A pilot study on utility of Malayalam version of Addenbrooke's Cognitive Examination in detection of amnestic mild cognitive impairment: A critical insight into utility of learning and recall measures

Ramshekhar Menon, Lekha VS, Sunitha Justus, P Sankara Sarma[1], Mathuranath PS[2]

Department of Neurology, Cognition and Behavioural Neurology Section, [1]Department of Biostatistics, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, [2]Department of Neurology, Cognitive and Behavioural Neurology Section, National Institute for Mental Health and Neuro Sciences, Bangalore, Karnataka, India

Abstract

Aims: This pilot study sought to determine whether the Malayalam adaptation of Addenbrooke's Cognitive Examination (M-ACE) can effectively identify patients with amnestic mild cognitive impairment (a-MCI) and the impact of measures of learning and free recall. **Materials and Methods:** A cohort of 23 patients with a-MCI aged between 55-80 years diagnosed as per current criteria and 23 group matched cognitively normal healthy controls (CNHC) were studied. The measures of acquisition and delayed recall were the Rey Auditory Verbal Learning Test (RAVLT) and Wechsler Memory Scale (WMS)-III (verbal and visual subsets) and Delayed Matching-to-sample Test (DMS)-48. Test scores of M-ACE registration and recall scores were included. To examine the differences in test performances between the groups, we compared the number of subjects with test scores less than 1.5 standard deviation (SD) of the control scores. Comparisons between a-MCI and controls were drawn using Fisher's exact test and Mann-Whitney U tests. **Results:** M-ACE registration component ascertained on a 24-point scale failed to demonstrate any differences between a-MCI and controls ($P = 0.665$) as opposed to recall judged on a cumulative 10-point scale ($P = 0.001$). Significant differences were noted in RAVLT list learning ($P < 0.001$) and list recall ($P = 0.003$), WMS-III paragraph learning ($P < 0.001$) and recall ($P = 0.007$), visual learning ($P = 0.004$) and recall ($P = 0.001$). **Conclusions:** M-ACE recall scores are an effective screening tool to identify patients with suspected a-MCI. Both word list and paragraph learning and recall components have been found to be sensitive to concretely identify a-MCI and impairment on at least 2 tests should be considered in the diagnostic criteria of MCI rather than rely on a single screening battery.

Key Words

Learning, mild cognitive impairment, neuropsychology, recall

For correspondence:
Dr. Ramshekhar Menon, Department of Neurology, Cognition and Behaviour Neurology Section, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum - 695 111, Kerala, India.
E-mail:rsnmenon@yahoo.com

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Introduction

With the increasing prevalence of Alzheimer's disease (AD)[1] and identification of a detectable pre-clinical phase of AD,[2,3] an entity encompassed under the broad terminology 'mild cognitive impairment' (MCI) came into prominence. Recognition of this entity is pertinent to future therapeutic measures that are inclined to target the group of MCI patients who are at risk of conversion to AD.[4] Neuropsychological testing administered as 'paper-and-pencil tests' such as word list recall and paragraph recall have been shown to be sensitive to MCI.[5,6]

Studies of MCI have relied almost exclusively on delayed recall or retention measures in diagnosis,[7] and more recent conceptualizations of MCI continue to rely on the retention deficit rather than acquisition or learning deficits in dichotomizing between amnestic and non-amnestic forms of the disorder.[8] Although retention measures have undoubtedly proven to be useful in MCI diagnosis and prodromal AD detection, it is still an open question whether learning measures are useful though it may seem to corroborate with the extent of gray matter loss.[9]

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Even when split into clinical subtypes, MCI is still a heterogeneous concept. Complicating factors include widely differing neuropsychological tests and diagnostic criteria used across studies in arriving at the MCI classifications as well as inconsistency and lack of clarity in how clinical subtypes are assigned. While it is understood that around 10-12% of patients diagnosed to have MCI, risk progression into dementia,[10] it is not clear from available criteria whether performance on at least 2 tests need to be considered while evaluating a specific domain or reliance on the results of a single comprehensive screening test should suffice.

