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The Japanese MCI Screen for Early Detection of Alzheimer's Disease and Related Disorders

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Early detection of Alzheimer's disease and related disorders in Japan is increasingly important. The Mild Cognitive Impairment Screen (MCIS)—derived from the National Institute of Aging CERAD neuropsychologic battery—differentiates normal aging from MCI and mild dementia with 97.3% and 99% accuracy, respectively. The Japanese MCIS (JMCIS), Mini-Mental State Examination (MMSE), quantitative SPECT (qSP), and quantitative MRI (qMRI) were used to classify 63 outpatients at Fukuoka University Hospital who were either normal or had MCI based on Clinical Dementia Rating scores of 0 and 0.5, respectively. Performance statistics for the JMCIS, MMSE, qSP, and qMRI were, respectively: (1) accuracy = 0.964, 0.768, 0.722, 0.733; (2) sensitivity = 0.958, 0.792, 0.688, 0.700; (3) specificity = 1.000, 0.625, 1.000, 1.000; and (4) κ validity = 0.813, 0.420, 0.296, 0.308. This initial study shows negligible differences between the English and Japanese MCIS, supporting its potential use for early detection in Japan.

Keywords: MCI Screen; MMSE; Neuroimaging; early detection; mild cognitive impairment; Alzheimer's disease and related disorders

Introduction

Japan's high life expectancy (females = 85.8 years, males = 79 years)[1] and low birth rate (1.32 children per couple)[2] have generated a disproportionately large proportion of the population being over 65 years old (21.1%) today.[3] By 2050, 35.7% will be over 65 years old.[3] Japan's aging population makes Alzheimer's disease and related disorders (ADRD) a major public health care concern with staggering costs and need for human resources. To address this crisis, the Japanese government has instituted nationwide programs focused on risk reduction of ADRD, metabolic syndrome, and other major chronic diseases of aging. However, early detection and treatment of ADRD remains an unaddressed issue.

The Mild Cognitive Impairment Screen (MCIS),[4] derived from data mining and analysis of the National Institute of Aging CERAD (Consortium to Establish Registry for Alzheimer's Disease) neuropsychologic test battery, is a 10-minute, electronically scored, staff-administered test. It was validated in academic and community specialty clinical settings to differentiate normal aging from (MCI) and from mild dementia with accuracy of 97.3% and 99%, respectively. It was further validated to have virtually identical accuracy in a primary care setting in the United States.[5]

The MCIS was translated into Japanese (JMCIS) and has been adopted for research and clinical use in Japan. The present article reports the results of the first validation study of the JMCIS in a Japanese population and compares them to the results obtained by the Mini-Mental State Examination (MMSE), quantitative single-photon emission with computed tomography (qSPECT) and quantitative magnetic resonance imaging (qMRI). The Clinical

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Dementia Rating Scale (CDR) served as the reference standard for validation.

This study was conducted as a part of a study to investigate an effect of exercise on MCI and is approved by the Fukuoka University ethics committee. All patients provided consent according to the ethics committee guidelines.

Methods

Sample

A total of 63 patients from the Fukuoka University Hospital memory clinic, Japan, were staged with the CDR, the primary outcome measure, and had scores of either 0 (normal aging) or 0.5 (MCI). These patients were also interviewed to gather their medical history, to diagnose major depressive disorder using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. In all, 11% (7/63) were diagnosed with major depression and excluded, leaving a sample of 56 patients for further analysis. Independent variables used to predict CDR classification were the JMCIS, the MMSE, plus SPECT, and MRI with volumetric analysis (SPECT, VSRAD, respectively).

