Neurology Asia 2016; 21(1) : 47 – 54

Diagnostic accuracy of neuropsychological tests for classification of dementia

[1]Takuya Yagi *MD PhD*, [1]Daisuke Ito *MD PhD*, [2]Daisuke Sugiyama *MD PhD*, [2]Satoko Iwasawa *MD PhD*, [3]Hajime Tabuchi *MD PhD*, [3]Mika Konishi *MD PhD*, [4]Machiko Araki *MD*, [5]Naho Saitoh, [1]Yoshihiro Nihei *MD PhD*, [3]Masaru Mimura *MD PhD*, [1]Norihiro Suzuki *MD PhD*

Departments of [1]Neurology, [2]Preventive Medicine and Public Health, [2]Neuropsychiatry, [4]Center for Preventive Medicine, [5]Rehabilitation Medicine, School of Medicine, Keio University, Tokyo, Japan

Abstract

Although numerous studies have shown that each neuropsychological test is effective for diagnosing mild cognitive impairment (MCI) or Alzheimer's disease (AD), studies comparing diagnostic accuracies of various neuropsychological tests are relatively rare and practical cutoff values are not available. The present study aimed to investigate the validity of neuropsychological tests and develop cutoff values for each in differentiating healthy control (HC), MCI and AD groups. A total of 84 HC, 187 with MCI and 195 with AD were evaluated by the selected seven neuropsychological tests using receiver operating characteristic (ROC) curve analysis. Logical Memory (LM) delayed recall (cutoff, 7) and Rey Auditory Verbal Learning Test (RAVLT) delayed recall (cutoff, 6) were effective for differentiating HC from MCI. To distinguish MCI and AD, Rey Osterrieth Complex Figure Test (ROCFT) 3 min-delayed recall (cutoff, 6) and LM immediate recall (cutoff, 4) were excellent. Delayed recall of verbal materials, as indexed by LM and RAVLT was sensitive for discriminating MCI from HC. Handling visual memory traces, as indexed by ROCFT and immediate verbal information by LM were sensitive for differentiating MCI and AD.

INTRODUCTION

Early and accurate detection of dementia through screening methods may benefit risk assessment and care management, and may eventually contribute to substantial cost savings. Screening methods should also be important in the future for the expected disease-modifying and preventive treatments for Alzheimer's disease (AD).[1-3] One of the basic problems is that there are no standard neuropsychological tests to differentiate among normal aging, mild cognitive impairment (MCI), and AD. Despite ongoing efforts in recent years to evaluate proper cognitive tests that help detect or diagnose the cognitive impairment continuum from normal aging through subjective memory complaints and MCI to AD[4-6], establishing appropriate classification of cognitive impairment with neuropsychological tests has remained challenging.[7] The mini mental state examination (MMSE)[8] is the most popular screening test used to assess patients with cognitive impairment in the memory clinic. The MMSE is administered in a short time, and is acceptable to both patients and healthcare workers.[9-10] However, MMSE has some limitations for detecting MCI and also is not sensitive for detecting subtle declines in cognitive function.[11-13] It is unclear how effective other neuropsychological tests are to differentiate healthy controls (HC), MCI and AD patients; there is a need to identify suitable and effective, validated neuropsychological screening measures.[14]

Although numerous studies have shown that each neuropsychological test is effective for diagnosing MCI or AD, studies comparing diagnostic accuracies of various neuropsychological tests are relatively rare and practical cutoff values are not available. The aim of the present study was, therefore, to determine which of the selected neuropsychological tests in current use are more effective to distinguish HC, MCI, and AD. This study identified neuropsychological tests effective for classification of HC, MCI, and AD through an analysis of diagnostic accuracy, and provided practical cutoff values for each test for diagnostic use.