The South Indian language, Malayalam version of Addenbrooke's Cognitive Examination (M-ACE) has been validated as a reliable and sensitive screening tool to diagnose AD[1,11] without any studies to guage its efficacy in detection of MCI. This pilot study sought to determine whether the M-ACE can effectively identify persistent cognitive impairments in patients with amnestic MCI (a-MCI) in comparison to a battery of standard neuropsychological tests. The pilot was intended to provide a framework for test selection and to decide on the minimum number of tests required when studying a large cohort with subjective memory impairment. The study also aimed to test the notion that the diagnosis of amnestic MCI is test driven and the importance of measurement of acquisition and not retention alone. The critical role of various tests deployed in diagnosing impairment across the memory domain was to be analyzed utilizing comparisons drawn on percentages of subjects with test scores less than 1.5 standard deviations (SD) of the control scores in addition to group mean comparisons.

Materials and Methods

Malayalam-speaking literate patients included were the attendees at the Memory and Neurobehavioral Clinic at a tertiary referral center in the state of Kerala, in the southern part of India. The study subjects were patients with amnestic MCI aged between 55-80 years diagnosed as per criteria outlined by Petersen *et al*., 2001.[12] For inclusion, patients should have subjective memory impairment with preserved general cognition. Objective evidence of impairment required that a subject scored less than 1.5 SD from the norm on at least two episodic memory tests out of four standardized tests. M-ACE was administered to verify general cognition with special interest in M-ACE registration and recall as specific measures of learning and retention. This battery has a global cognitive scale (mini — mental state examination, MMSE), and tests for memory (immediate and delayed recall of a seven-item address list), verbal fluency (initial letter P and categories of animals), confrontation naming (ten items), and constructional praxis (copying two line-drawings). It also assesses executive functions and constructional ability (clock-drawing),[13] remote memory, and language. Regsitration/learning is scored on a 24-point scale which has 3 points for registration of 3 words and 21 points for a 3-trial learning of an address. The recall score was drawn from a 10-point scoring which included a 5-min recall of the three items presented previously and 7-point recall of the address. Subjects were required to have depression score on the Hospital Anxiety Depression Scale (HADS) of less than 7, a Clinical Dementia Rating Scale (CDR) of ≤ 0.5, were still functioning independently in the community and should have a normal general cognition (i.e., MMSE > 24). Inclusion criteria for cognitively normal healthy control subjects (CNHC) were age range of 55-80 years with formal education of more than 8 years with no history of subjective memory complaints and no major neurological, psychiatric, or medical co-morbidities. The standard measures of acquisition (learning) and retention (recall) considered were Malayalam versions of Wechsler Memory Scale-Revised (WMS-R) Logical Memory Test with Story A & B, Rey Auditory Verbal Learning Test (RAVLT), WMS-R Visual Memory Subsets, and the Delayed Matching-to-Sample Test (DMS-48) which have been validated previously.[14,15] Details of these tests are mentioned in Appendix.

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) statistics 17.0 (Chicago IL, USA). We summarized the quantitative data as mean ± standard deviation (SD) and categorical data as percentages (%). To examine the difference in the neuropsychological data between different groups of subjects, we used the comparison derived between percentages of subjects with scores in each group less than mean-1.5 SDs of the control subtest scores as demonstrated in Table 1. It was hypothesized that for a given test, performance may vary within a control group, hence the relevance to determination of variance for individual test results of the group. Group mean comparisons were drawn; however, considering the limited sample size in this pilot study, small deviations could reflect on the tests of significance. While Fisher's exact tests were used to compare categorical data, Mann-Whitney U tests was used to compare the scores between subjects with a-MCI and controls. A P value of <0.05 was considered significant.

