered MCI patients for each study. In fact, conversion rates from MCI to AD were very high in some studies. Such an increase in the ratio of converters may result in a decrease in false-positive cases.

Considering the higher mean PET scores of converters in the 1st and 2nd year of follow-up, we hypothesized that the rapid converters showed more distinct AD/DLB-like hypometabolism compared to the slower converters. Although a threshold effect might exist, overall accuracy of the PET score was better than that of visual assessment at all time intervals, as shown in Table 2. As the PET score is a numerical index, PET score threshold can be optimized to maximize the prediction accuracy. The best performance of PET score was achieved at the 2-year follow-up interval. In other words, the PET score was efficient at identifying rapid converters during the 2-year follow-up.

Multivariate logistic regression analysis demonstrated that the PET score derived from ^{18}F-FDG-PET was the most significant predictor for conversion to AD among amnestic MCI patients across institutions where various types of PET or PET-CT devices were used. These results were in line with recent reports using data from the Alzheimer's Disease Neuroimaging Initiative [12–14]. Furthermore, WMS-R-LM was identified as a significant predictor for conversion to AD. A combination of statistically significant predictors, both PET score and WMS-R-LM, could assist in early stratification of patients into high- or low-risk groups.

On the other hand, the VSRAD® z-score for MRI failed to identify MRI as a predictor to distinguish AD converters from non-converters. Our results were in line with a previous study showing that ^{18}F-FDG PET is a better predictor of conversion than MR imaging [12, 14]. The possible reasons why FDG PET offers greater accuracy or sensitivity than other biomarkers at the MCI stage are not fully understood, although there is growing consensus that metabolic deficits are greater in magnitude than volumetric changes earlier in the disease.

The present study had some limitations. First, our neuropsychological test batteries were limited and did not include tests specifically designed to assess cognitive function for the early diagnosis of AD, although the MMSE and WMS-R-LM are more practical for use in a routine clinical scenario. Second, the mean age of individuals in the normal database for 3D-SSP was lesser than that of the patient group. Further analysis would be needed using an age-matched normal database. Third, although only a VBM using VSRAD® was used to evaluate volumetric changes of MRI, different methodologies such as cortical approaches rather than voxel-based approaches should be further applied [31]. Fourth, the primary outcome (conversion to AD) contained some error because some patients classified as non-converters may convert to AD with longer follow-up. Therefore, improvement of specificity and diagnostic accuracy of the PET image interpretation can be expected due to a decrease in false-positive cases provided by a longer follow-up period.

CONCLUSIONS

Visually assessed ^{18}F-FDG-PET is a very sensitive but relatively nonspecific measure for predicting conversion to AD in patients with MCI. On the other hand, the PET score is the most statistically significant predictive factor for conversion from MCI to AD, and the diagnostic performance of the PET score is more promising for rapid converters over 2 years.

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Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/14-1338r1).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-141338.

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ORIGINAL ARTICLE

Current activities of medical centers for dementia in Japan

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Aim: We investigated the current activities of medical centers for dementia (MCD), and proposed recommendations for a national dementia strategy.

Methods: A questionnaire was mailed to 172 hospitals designated as MCD as of 7 August 2012.

Results: Data from 117 MCD that adequately responded and were designated by 1 April 2012 were analyzed. The mean and median numbers of medical consultations per MCD were 1035 and 595/year (range 114–8541/year), those of patients diagnosed with dementia-related disorders were 266 and 231/year (range 3–1179/year), those of patients with dementia-related disorders admitted to the MCD hospital were 89 and 47/year (0–1176/year), and mean and median proportions of patients discharged within 2 months were 45.5 and 36.8% (range 0–100%). Outreach services in collaboration with a community general support center were provided in 23.9%, while training for community general support center staff members was carried out in 66.7%. Of MCD hospitals, 31.6% were designated as an emergency medical hospital, and of these, specialist liaison-team services for patients with dementia in the emergency room were provided in 56.8%.