Address Correspondence to: Daisuke Ito M.D. Ph.D., Department of Neurology, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. Tel: +81-3-5363-3788; E-mail: d-ito@jk9.so-net.ne.jp

METHODS

Subjects

Between April 2008 and April 2013, 466 consecutive participants, aged from 60 to 89 years at the first medical examination, were recruited from the memory clinic of Keio University Hospital as a retrospective clinical cohort. Patients underwent a complete standardized diagnostic evaluation, including history, physical and mental status examination, laboratory analysis, imaging studies and neuropsychological tests, in an outpatient visit. Experienced neurologists and psychiatrists (dementia practice specialists) evaluated all the participants and made the diagnosis based on the clinical course for more than six months and the results of all examinations, including neuropsychological tests. Enrolled HCs presented to our memory clinic with complaints of memory impairment, but they all maintained their activities of daily living (ADL) and had well-preserved cognitive function based on the results of neuropsychological tests and by history. Although the HC group demonstrated no significant MRI findings, they were not 'normal' in the strict sense, because they complained of subjective cognitive impairment.[15] Thus, the individuals in this group could have possibly had preclinical AD.[1] However, they were regarded as normal for the purpose of the present study based on the preserved ADL and cognitive function. The diagnosis of MCI or AD for each patient was confirmed according to the established criteria, following a complete standardized diagnostic evaluation.[16-17] The patients diagnosed with MCI in this study had amnestic MCI, including both single- and multi-domain.[18] Imaging studies, including magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT), were used as supportive diagnostic tools to rule out other types of neurological disorders that cause cognitive impairment. Participants included 84 HCs, 187 patients with MCI, and 195 patients with AD. Other types of dementia, including dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), and vascular dementia (VD), were excluded from the present study due to the low number of cases. The overall study was approved by the Keio University School of Medicine Ethics Committee.

Neuropsychological tests

The following neuropsychological tests were selected to evaluate cognitive functions, including general intelligence, memory, and frontal lobe functions: MMSE, Raven's Coloured Progressive Matrices (RCPM), Logical Memory Subtest of Wechsler Memory Scale-Revised (LM), Rey Auditory Verbal Learning Test (RAVLT), Rey-Osterrieth Complex Figure Test (ROCFT), Modified Stroop test (Stroop), Trail Making Test (TMT), and Verbal Fluency (VF). These tests were administered on the patient's first visit. All tests were administered during a single 90-min session by trained research neuropsychologists. The tests were conducted according to standard administration procedures.[8,19-20] For LM, the procedure was based on the online Alzheimer's Disease Neuroimaging Initiative-2 (ADNI2) protocol (see http://www.adni-info.org/Scientists/Pdfs/ADNI2_Procedures_Manual_20130624.pdf). Scores for LM Immediate Recall (LM I) and Delayed Recall (LM II) (Story "A" only), as well as LM II corrected for education years, were calculated in the present study.[21] For RAVLT, the number of items that the participants could recall in list A after the interference of List B was used. The ROCFT consisted of a copy trial of the complicated figure followed by a recall trial 3 min later, which were called ROCFT Copy and ROCFT 3 min, respectively. The Stroop test consisted of three parts, which were always presented to the participants in the following order: Card D (Dot), Card W (Word), and Card C (Color), called Stroop 1, Stroop 2 and Stroop 3, respectively, in this study, and the time required (sec) was used as the index parameter.[20] Participants were allowed up to a maximum of 600 sec (10 min) to complete the TMT A and TMT B, or a maximum 300 sec (5 min) to complete the Stroop test. The VF performance was scored based on the total number of produced words for the initial letters and the categories. Based on this database, the validity of each neuropsychological test was investigated.

For sub-analysis, the participants in this study aged from 60 to 89 years were divided into two groups; the younger group (60-74 years old) and the older group (75-89 years). To select the group with less-impaired cognitive function by MMSE score, a cutoff value of 21/22 was used, in order to recruit a substantial number of mild AD participants for statistical analysis purposes.

Statistical analysis

Demographic characteristics were compared across diagnostic groups using one-way analysis of variance (ANOVAs) with Tukey Kramer's test JMP 10 (SAS Institute Inc., USA). For statistical

analysis of results, the area under the receiver operating characteristic (ROC) curve (AUC) was used to measure the accuracy of discrimination among HC, MCI, and AD. The AUC and the standard error were calculated using the method proposed by Hanley and McNeil.[22] A sub-analysis of two age-classified groups, the younger group (60-74 years old) and the older group (75-89 years), was also performed, and there was also a focus on the mild group scoring 22 and more on the MMSE. The AUC values for each test within each age-classified subgroup were compared for statistical significance (Table 3). A cutoff score for each test that optimally differentiated diagnostic groups was determined using the Youden index[23], which maximizes the trade-offs between sensitivity and specificity.