Results

Demographic variables

Twenty-three consecutive literate patients of MCI and 23 CNHC were selected for inclusion in this pilot study. Mean age of the MCI cohort was 68.4 ± 5.4 years and that of the control group was 64.9 ± 6.4 years (P = 0.060). The mean education status in years of the MCI group was 11.6 ± 2.5 years and that of the control group was 13.1 ± 3.2 (P = 0.104). The range of formal education in the entire cohort was 8-18 years. As this difference was largely non-significant, these differences were unlikely to account for the test performance between the two groups. The MCI group comprised 9 females (39.1%) and the control group had 13 females (56.5%) (P = 0.188).

Neuropsychology results

The diagnosis of amnestic MCI was based on a performance score < mean-1.5 SD on recall subsets of at least two of four standardized tests for memory, i.e., RAVLT, WMS-R logical memory verbal and visual subsets, and DMS-48. On group mean comparisons of test scores [Table 2] using Mann-Whitney U tests between the MCI and the control groups, tests demonstrating significant differences between the groups included MMSE, ACE which included ACE-registration and recall scores, WMS-R

Table 1: Normative cut-off scores obtained from control population

Variable	*N*	Mean	Std. Deviation	Mean-1.5*SD
MMSE	23	28.96	.928	27.56
ACE Registration	23	20.65	2.690	16.62
ACErecall	23	7.22	1.906	4.36
ACE	23	88.57	5.492	80.33
P_fluency	23	5.30	1.105	3.65
Animals fluency	23	5.39	.722	4.31
WMS story A immediate	23	9.61	3.551	4.28
WMS story A delayed	23	6.13	2.865	1.83
WMS story B immediate	23	8.78	2.430	5.14
WMS story B delayed	23	6.17	2.741	2.06
WMS visual immediate	23	23.87	6.851	13.59
WMS forward digit span	23	6.39	1.530	4.10
WMS backward digit span	23	5.30	1.521	3.02
WMS visual delayed	23	17.26	6.594	7.37
RAVLT trial 1	23	5.13	1.687	2.60
RAVLT trial 2	23	8.00	1.679	5.48
RAVLT trial 3	23	9.35	2.166	6.10
RAVLT trial 4	23	10.61	2.271	7.20
RAVLT trial 5	23	11.96	2.011	8.94
RAVLT 20min recall	23	9.43	3.800	3.74
TRAIL_A	23	2.142	1.0582	0.55
TRAIL_B	23	3.678	1.9286	0.79
WCST_categories passed	22	5.045	1.7037	2.49
DMS-48 immediate_	22	40.00	6.554	30.17
Doubles subsetimmediate	22	12.68	2.317	9.21
Unique subset immediate	22	14.32	2.338	10.81
Abstract subsetimmediate	22	12.91	2.348	9.39
DMS-48_delay	22	39.68	8.156	27.45
Doubles subset delay	22	12.59	2.873	8.28
Unique subset delay	22	14.00	2.777	9.83
Abstract subset delay	22	13.09	3.206	8.28

MMSE = Mini — mental state examination, ACE = Addenbrooke's cognitive examination, WMS-R = Wechsler memory scale-revised, RAVLT = Rey auditory verbal learning test, DMS = Delayed matching-to-sample Test, WCST = Wisconsin card sorting test

verbal and visual subsets of immediate and delayed recall, RAVLT cumulative learning and 20-min recall scores. Though the results were statistically significant, the wide SD of the MCI cohort precludes over interpretation of these results, thereby signifying the heterogeneity within the group on performance on any given test. It could also be noted that the performances of both the control and test cohorts were poor on the logical memory story learning and recall segments as evident from Table 2 and this could have skewed the normative scores. On the DMS-48 significant differences were noted in the delayed recall of objects presented as "doubles" and not in the cumulative scores. The normative data obtained from the group of 23 controls studied is indicated in Table 3. These formed the basis for comparing the number of subjects in each study group as these were education matched, who demonstrated impairment in terms of performance below mean-1.5SD of control scores [Table 1] on individual tests. Using this method tests demonstrating significance included MMSE, total ACE (including ACE- recall components), WMS-R verbal and visual acquisition and recall subsets and RAVLT acquisition and recall subsets.