Clinical Dementia Rating Scale

The CDR is a well-validated measure of the severity of ADRD,[6] which served as the primary outcome. The present sample had 8 normal aging (CDR = 0) and 48 MCI (CDR = 0.5) patients. A CDR score of 0.5 corresponds to MCI of either amnestic, nonamnestic, or mixed types, depending upon the results of the 6 CDR subscores, which measure memory and executive function plus complex to basic activities of daily living. All patients with CDR = 0.5 had subjective memory loss that was confirmed by a reliable informant, so they had either amnestic or mixed MCI, the characteristics of which conform to criteria defined by Petersen et al.[7]

Mini-Mental State Examination

The MMSE is the most widely used screening test for ADRD and therefore serves as a useful frame of reference for the performance of the other tests in this study. A cutoff point for the MMSE was selected to classify patients as normal or MCI. Among published studies of normal aging versus MCI, an MMSE score >28 for normals gave the highest sensitivity when the specificity was fixed at 90% or higher.[8] Accordingly, in the present study, we classified scores of 29 or 30 as normal aging and scores of 28 or below as MCI.

Mild Cognitive Impairment Screen

For classification of normal aging versus MCI with the JMCIS, the criteria used were the same as those applied in a large primary care study in the United States.[5] Briefly, the classification was based on a nonparametric receiver-operating characteristic curve that corresponded to an unbiased measure of overall accuracy of 97.3%.[4] A point on the receiver operating characteristic curve corresponding to a sensitivity of 96% for MCI and a specificity of 88% for normal aging was used to classify each case in the sample of the present study.

Quantitative SPECT Analysis

Quantitative SPECT quantifies brain tissue activity and is most often used for differential diagnosis. However, it is useful to examine its performance as a screening tool so that the relative power of the simpler and less expensive tests of the MMSE and JMCIS can be appreciated. 36 patients were quantitatively studied with 99mTx-ethyl cysteinate dimer (99m Tc-ECD) SPECT (qSPECT) using a Shimazu 3-headed gamma camera (IRIX). 600 MBp of 99m Tc-ECD was injected intravenously, and patients were scanned 10 minutes later. Data were collected with a matrix size of 128 × 128. SPECT images were reconstructed using a Shepp & Logan Hamming filter, and then the Chang attenuation correction was applied. Voxel-based analysis was performed using the "easy Z-score" imaging system (sZIS) on MatLab.[9]

Patients were classified as having MCI when qSPECT showed hypoperfusion of the posterior cingulate gyrus and precuneus. With regard to the differential diagnosis of the underlying etiology of MCI, patients were diagnosed by the pattern of qSPECT hypoperfusion: (1) AD = parietal and temporal lobe hypoperfusion; (2) Lewy body disease = occipital lobe hypoperfusion; (3) Frontal-temporal lobe degeneration = frontal lobe with or without temporal lobe hypoperfusion.

Quantitative MRI Analysis

Quantitative MRI has been examined for its utility as an ADRD screening tool, particularly in terms of

Table 1. Characteristics of the Sample of Normal Aging and MCI Patients[a]

CDR Class	N	Age (years)	Women	Years of Education	MMSE
Normal (0)	8	65.3 ± 6.9	62.5%	14 ± 2.1	28.6 ± 2.1
MCI (0.5)	48	71.8 ± 8.6	58.3%	12.1 ± 2.8	27.1 ± 1.7

Abbreviations: CDR, Clinical Dementia Rating Scale; N, group sample size; MMSE, Mini-Mental State Examination.
[a]Continuous variables are summarized as mean ± standard deviation; gender is summarized as percentage of women. For each variable, *P* values measure the probability that the normal and MCI groups do not differ. χ^2 Test was used for gender and one-way ANOVA for the other variables, which were continuous.

hippocampal volume and diagnosis of AD during the MCI stage (see appendix B in Trenkle et al[5]). It is therefore useful to examine its performance as a screening test for normal aging versus MCI. A total of 45 patients were quantitatively studied with MRI using a Philips Achieva 1.5T instrument. T2-weighted FLAIR axial, diffusion-weighted axial, 3D T1-weighted sagittal, and 3D T1-weighted axial coronal views were acquired. The 3D T1-weighted views were sent to VSRAD[10] software and cortical and hippocampal atrophy was quantified as a standardized *z* score. Patients with cortical or hippocampal atrophy *z* scores ≥1.0 were classified as MCI, and those with *z* scores <1.0 were classified as normal.