RESULTS

Descriptive characteristics of the study population

Table 1 presents demographic and psychometric characteristics along with significance values. The diagnostic groups differed significantly in age; the AD group was significantly older than the HC (P<0.001) or MCI (P<0.05) groups. For education years, the AD group was significantly lower than the HC (P<0.001) or MCI groups (P<0.05). Table 1 also presents results of performance on the individual assessment measures. The AD group performed significantly worse than did the MCI and HC groups on each task.

Table 1: Demographic characteristics and cognitive performance for HC, MCI, and AD participants

Characteristics	Normal (n = 84)	MCI (n =187)	AD (n = 195)
Age (years)	73.1 (6.9)	75.6 (6.2) *	77.4 (6.5) **,†
Gender (F) (%)	67.9	55.1	66.7
Education (years)	14.6 (2.2)	13.6 (2.6)	12.6 (2.9) **, †
CDR	0.10 (0.20)	0.47 (0.22) **	0.94 (0.45) **, ††
MMSE	28.3 (1.8)	25.9 (2.4) **	20.0 (4.3) **, ††
RCPM	31.1 (3.7)	27.9 (4.7) **	22.9 (6.8) **, ††
Logical MemoryI	11.1 (4.1)	6.8 (3.7) **	3.1 (2.5) **, ††
Logical MemoryII	9.3 (4.2)	3.8 (3.7) **	0.9 (1.6) **, ††
Logical MemoryIIE	3.6 (4.2)	-1.9 (4.1) **	-2.6 (3.6) **, ††
RAVLT	9.1 (3.8)	4.5 (3.4) **	1.8 (2.2) **, ††
ROCFT Copy	34.8 (1.8)	34.1 (2.8)	30.4 (7.7) **, ††
ROCFT 3min	16.4 (6.6)	9.7 (6.6) **	3.0 (3.8) **, ††
Stroop 1	17.6 (5.0)	20.49 (6.5)	31.2 (33.0) **, ††
Stroop 2	21.3 (7.8)	27.1 (10.5)	43.7 (40.5) **, ††
Stroop3	29.2 (15.2)	36.9 (15.6)	61.2 (53.2) **, ††
TMT A	147.6 (85.4)	178.5 (81.9)	269.2 (148.9) **, ††
TMT B	205.4 (131.2)	283.8 (150.4) **	450.0 (163.0) **, ††
VF Category	37.7 (9.2)	30.2 (8.2) **	22.8 (8.5) **, ††
VF Initial letter	24.6 (8.5)	19.9 (6.4) **	16.3 (7.7) **, ††

Values are mean (SD). Significant differences among groups for each value were examined by the Tukey Kramer's test (*P<0.05 vs. HC; **P<0.001 vs. HC; †P<0.05 vs. MCI; ††P<0.001 vs. MCI), while the sex ratio was examined by Pearson's chi-square test. CDR: Clinical Dementia Rating, MMSE: Mini-mental state examination, LM IIE: LM II with education correction, TMT: Trail Making Test, VF: Verbal Fluency.

The AUC values and cut off points for the neuropsychological tests for all participants

Table 2 summarizes the ROC analysis data of all the participants for each assessment measure with AUC values and proper cutoff scores to differentiate each diagnostic group. Neuropsychological tests with AUC values exceeding 0.8 were considered to have an excellent diagnostic performance status. To differentiate between HC and MCI, AUC values for LM II (0.83±0.03, cutoff, 7), LM II with education correction (0.83±0.03, cutoff, -1) and RAVLT (0.82±0.03, cutoff, 6) had AUC values exceeding 0.8. These findings demonstrate that LM II, LM II with education correction, and RAVLT are excellent for differentiating between HC and MCI, indicating that verbal memory impairment is sensitive in MCI. To distinguish between MCI and AD, AUC values for LM I (0.80±0.02, cutoff, 4) and ROCFT 3 min (0.81±0.02, cutoff, 6) had AUC values exceeding 0.8. These findings indicate that handling visual memory traces, as indexed by ROCFT 3 min, and immediate verbal information, as indexed by LM I, are sensitive for differentiating between MCI and AD.