Discussion

This pilot case-control study confirmed the utility of M-ACE as an effective tool to detect amnestic MCI. While measures of registration, recall and other components in this tool have been standardized previously in a community,[16] its utility in diagnosis of MCI has not been studied. The fact that our cohort comprised pure amnestic forms of MCI was evident from the normal performances on Wisconsin Card Sorting Test (WCST) and Trail A & B components. Existing criteria for MCI necessiate objective demonstration of performance 1.5 SD below age-adjusted normative means on memory testing.[17] Most subsequent studies have validated this approach,[18,19] but others have used lenient cutoffs of < 1.0 SD.[20,21] In this pilot, we have attempted to replicate a real life situation as would be seen in a community comprising individuals with overt or latent memory impairment along with objectively cognitively normal individuals. While individual matching for age, sex, and education status may not be possible in this situation, it is not certain whether individuals diagnosed with MCI may need to demonstrate neuropsychological deficits in single screening tests,[22,23] multiple sub-component tests,[18] or average of various tests across various cognitive domains.[19] Screening an MCI cohort based on age- and education- based normative data generated from previous studies on dementia may not be of complete relevance as test scores are likely to be higher in an MCI cohort, albeit lower than that of CNHC. Generation of values from a control group within a cohort as in this pilot may help to deal with this limitation. This pilot study compared a screening test battery with reference neuropsychological tests and demonstrated the importance of including durable measures of learning and recall. A recent comprehensively done study conducted cross-sectional and longitudinal analysis of a small cohort of neurologically normal, community-dwelling older adults.[22] At baseline and follow-up the participants were diagnosed as normal or MCI by means of five different strategies based on the number of neuropsychological tests and cut-off levels required to define impairment. The results showed that the number of participants diagnosed as having MCI ranged from 10-74% of the sample, depending on the rigorosity of the criteria for impairment. However, the most conservative strategy for diagnosing MCI, i.e., requiring a performance that was 1.5 SDs below the normative mean in more than two tests for a domain as done in our study, revealed the best validity on a longitudinal followup. It can be seen from our group mean comparisons that the patient cohort scores demonstrated wide standard deviations emphasizing the variability of reliance on the face value of the test scores as well as the limitations of sample size. Hence, the second method of comparison of test performances below 1.5 SD from the mean normative scores as expressed in Table 1 seemed

Table 2: Group mean comparisons of test scores between mild cognitive impairment (MCI) and matched cognitively normal healthy control (CNHC)

Test	Test scores-mean (standard deviation, SD)	Control scores-mean (standard deviation, SD)	*P*-value (Mann-Whitney U)
MMSE	27.1 (2.5)	29.0 (0.9)	0.002
ACE registration score	19.0 (2.7)	20.7 (2.7)	0.021
ACE recall	3.7 (2.8)	7.2 (1.9)	<0.001
ACE total score	79.7 (9.6)	88.6 (5.5)	0.001
Lexical fluency	5.3 (1.2)	5.3 (1.1)	0.964
Category fluency	4.7 (1.6)	5.4 (0.7)	0.187
WMS-R logical memory test immediate (Story A)	5.7 (3.7)	9.6 (3.6)	0.001
WMS-R logical memory test delayed (Story A)	3.0 (2.6)	6.1 (2.9)	0.001
WMS-R logical memory test immediate (Story B)	4.4 (2.7)	8.8 (2.4)	<0.001
WMS-R logical memory delayed (Story B)	2.7 (2.3)	6.2 (2.7)	<0.001
WMS – visual reproduction copying immediate score	17.5 (8.6)	23.9 (6.9)	<0.001
WMS – visual reproduction copying delayed score	8.0 (7.8)	17.3 (6.6)	0.009
WMS forward digit span	6.1 (1.3)	6.4 (1.5)	0.464
WMS backward digit span	4.7 (1.6)	5.3 (1.5)	0.077
RAVLT list 1	4.3 (1.1)	5.1 (1.7)	0.073
RAVLT list 2	5.5 (1.4)	8 (1.7)	<0.001
RAVLT list 3	6.8 (1.5)	9.4 (2.2)	<0.001
RAVLT list 4	7.2 (2.1)	10.6 (2.3)	<0.001
RAVLT list 5	7.9 (2.1)	12.0 (2.0)	<0.001
RAVLT 20-min recall	3.7 (2.9)	9.4 (3.8)	<0.001
Trail A time in minute	2.8 (2.0)	2.1 (1.1)	0.356
Trail B time in minute	4.8 (3.0)	3.7 (1.9)	0.287
WCST categories passed	4.0 (2.1)	5.0 (1.7)	0.136
DMS-48 immediate score	32.3 (11.7)	40 (6.6)	0.069
DMS-48 delayed score	34.5 (9.9)	39.7 (8.2)	0.154