Combination of SPECT and VSRAD

A total of 25 patients were studied with both SPECT and VSRAD, and were classified as normal if both studies were normal, or as impaired if either study was impaired.

Statistical Methods

The patient groups of normal aging (CDR = 0) and MCI (CDR = 0.5) were the primary outcome measure that served as the reference standard for all statistical comparisons. We tested for significant differences between these groups using one-way ANOVA for age, education, and MMSE. For the discrete variable of gender, we tested for significant group differences using the χ^2 square statistic.

The following statistics were computed to evaluate screening performance of the independent measures (JMCIS, MMSE, qSPECT, and qMRI results) in classifying CDR stage: sensitivity, specificity, accuracy, positive predictive value, negative predictive value, and κ. For predictive value calculations, we used the same prevalence (0.16) that was used with the English MCIS in a previous study.[5] The κ statistic measures classification accuracy after removing chance associations; in this context, κ measures the validity of each screening test.[5]

Table 2. Performance Statistics of Each Method for Classifying the Reference Standard of Normal (CDR = 0) and MCI (CDR = 0.5) Groups

Method	N	Acc	Sn	Sp	PPV	NPV	κ (std)
JMCIS	56	.964	.958	1.000	0.813	1.000	0.868 (0.13)
MMSE	56	.768	.792	.625	0.420	0.897	0.305 (0.12)
qSPECT	36	.722	.688	1.000	0.296	1.000	0.328 (0.12)
qMRI	45	.733	.700	1.000	0.308	1.000	0.342 (0.11)
qSPECT + qMRI	25	.840	.833	1.000	0.487	1.000	0.553 (0.12)

Abbreviations: JMCIS, Japanese version of the MCI Screen; MMSE, Mini-Mental State Examination; qMRI, quantitative MRI measure (standardized *z*-score) of cortical and hippocampal atrophy (see Methods section); qSPECT, quantitative SPECT analysis; qSPECT + qMRI, classification based on combination of qSPECT and qMRI results; N, group sample size; Acc, overall accuracy of classification method; Sn, sensitivity for correctly classifying MCI group (CDR = 0.5); Sp, specificity for correctly classifying normal aging group (CDR = 0); PPV, positive predictive value for MCI classification based on MCI prevalence = 0.16; NPV, negative predictive value for normal classification based on normal prevalence =0.84; κ (std), kappa statistic and standard deviation, which measure the classification method's validity. All classification methods had κ values indicating better than chance prediction ability.

Results

Table 1 shows the sample demographics and distribution by diagnosis. There were no significant differences between normal and MCI groups for age, years of education, gender, or MMSE score.

The distribution of etiologic diagnoses for the 36 patients evaluated with qSPECT was as follows: nondiagnostic = 21 (58.3%), AD = 10 (27.8%), Lewy body disease = 4 (11.1%), frontal-temporal lobe disease = 1 (2.8%).

Table 2 shows, for each predictor, the sensitivity, specificity, accuracy, positive predictive value, negative predictive values, and validity (κ statistic and its standard deviation) of classifying CDR stage. The κ-based validity of all measures significantly predicted CDR stage better than chance ($P \leq .007$). The JMCIS

always yielded substantially higher performance statistics than the other predictors.