Conclusions: Most MCD are considered to function fairly well in line with the guidelines published by the Ministry of Health, Labour and Welfare. However, there is a huge discrepancy in the number of patients diagnosed with dementia-related disorders and the length of stay for inpatient care among facilities. To make all MCD function adequately, the activity of MCD should be monitored longitudinally using the standardized assessment methods. **Geriatr Gerontol Int 2014; 14 (Suppl. 2): 23–27.**

Keywords: community-based integrated care system, early diagnosis, medical center for dementia, outreach service, specialist liaison-team service.

Introduction

Early diagnosis and intervention of dementia is crucial for both patients with dementia and their families in order to maintain their quality of life and allow them to continue to live well within the community. In 2012, a report entitled "Future Directions of Policies on Dementia" was published, and "A Five-Year Plan for Promotion of Dementia Measures (Orange Plan)" was subsequently announced by the Japanese Ministry of Health, Labour and Welfare (MHLW). In these documents, the importance of early diagnosis and intervention in dementia was emphasized, and adequate placement of specialized medical services including Medical Centers for Dementia (MCD) was proposed.

In 2008, the MCD was established by the MHLW as a new national health program for improving the local situation of medical care for dementia.[1] In 2010, two types of MCD were introduced: the regional-type MCD and the core-type MCD. According to the guidelines published by the MHLW, the regional-type MCD is required to: (i) provide specialized medical services for dementia including medical consultation, differential diagnosis and initial intervention, and medical treatment for the acute phase of neuropsychiatric symptoms and concurrent medical conditions, and (ii) promote community-based integration of dementia care including education for primary care physicians and other community professionals, participation in a local liaison council for dementia care, and dissemination of information to the public. In addition to these functions, the core-type MCD is required to: (iii) provide emergency services for concurrent medical conditions. As of 1

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October 2013, there were 237 MCD (226 regional type and 11 core type) throughout Japan.

In the present study, we investigated the current activities of MCD, and proposed recommendations for a future national dementia strategy in Japan.

Methods

A questionnaire that inquired about the current activities of the MCD was mailed to 172 hospitals designated as MCD as of 7 August 2012. The questionnaire included: (i) basic characteristics of the MCD facilities; (ii) functions expected for provision of specialized medical services; (iii) functions expected for promotion of community-based integration of dementia care; and (iv) functions expected for provision of emergency services.

The study protocol was approved by the Ethics Committee of the Tokyo Metropolitan Institute of Gerontology (TMIG-24-964). Statistical analyses were carried out using SPSS software version 20 (IBM SPSS, Chicago, IL, USA). For group comparisons, Mann–Whitney *U*-test was used for non-parametric variables.

Results

Of 172 MCD, 118 adequately responded (response rate: 68.6%). Of these, data from 117 MCD that had been designated by 1 April 2012 were exclusively analyzed.

Characteristics of MCD facilities

Table 1 shows the characteristics of the MCD facilities analyzed in the present study. Of 117 MCD facilities, 42.7% were general hospitals and 57.3% were psychiatric hospitals. The commonest establisher was an incorporated medical institutive agency (46.2%), followed by prefectural or city government (12.0%), incorporated educational institutive agency (10.3%), incorporated public service agency (9.4%) and municipality government (6.0%). Psychiatric beds were available in 84.6% of facilities. Of all facilities, 92.3% had a department of psychiatry, 76.9% a department of internal medicine and 50.4% a department of neurology.

Activities of MCD

Activities of the MCD analyzed in the present study are shown in Table 2.

Table 1 Characteristics of medical centers for dementia

Characteristics	*n*	Proportion
Type of facility		
General hospital	50	42.7%
Psychiatric hospital	67	57.3%
Establisher		
Incorporated educational institutive agency	12	10.3%
National government, including national incorporated administrative agency	3	2.6%
Prefectural or city (designated by ordinance) government, including local incorporated administrative agency	14	12.0%
Municipality government	7	6.0%
Incorporated public service agency	11	9.4%
Incorporated medical institutive agency	54	46.2%
Others	15	12.8%
No answer	1	0.9%
Psychiatric beds		
Possessed	99	84.6%
Not possessed	18	15.4%
Clinical departments included in MCD facility		
Psychiatry	108	92.3%
Internal medicine	90	76.9%
Neurology	59	50.4%
Rehabilitation	48	41.0%
Cardiovascular	45	38.5%
Radiology	44	37.6%

MCD, medical center for dementia.