MMSE = Mini — mental state examination, ACE = Addenbrooke's cognitive examination, WMS-R = Wechsler memory scale-revised, RAVLT = Rey auditory verbal learning test, DMS-48 = Delayed matching-to-sample Test-48, WCST = Wisconsin card sorting test

Table 3: Comparison of the proportion of subjects with neuropsychological test scores less than the mean minus 1.5 standard deviation (SD) of the normative scores

Test	Controls[a] (*n* = 23)	MCI cohort[b] (*n* = 29)	a *versus* b
	n (%)	*n* (%)	*P* value (Fisher's exact test)
MMSE	2 (8.7)	9 (39.1)	0.016
ACE registration score	2 (8.7)	4 (17.4)	0.665
ACE recall	2 (8.7)	13 (56.5)	0.001
ACE total score	2 (8.7)	11 (47.8)	0.003
Lexical fluency	1 (4.3)	2 (8.7)	1.000
Category fluency	2 (8.7)	7 (30.4)	0.135
WMS-R logical memory test immediate	3 (13)	17 (73.9)	<0.001
WMS-R logical memory test delayed	2 (8.7)	10 (43.5)	0.007
WMS – visual reproduction copying immediate score	1 (4.3)	9 (39.1)	0.004
WMS – visual reproduction copying delayed score	2 (8.7)	13 (56.5)	0.001
WMS forward digit span	2 (8.7)	3 (13.0)	1.000
WMS backward digit span	3 (13.0)	6 (26.1)	0.459
RAVLT list 1	1 (4.3)	1 (4.3)	1.000
RAVLT list 2	1 (4.3)	14 (60.9)	<0.001
RAVLT list 3	2 (8.7)	9 (39.1)	0.016
RAVLT list 4	2 (8.7)	11 (47.8)	0.003
RAVLT list 5	1 (4.3)	12 (52.2)	<0.001
RAVLT 20-min recall	2 (8.7)	11 (47.8)	0.003
RAVLT total learning score	2 (8.7)	13 (56.5)	0.001
Trail A time	1 (4.3)	1 (4.3)	1.000
Trail B time	0 (0)	1 (4.3)	1.000
WCST categories passed	5 (21.7)	7 (30.4)	0.502
DMS-48 immediate score	1 (4.3)	10 (43.5)	0.002
DMS-48 delayed score	2 (8.7)	4 (17.4)	0.665

MMSE = Mini — mental state examination, ACE = Addenbrooke's cognitive examination, WMS-R = Wechsler memory scale-revised, RAVLT = Rey auditory verbal learning test, DMS = Delayed matching-to-sample Test, WCST = Wisconsin card sorting test

more relevant. While the results of our pilot study needs to be validated in a larger cohort using M-ACE as a screening tool along with other definitive tools, correlating with results of neuroimaging and longitudinal follow-up, diagnosis of MCI is probably best considered using values from two or more neuropsychological tests for the memory domain to avoid over-diagnosis. This difference between tests is likely to be a consequence of the weight of learning and retention scores utilized to arrive at the results.