Discussion

Mild cognitive impairment is not a diagnosis; it is a syndrome whose differential diagnosis is comparable to that of the dementia syndrome.[4,5] Mild cognitive impairment is the earliest clinical stage of dementing disorders. Its detection is increasingly being recognized as essential to improved treatment outcome. The present study validates the use of the JMCIS for classifying normal aging versus MCI. For all screening performance measures, the JMCIS results are highly similar to those of the two studies using the English MCIS on a combined sample of 397 normal aging versus MCI subjects[4,5] in terms of accuracy (0.964 vs 0.956-0.973), sensitivity (0.96 vs 0.79-0.94), specificity (1.00 vs 0.97-0.99), positive predictive value (0.81 vs 0.86-0.95), negative predictive value (1.000 vs 0.96-0.99), and κ-based validity (0.87 vs 0.82-0.93). The present study supports the conclusion that cultural, educational, and linguistic differences attributable to Japan and the United States have a negligible effect on the performance of the MCIS. However, further validation studies with a larger Japanese sample are needed to confirm this conclusion.

The design of the MCIS helps explain the similarity in classification accuracy across cultures as divergent as those of the United States and Japan. First, the MCIS is based on statistical evaluation of the full CERAD neuropsychologic test battery to exclude those tests with negligible statistical contribution to early detection of a wide variety of ADRD etiologies. As such, the foundation of the MCIS is relatively robust to sample differences in underlying ADRD etiology. Second, the CERAD battery is well validated and has been used by the US National Institute of Aging Alzheimer's Disease Research Centers for more than 20 years. Third, the MCIS was further refined by using the basic format of the CERAD Wordlist for Immediate and Delayed Recall, which is very simple, and can be administered in a wide variety of clinical settings with high statistical reliability, regardless of level of administrator expertise.[5] Fourth, the performance of the MCIS was substantially improved over that of the CERAD Wordlist by applying advanced methods of pattern analysis to the item responses.[4] These methods minimized, to less than 1%, the effects of age, gender, and education on classification results once the effect of pattern of recall was accounted for. Finally, the specific words used in the 8 equivalent sets of MCIS 10-wordlists are comparable because the words in each wordlist were selected from an initial set of 1 million common nouns and had to meet at least the following criteria: (*a*) only one or two syllables; (*b*) high frequency of usage for writing and speaking across a wide variety of occupations; (*c*) begins with a unique letter or sound; and (*d*) low statistical associability for each of the 45 word-pairs in each 10-word list. Initial testing of the wordlists in the Japanese version of the MCIS identified only a few words that needed to be replaced due to differences between English and Japanese. Such criteria provide a plausible rationale for the similarity of classification accuracies using English and Japanese MCIS versions.

One other intriguing finding of the present study is related to the role of neuroimaging in evaluating ADRD. The present study shows that for screening of normal aging versus MCI, neuroimaging performs substantially more poorly than the JMCIS, and about as well as the MMSE. Similar results have also been reported for fluoro-deoxy-glucose positron emission tomography (PET) and volumetric MRI studies.[5] It therefore appears that neuroimaging's primary role is for differential diagnosis of a dementing disorder and not for screening to detect ADRD early.

The present study provides initial validation that the Japanese and English versions of the MCIS give highly similar screening classification accuracy (96.4% vs 97.3%, respectively) in differentiating normal aging from MCI. By extension from the accuracy of the English MCIS in differentiating normal aging versus mild dementia (99%), the Japanese MCIS classification accuracy for differentiating normal aging versus MCI-to-mild dementia should be in the range of 96.4% to 99%. These findings support the hypothesis that cultural, linguistic, and demographic differences between Japan and the United States have negligible effect on MCIS screening performance, which makes it useful for early detection of ADRD in Japan.

The importance of these findings is underscored by an international workgroup's recently proposed revision of the ADRD diagnostic criteria of the National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders (NINCDS-ADRDA).[11] These criteria focus on a clinical core of early and significant episodic memory impairment, plus the presence of at least one abnormal biomarker (eg, molecular neuroimaging with

PET, structural neuroimaging with MRI, cerebrospinal fluid analysis of β-amyloid and tau proteins). Both research and clinical practice will therefore benefit from the availability of more accurate, usable tools for early detection.

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