The AUC values and cut off points for the neuropsychological tests for participants aged 75 and over or those aged below 75 years

To explore the aging effect on diagnostic accuracy of the neuropsychological tests, the participants were divided into two groups; the younger group (60-74 years) and the older group (75-89 years) (Table 3). In younger participants (HC; n=47, MCI; n=80, AD; n=54), three tests, RAVLT (0.84±0.04, cutoff, 8), LM II (0.82±0.04, cutoff, 7) and ROCFT 3 min (0.81±0.04, cutoff, 16.5), had AUC values exceeding 0.8 to differentiate between HC and MCI, whereas only ROCFT 3 min was prominently effective for this age group in differentiating MCI from AD (AUC 0.86±0.03 cutoff, 6), indicating that visual memory is likely to be prominently disturbed in the younger AD group. Among older participants (HC; n=37, MCI; n=107, AD; n=141), the highest AUC value to differentiate between HC and MCI was found for LM II with education correction (0.85±0.04, cutoff, -1). Notably, none of the neuropsychological tests exceeded an AUC value of 0.8 to differentiate between MCI and AD in the older group. There was a significant difference between the younger group and the older group

Table 2: Values for area under ROC for neuropsychological tests to distinguish HC, MCI and AD, for all study participants

	HC vs MCI AUC (SE)	Cut off	MCI vs AD AUC (SE)	Cut off
RCPM	0.71 (0.04)	32	0.72 (0.03)	25
Logical MemoryI	0.78 (0.03)	9	0.80 (0.02)	4
Logical MemoryII	0.83 (0.03)	7	0.76 (0.02)	2
Logical MemoryIIE	0.83 (0.03)	-1	0.68 (0.03)	-3
RAVLT	0.82 (0.03)	6	0.75 (0.03)	4
ROCFT Copy	0.61 (0.04)	35	0.65 (0.03)	33.5
ROCFT 3min	0.77 (0.03)	15.5	0.81 (0.02)	6
Stroop 1	0.65 (0.03)	18	0.65 (0.03)	21
Stroop 2	0.72 (0.03)	23	0.71 (0.03)	29
Stroop 3	0.70 (0.03)	30	0.71 (0.03)	35
TMT A	0.67 (0.03)	112	0.72 (0.03)	200
TMT B	0.70 (0.03)	165	0.75 (0.02)	290
VF Category	0.74 (0.03)	34	0.73 (0.03)	26
VF Initial letter	0.65 (0.04)	25	0.65 (0.03)	17

Table 3: Values for the area under ROC for neuropsychological tests to distinguish HC, MCI, and AD, in participants aged 60 to 74 or aged 75 to 89

	Age between 60 and 74 HC (n=47), MCI (n=80), AD (n=54)				Age between 75 and 89 HC (n=37), MCI (n=107), AD (n=141)			
	HC vs MCI AUC (SE)	Cut off	MCI vs AD AUC (SE)	Cut off	HC vs MCI AUC (SE)	Cut off	MCI vs AD AUC (SE)	Cut off
RCPM	0.73 (0.05)	32	0.70 (0.04)	25	0.68 (0.05)	30	0.72 (0.03)	27
Logical MemoryI	0.79 (0.04)	12	0.84 (0.03)	4	0.76 (0.05)	9	0.77 (0.03)	4
Logical MemoryII	0.82 (0.04)	7	0.79 (0.04)	3	0.84 (0.04)	7	0.73 (0.03)	1
Logical MemoryIIE	0.80 (0.04)	2	0.74 (0.04)	-1	0.85 (0.04)	-1	0.63 (0.04)	-3
RAVLT	0.84 (0.04)	8	0.78 (0.04)	4	0.77 (0.05)	6	0.72 (0.03)	3
ROCFT Copy	0.62 (0.05)	34.5	0.63 (0.05)	34	0.57 (0.06)	34.5	0.65 (0.04)	33
ROCFT 3min	0.81 (0.04)	16.5	0.86 (0.03) *	6	0.73 (0.05)	10.5	0.78 (0.03)	2.5
Stroop 1	0.66 (0.05)	17	0.60 (0.05)	21	0.62 (0.05)	22	0.65 (0.03)	33
Stroop 2	0.78 (0.04)	21	0.63 (0.05)	25	0.63 (0.05)	23	0.73 (0.03)	29
Stroop 3	0.74 (0.04)	31	0.63 (0.05)	40	0.64 (0.05)	28	0.72 (0.03)	36
TMT A	0.72 (0.05)	117	0.64 (0.05)	172	0.60 (0.05)	148	0.73 (0.03)	200
TMT B	0.76 (0.04)	158	0.77 (0.04)	288	0.62 (0.05)	245	0.72 (0.03)	575
VF Category	0.76 (0.05)	34	0.71 (0.04)	32	0.69 (0.05)	30	0.73 (0.03)	26
VF Initial letter	0.75 (0.05)	22	0.56 (0.05)	15	0.53 (0.06)	25	0.67 (0.03)	17

Statistical analysis was performed for aged between 60 and 74 vs. aged between 75 and 89 for each differentiation. *P<0.05 vs. aged between 75 and 89.

in the diagnostic capacity of ROCFT 3 min to differentiate between MCI and AD (p=0.04).