There is no standard protocol for the neuropsychological batteries to be employed. Studies to date vary in the number of cognitive domains assessed beyond memory (e.g., language, executive function, visual-spatial/ perceptual ability, attention), procedures for assessing memory (e.g., verbal list learning and retention, prose paragraph recall, memory for visually-presented designs), criteria for determining the presence of impairment on a single cognitive measure, and in criteria for determining impairment across multiple same-domain cognitive measures (e.g., requiring impaired performance on one versus two language measures). In our study non-memory domains were also tested in M-ACE, WCST, Trail A & B to verify that the cohort was a homogenous a-MCI cohort. While the relevance of a delayed recall construct cannot be debated (as shown in the consistent measures in Tables 1 and 2), it has been demonstrated that individuals with learning deficits (regardless of the level of their retention abilities) at baseline showed a significantly higher likelihood of developing AD over 2 years compared to those with a retention deficit (regardless of the level of their learning abilities).[23] However it is evident from Table 1 that registration measures on the 24-point scale

of M-ACE did not replicate the significance of the results on group mean comparisons as opposed to the 10-point recall results. This emphasizes on the need to stringently employ age- and education-standardized normative scores if M-ACE registration components are to be utilized as part of a screening test battery for MCI.[16] The significance of learning measures of standard tools such as the RAVLT, WMS-R verbal and visual subsets and, in our study, the DMS-48 cannot be over-emphasized. One problem with education-adjusted scores is that it can potentially result in misclassification for some borderline cases if age is not taken into account and we have tried to minimize this bias in the results by including subjects who had a minimum of 8 years of formal school education.

Our results are consistent with prior studies that have also reported differential sensitivity of learning and retention measures in MCI and prodormal AD.[24,25] Interpretation of the results of our observational cohort study vis-a-vis the utility of learning and retention measures from M-ACE should be interpreted with caution as it was a pilot study constrained by the limited number of subjects. The results do suggest its potential relevance while screening an elderly community for MCI. Cumulative learning trials may prove to be a reliable index for initial diagnosis of MCI, but inclusion of additional variables from standardized tests should improve the overall accuracy and may represent the ideal strategy to identify subjects who need to be closely followed up for progression to AD.

Appendix

The WMS or WMS-R contains sub-tests like Logical Memory Passage, Visual Reproduction, and Paired Associate Learning. Logical Memory Passage is a test of paragraph or prose recall and has an immediate recall and delayed recall. The examiner reads two stories, stops after each reading, and asks for an immediate free recall. After a delay of 30 min, delayed recall is taken as an attempted verbatim recitation. Story 1 contains 24 memory units and Story 2, 23 memory units. The total score is the total number of ideas recalled for both stories together.[26-28]

The *RAVLT* consists of word lists A and B. There are 15 words in each list. List A is read out first at the rate of one word per second. The subject has to recall as many words as possible, in any order. List A is repeated 5 times, the total leading to a maximum possible score of 75 (15 x 5). Then the examiner presents a second list of 15 words (List B). The subject has to recall the words from this list also. Immediately following this, the subject is asked to recall as many words as possible from List A. Delayed recall of List A is given after 20–30 min. The score for each trial is the number of words correctly recalled. After the delayed recall, recognition is tested by asking the respondent to indicate which of the 50 words in a list read aloud (a mix of words from both lists A and B, as well as semantically or phonemically similar words to Lists A and B) from List A, and which were not.

The *WMS-R Visual Reproduction Subsets* requires the subject to draw from memory simple geometric figures. Each of the visual reproduction cards is shown for ten seconds. Following each presentation, immediate recall is tested. The subjects then draw from memory what they remember of the design. A delayed recall is taken after 30 min.

The *DMS-48* is a unique test to identify patients with amnestic mild cognitive impairment and was included in this study due to its dependence for visual recognition memory and is believed to be quite specific for testing encoding and retrieval of 48 objects presented to the subject as "unique," "abstract," and "doubles." The items are categorized semantically as: 1) abstract items: Targets and distracters are abstract patterns that cannot be verbalized; 2) paired items: Targets and distracters are concrete objects belonging to the same semantic category and with similar shape, color, and name to prevent the use of verbal strategies; and 3) unique items: Targets and distracters are dissimilar concrete objects [7]. This was included to gauge its validity as a visual memory test.

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