Table 2 Activities of medical centers for dementia

Activities	*n*	Proportion or range
To provide specialized medical services		
Regularly employ specialists and equipment (no. facilities)		
Medical specialist in dementia†	114	97.4%
Psychologist	101	86.3%
Psychosocial worker or public health nurse	108	92.3%
Special medical consultation room	114	97.4%
Medical consultations (mean number per MCD per year, (median))		
Telephone	687, (360)	15–7458
Interview at center	297, (165)	6–1683
Home visit	7, (0)	0–153
Other (e.g. email)	11, (0)	0–405
Total	1035, (596)	114–8541
Medical examinations provided within facility (number of facilities)		
Blood tests	114	97.4%
Urine tests	112	95.7%
Electrocardiography	109	93.2%
Chest radiography	107	91.5%
Neuropsychological tests	113	96.6%
Brain computed tomography	113	96.6%
Brain magnetic resonance imaging	58	49.6%
Brain single photon emission computed tomography	38	32.5%
Patients diagnosed, (mean number per MCD per year (median))		
Dementia-related disorders	266, (231)	3–1179
Alzheimer disease (including Alzheimer's disease with CVD)	178, (141)	0–747
Vascular-type dementia	22, (15)	0–123
Lewy body disease	13, (6)	0–192
Frontotemporal dementia	6, (3)	0–51
Normal pressure hydrocephalus	3, (0)	0–87
Dementia due to alcohol-related disorders	2, (0)	0–30
Dementia due to other diseases	14, (6)	0–114
Non dementia-related diseases	38, (21)	0–384
Other symptomatic or organic disorders	5, (3)	0–66
Mood disorder	11, (6)	0–168
Schizophrenia, schizotypal disorders, delusional disorders	4, (3)	0–39
Epilepsy	1, (0)	0–12
Normal	14, (6)	0–150
Total	318, (279)	3–1179
Patients with dementia-related disorders referred from primary care, (mean number per MCD per year (median))	160, (131)	0–828
Patients with dementia-related disorders referred to primary care, (mean number per MCD per year (median))	91, (60)	0–621
Patients with dementia-related disorders admitted to MCD hospital, (mean number per MCD per year (median))	89, (47)	0–1176
Patients with dementia-related disorders discharged within 2 months, (mean % per MCD per year (median))	45.5, (36.8)	0–100
To promote community-based integration of dementia care		
Training for primary care physicians (no. facilities)	85	72.6%
Training for CGSC staff members (no. facilities)	78	66.7%
Local liaison council for dementia care (no. facilities)	105	89.7%
Case conferences together with community staff members (no. facilities)	97	82.9%
Outreach counseling services by visiting patients' homes in collaboration with CGSC (number of facilities)	28	23.9%
Outreach advisory services by visiting other medical or long-term care facilities (no. facilities)	20	17.1%
To provide emergency services for concurrent medical conditions		
Designated an emergency medical hospital (no. facilities)	37	31.6%
Specialist liaison team services for patients with dementia in ER (no. facilities within 37 emergency medical hospitals)	21	56.8%
Specialist liaison team services for patients with dementia in general inpatient wards (no. facilities)	52	44.4%
Education programs for medical staff working in general inpatient wards (no. facilities)	54	46.2%
Beds for emergency patients on holiday (no. facilities)	39	33.3%

†Medical specialist for dementia is defined as: (i) medical specialist qualified by the Japanese Psychogeriatric Society or the Japan Society of Dementia Research; or (ii) clinical doctors providing specific medical services for dementia for more than 5 years. CGSC, community general support center; CVD, cerebrovascular disease; ER, emergency room; MCD, medical center for dementia.