To evaluate the diagnostic capacity of these tests in patients with less-impaired global cognitive function, participants who scored 22 or more on the MMSE were analyzed. The diagnostic accuracy of neuropsychological tests was investigated (Table 4). ROC curve analysis revealed the same results as are shown in Table 3, indicating that the ROCFT 3 min was effective to discriminate among HC, MCI and AD in the younger group, and only the LM II was effective to differentiate MCI from HC in the older group.

DISCUSSION

This study provide several important insights into the selection of neuropsychological tests for use, and information regarding appropriate cutoff values for each test. First, to distinguish between HC and MCI, LM II and RAVLT were found to be most effective. Because the MMSE, which is the most commonly-used instrument for screening global cognitive function, comprises subscales assessing orientation, attention, language, and visuospatial abilities, as well as memory, it is inadequate for evaluation of the patient with amnestic MCI single-domain. Accordingly, administering the LM II and RAVLT tests, which quantitatively assess verbal memory, seems to be more appropriate for distinguishing MCI from HC. In the Alzheimer's Disease Neuroimaging Initiative-2 (ADNI, http://www.adni-info.org/), LM II is recommended to determine levels of MCI. The results of the current study support the ADNI2 protocol and provide strong evidence emphasizing the importance of the LM for diagnosis of MCI. The RAVLT also has been used to evaluate various aspects of memory function, including short-term memory, learning, immediate and delayed recall and recognition.[19] Although further study

Table 4: Values for area under ROC for neuropsychological tests to distinguish HC, MCI, and AD in participants who scored more than 22 points on the MMSE

	Age between 60 and 74 HC (n=47), MCI (n=77), AD (n=27)				Age between 75 and 89 HC (n=37), MCI (n=100), AD (n=53)			
	HC vs MCI AUC (SE)	Cut off	MCI vs AD AUC (SE)	Cut off	HC vs MCI AUC (SE)	Cut off	MCI vs AD AUC (SE)	Cut off
RCPM	0.72 (0.05)	32	0.62 (0.06)	32	0.67 (0.05)	30	0.61 (0.05)	28
Logical MemoryI	0.78 (0.04)	12	0.81 (0.04)	6	0.76 (0.05)	9	0.67 (0.04)	6
Logical MemoryII	0.81 (0.04)	7	0.79 (0.05)	2	0.83 (0.04)	7	0.64 (0.05)	2
Logical MemoryIIE	0.80 (0.04)	2	0.74 (0.05)	0	0.84 (0.04)	-1	0.60 (0.05)	-3
RAVLT	0.84 (0.04)	9	0.76 (0.05)	4	0.76 (0.05)	6	0.59 (0.05)	3
ROCFT Copy	0.62 (0.05)	34.5	0.53 (0.07)	35.5	0.55 (0.06)	34.5	0.53 (0.05)	34.5
ROCFT 3min	0.80 (0.04)	16.5	0.84 (0.04)	*10.5	0.71 (0.05)	10.5	0.70 (0.04)	5.5
Stroop 1	0.66 (0.05)	17	0.50 (0.06)	19	0.63 (0.05)	22	0.54 (0.05)	19
Stroop 2	0.78 (0.04)	21	0.53 (0.07)	25	0.62 (0.05)	26	0.60 (0.05)	29
Stroop 3	0.74 (0.04)	31	0.57 (0.07)	34	0.63 (0.05)	28	0.60 (0.05)	35
TMT A	0.71 (0.05)	111	0.60 (0.07)	172	0.59 (0.05)	148	0.62 (0.05)	200
TMT B	0.76 (0.04)	149	0.71 (0.06)	171	0.61 (0.05)	245	0.66 (0.05)	256
VF Category	0.75 (0.04)	34	0.62 (0.06)	32	0.68 (0.05)	30	0.62 (0.05)	27
VF Initial letter	0.74 (0.05)	22	0.54 (0.07)	24	0.53 (0.06)	25	0.57 (0.05)	17

Values for area under ROC for neuropsychological tests to distinguish HC, MCI, and AD in participants who scored more than 22 points on the MMSE.

is needed to evaluate sub-items, including the learning curve, we propose that examining the delayed recall function by RAVLT is reliable for distinguishing MCI from HC.

To distinguish between MCI and AD, the ROCFT 3 min was the most effective, especially for people aged under 75. The results are partially consistent with a previous report that early-onset AD patients performed worse than late-onset AD patients on visuospatial functioning[24], suggesting that the ROCFT 3 min recall, which assesses retention of recent visual information, is useful, practically speaking, in the younger AD group. On the other hand, LM II and RAVLT were not as useful to differentiate between MCI and AD as to differentiate between HC and MCI. Because the values of LM II and RAVLT in AD are 0.9 ± 1.6 and 1.8 ± 2.2, respectively, we assume that the complicated verbal mnemonic items assessed by these tests are already impaired in MCI to the level that it is difficult to use this aspect to differentiate between MCI and AD. Rather, handling immediate verbal information, as indexed by LM immediate recall, the value of which is 3.1±2.5 and does not reach floor effect, is sensitive for differentiating between MCI and AD.

Consistent with a number of reports regarding frontal lobe dysfunction in MCI and AD[25-27], there were significant differences ($p<0.001$) between the MCI and AD groups for all frontal tests used in this study (Stroop, TMT, VF) (Table 1). However, in this study, frontal lobe function tests failed to exceed the AUC value 0.8 in ROC analysis. The reason for this remains unknown, but we suspect it may have to do with the fact that patients with frontal lobe disturbance are difficult to do an outpatient visit, and so enrollment of these patients consequently was decreased. Another possible reason is that the AD group in this study was composed of the participants with relatively mild symptoms, for whom CDR and MMSE were 0.94±1.6 and 20±2.2, respectively. Pathological

analysis and recent PET imaging revealed that neurofibrillary tangles first appear in the hippocampus and then spread to other neocoritcal regions, including the frontal cortex, with further cognitive decline as scored by MMSE.[28-29] So it was difficult to show the diagnostic efficiency of frontal lobe function tests in this study. Future studies, therefore, should focus on the association of changes over time in frontal lobe test results with progress and prognosis estimation of AD.

When interpreting the results of the present study, several limitations should be kept in mind. First, FTD, VD and DLB patients were excluded from this study, so further investigation is needed to evaluate use of tests assessing frontal lobe functions to differentiate FTD, VD, DLB and AD. Secondly, education years differ among groups, as shown in Table 1. Although correction with education years of the LM II results was not very effective in this study, the next study should assess how differences in education background affect the diagnostic utility of the tests used. Third, the HC group was basically composed of "CDR 0" individuals, i.e., "cognitively" preserved normal persons, but this group included those with so-called "subjective cognitive impairment".[30] We thought that it was practical to compare performance on our neuropsychological tests among the AD, MCI and HC groups in the outpatient clinic, but a future study should investigate a larger number of truly "normal" individuals. Finally, the biases including seletion bias and information bias as a result of the retrospective study should be taken into account.

In conclusion, we propose that this study of a clinic-based cohort provides a useful perspective on the diagnostic accuracy of various neuropsychological tests for HC, MCI and AD. The LM, RAVLT, and ROCFT 3 min tests could be useful for routine practice in the memory clinic. Although a future prospective study is needed to evaluate efficiencies of these neuropsychological tests for prognosis estimation and selecting drugs, the current results provided important insights into the selection of appropriate neuropsychological tests for diagnostic use, and revealed cutoff values for each.

ACKNOWLEDGEMENTS

We are grateful to the following individuals for clinical assistance: Dr. Yutaka Kato, Dr. Daisuke Fujisawa, and Dr. Mizuki Oka, Department of Neuropsychiatry, School of Medicine, Keio University, Japan; Ms. Michiko Oda, Keio University Memory Clinic; and Dr. Harumasa Takano, National Institute of Radiological Sciences, Japan. The authors have no financial support and no financial interest related to this manuscript.