To provide specialized medical services, 97.4% of the MCD regularly employed medical specialists in dementia, 86.3% psychological specialists and 92.3% psychosocial workers or public health nurses. Special medical consultation rooms were available in 97.4% of the MCD. Medical consultations were most frequently provided by telephone (mean 687/year; median 360/year), followed by face-to-face interview at the MCD (mean 297/year; median 165/year). Mean and median total numbers of medical consultations per MCD were 1035/year and 596/year. Medical investigations, including blood tests, urine tests, electrocardiography, chest X-ray, neuropsychological tests and brain X-ray computed tomography, were provided within the facility in more than 90% of the MCD. Brain magnetic resonance imaging was provided within the facility in half of the MCD, and brain single photon emission computed tomography in one-third of the MCD. The mean and median numbers of patients diagnosed with dementia-related disorders (including mild cognitive impairment) per MCD were estimated to be 266/year and 231/year. Among these patients, 160 (mean) and 131 (median) were referred from primary care, and 91 (mean) and 60 (median) were referred to primary care. The mean and median numbers of patients with dementia-related disorders admitted to the MCD were 89/year and 47/year. Of these patients, 45.5% (mean) and 36.8% (median) were discharged within 2 months.

To promote community-based integration of dementia care, 72.6% of the MCD provided training for primary care physicians, 66.7% training for staff members of community general support centers (CGSC), 89.7% participated in a local liaison council for dementia care and 82.9% participated in individual case conferences with community staff members. Outreach counseling services by visiting patients' homes in collaboration with the CGSC were provided in 23.9%, and outreach advisory services by visiting other medical or long-term care facilities were provided in 17.1%.

To provide emergency services for concurrent medical conditions, 31.6% of MCD facilities were designated as an emergency medical hospital; of these, 56.8% provided specialist liaison-team services for patients with dementia in the emergency room (ER), and 44.4% provided such services for patients with dementia in general inpatient wards. For medical staff working in general inpatient wards, 46.2% of MCD provided education programs. For emergency patients with dementia on holiday, spare beds were available in 33.3% of MCD.

Discussion

Most MCD are considered to function fairly well in line with the guidelines published by the MHLW. Compared with the findings of a previous report on the Dementia Center for the Elderly (DCE),[2] which was established as a specialized medical service for dementia in 1989 and suspended in 2007, the MCD apparently more frequently provided medical consultations by telephone (median 360 *vs* 68) and face-to-face interview (median 165 *vs* 77), and more frequently diagnosed Alzheimer's disease (median 141 *vs* 42) and all diseases (median 279 *vs* 93) per facility per year.

However, there is a huge discrepancy in the level of activities among facilities. For example, the number of patients provided with medical consultation services ranged from 114 to 8541/year, and the number of patients diagnosed with dementia-related disorders ranged from three to 1179/year. In 2.6% of MCD, medical specialists in dementia were not employed and/or medical consultation rooms were not available. To make all MCD function adequately, it is recommended that the activities of MCD should be monitored longitudinally using standardized assessment methods and, if they do not function well, the reason should be thoroughly investigated.

A discrepancy in the length of stay for inpatient care was also found. The proportion of patients with dementia-related disorders discharged within 2 months ranged from 0% to 100% among facilities. When comparing types of facilities (general hospitals *vs* psychiatric hospitals), the proportion of patients with dementia discharged within 2 months was significantly higher in general hospitals than in psychiatric hospitals (median 87.7% *vs* 25.9%, $P < 0.001$, Mann–Whitney U-test). This discrepancy might in part be explained by the following reasons: (i) in general hospitals, in order to keep beds free for new acute inpatients and to obtain the medical treatment fee effectively, patients with dementia might tend to be discharged within the short-term and moved to long-term care facilities or psychiatric hospitals; and (ii) patients with dementia with a complex background (e.g. severe neuropsychiatric symptoms, vulnerable family caregivers, financial problems) might be more likely to be admitted to psychiatric hospitals. It is not easy for these patients to be discharged, because it is usually difficult to arrange sufficient community support and sufficient facilities where they can live long term. Therefore, it is recommended that MCD should contribute to the establishment of community-based integrated care systems in collaboration with local governments, so as to allow people with dementia and their family caregivers to live well in the community.

In the context of establishment of community-based integrated care systems, it is crucial for MCD to collaborate with the CGSC.[3] In 2006, CGSC was established nationwide to exercise a practical level of coordination necessary to implement community-based integrated care. Currently, there are approximately 4000 CGSC in areas where elderly people conduct their