DISCLOSURE

Financial support: None

Conflict of interest: None

REFERENCES

1. Sperling RA, Aisen PS, Beckett LA, *et al*. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; 7:280-92
2. Ismail Z, Rajji TK, Shulman KI. Brief cognitive screening instruments: an update. *Int J Geriatr Psychiatry* 2010; 25:111-20
3. Weimer DL, Sager MA. Early identification and treatment of Alzheimer's disease: social and fiscal outcomes. *Alzheimers Dement* 2009; 5:215-26
4. Winblad B, Palmer K, Kivipelto M, *et al*. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* 2004; 256:240-6
5. Tang-Wai DF, Knopman DS, Geda YE, *et al*. Comparison of the short test of mental status and the mini-mental state examination in mild cognitive impairment. *Arch Neurol* 2003; 60:1777-81
6. Standish TI, Molloy DW, Cunje A, Lewis DL. Do the ABCS 135 short cognitive screen and its subtests discriminate between normal cognition, mild cognitive impairment and dementia? *Int J Geriatr Psychiatry* 2007; 22:189-94
7. Lonie JA, Tierney KM, Ebmeier KP. Screening for mild cognitive impairment: a systematic review. *Int J Geriatr Psychiatry* 2009; 24:902-15.
8. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12:189-98.
9. Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. *J Psychiatr Res* 2009; 43:411-31.
10. Harvan JR, Cotter V. An evaluation of dementia screening in the primary care setting. *J Am Acad Nurse Pract* 2006; 18:351-60.
11. Benedict RH, Brandt J. Limitation of the Mini-Mental State Examination for the detection of amnesia. *J Geriatr Psychiatry Neurol* 1992; 5:233-7.
12. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc* 1992; 40:922-35.

13. Holsinger T, Deveau J, Boustani M, Williams JW, Jr. Does this patient have dementia? *JAMA* 2007; 297:2391-404.
14. Cullen B, O'Neill B, Evans JJ, *et al*. A review of screening tests for cognitive impairment. *J Neurol Neurosurg Psychiatry* 2007; 78:790-9.
15. Reisberg B, Gauthier S. Current evidence for subjective cognitive impairment (SCI) as the pre-mild cognitive impairment (MCI) stage of subsequently manifest Alzheimer's disease. *Int Psychogeriatr* 2008; 20:1-16
16. Albert MS, DeKosky ST, Dickson D, *et al*. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; 7:270-9
17. McKhann GM, Knopman DS, Chertkow H, *et al*. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; 7:263-9.
18. Petersen RC, Doody R, Kurz A, *et al.* Current concepts in mild cognitive impairment. *Arch Neurol* 2001; 58:1985-92.
19. Lezak MD. Neuropsychological assessment. 4th ed. Oxford; New York: Oxford University Press, 2004:xiv, 1016.
20. Perret E. The left frontal lobe of man and the suppression of habitual responses in verbal categorical behaviour. *Neuropsychologia* 1974; 12:323-30.
21. Petersen RC, Aisen PS, Beckett LA, *et al*. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. *Neurology* 2010; 74:201-9
22. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; 143:29-36.
23. Youden WJ. Index for rating diagnostic tests. *Cancer* 1950; 3:32-5.
24. Smits LL, Pijnenburg YA, Koedam EL, *et al*. Early onset Alzheimer's disease is associated with a distinct neuropsychological profile. *J Alzheimers Dis* 2012; 30:101-8.
25. Ashendorf L, Jefferson AL, O'Connor MK, *et al*. Trail Making Test errors in normal aging, mild cognitive impairment, and dementia. *Arch Clin Neuropsychol* 2008; 23:129-37.
26. Chen NC, Chang CC, Lin KN, *et al*. Patterns of executive dysfunction in amnestic mild cognitive impairment. *Int Psychogeriatr* 2013; 25:1181-9.
27. Weakley A, Schmitter-Edgecombe M, Anderson J. Analysis of verbal fluency ability in amnestic and non-amnestic mild cognitive impairment. *Arch Clin Neuropsychol* 2013; 28:721-31.
28. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol* 1991; 82:239-59.
29. Maruyama M, Shimada H, Suhara T, *et al*. Imaging of tau pathology in a tauopathy mouse model and in Alzheimer patients compared to normal controls. *Neuron* 2013; 79:1094-108.
30. Stewart R. Subjective cognitive impairment. *Curr Opin Psychiatry* 2012; 25:445-50.