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Original Article

Differential Deficits in Attention, Working and Semantic Memory Discriminates Between Mild Cognitive Impairment and Alzheimer's Disease

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Abstract

To assess the prognosis of mild cognitive impaired (MCI) patients effectively and the possible conversion of MCI to Alzheimer's disease (AD), cognitive deficits in MCI compared to AD, needs to be studied. To achieve this aim, various domains of cognition (working memory, semantic memory and attention) were assessed both in Alzheimer's disease (AD) and mild cognitive impairment (MCI) patients and were compared with age and sex matched healthy controls. The scores of cognitive functions were also correlated with the mini-mental state examination scores and clinical dementia ratings.

MCI patients had significant deficits in working memory with intact semantic memory and attention while AD patients had significantly more deficits in working memory, attention and semantic memory as compared to controls. Thus, presence of working memory deficit with intact semantic memory and attention could be a sign of MCI and further, a deficit in semantic memory and attention could be a sign of progression to AD. Presence of deficits in all the three domains of cognition emerges as a feature of AD. Further, correlation studies support that MMSE is correlated better with the cognitive deficits than CDR.

Introduction

Neurodegenerative disorders like dementia have become a growing public health problem not only in developed but also in developing country like India. According to WHO, by the year 2020, approximately 70% of the world's population aged 60 and above will be living in developing countries, with 14.2% in India (1). In this age group, cognitive abnormalities are being reported and could manifest as dementia.

Alzheimer's disease (AD) is the most frequent form of dementia, with a spectrum of cognitive abnormalities. Mild cognitive impairment (MCI) is defined as a transition state between age-related memory decline and AD. MCI is characterized by loss of short-term memory like losing things, forgetting date or events etc (2-4). It is critical to assess and differentiate Age-associated memory impairment (AAMI), wherein functional abilities are

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not much affected vis a vis dementia which is an alarming issue (5).

Cognitive assessment remains central to study the course of AD (6). Neuropsychological assessment is a simple, non invasive and diagnostic approach, which can be learnt by non specialist trainers as well. Thus, implementing the same at primary health centers will for sure help reduce the national burden of cognitive decline, by early diagnosis and appropriate referral for treatment.

Direct correlation between subjective cognitive impairment and risk of developing objective deficits over time has been reported (7). Contrary to this, subjective deficits that are not detectable using objective measures have also been reported (8). Therefore the need of both subjective and objective assessment of cognition to study ongoing pathological and degenerative processes is important in both MCI and AD patients as compared to age matched controls. In the present study, for subjective assessment, MMSE and CDR questionnaires were used and objective assessment was done using cognitive function tests targeting the domains as explained henceforth.

It is often debated whether MCI is an independent entity or a prodrome of Alzheimer's disease? For predicting the conversion from MCI to AD, cognitive markers are recognized as being more robust predictors, as compared to imaging and other biochemical biomarkers (7). According to literature, usually 10% of subjects convert from MCI to AD, and others remain stable and can infact improve with time (8-11).

Efforts have been made to distinguish MCI from AD (13). One of the distinguishing features, which is often reported is its effect on the daily functions. In dementia, routine activities are often affected versus MCI, wherein little or no impairments are seen (14). Deficits in episodic and semantic memory (naming of objects (18-20), naming and recognition of faces of famous people (21, 22) and verbal fluency (23, 24) have been reported in AD (15-17). Further, it is often observed and reported that in AD patients, memory deficit is followed by attentional difficulties (25-27), including auditory (28) and visual selective processing (29-32) and attention shifting (33).

Episodic memory deficits in AD are well reported in the existing literature. But, not enough published literature is available pertaining to semantic memory, working memory and attention in both AD and MCI patients.

Thus, it is pivotal to assess and compare the cognitive domains, which are effected differentially in MCI and AD. Further which deficits can predict the conversion of MCI into AD. This knowledge will not only aid in treatment but also and prognosis of the disease.

The present study was undertaken to assess various domains of cognition to find a potential domain, which can differentiate MCI from AD as compared to controls. Further,the cognitive scores and dementia scores as assessed by mini-mental state examination scores and clinical dementia ratings, respectively, needs to be correlated with the cognitive function scores.

Material and Methods

Participants: The study was approved by Institute's ethical committee. Twenty-seven AD (21 males & 6 females) diagnosed with AD, according to National Institute of Neurological and Communicative Disorders and Stroke/the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) criteria (27) and twenty-six MCI patients (19 males & 7 females), diagnosed according to criteria defined by Petersen (2) of either gender with age above 60 years were recruited from the outpatient dementia clinic of Department of Neurology, All India Institute of Medical Sciences (AIIMS) and twenty-six (16 males & 10 females) age matched healthy subjects were enrolled on voluntarily basis. Patients with severe AD, any psychiatric illness, head trauma or other neurological condition that could account for the cognitive impairment were excluded from the study.

Type of study: Observational case control study

Study Protocol: An informed consent was taken and

detailed history and general physical examination was done. Following neuropsychological assessment was done in the patient population and healthy controls.

Questionnaires

a. Mini-Mental State Examination (MMSE)

b. Clinical Dementia Rating (CDR)

Based on the MMSE scores, the patients were divided into AD or MCI and control groups:

- MMSE 27-30: Control
- MMSE 21-26: MCI
- MMSE 11-20: AD

Cognitive function tests:

a. Working Memory Test: Working Memory was assessed using word and picture memory (34). In word memory, subjects were shown 10 common words consecutively on a computer screen, each presenting for 2s and subjects were asked to read aloud and memorize the words for 15s period (retention period). Following which, they had to name as many words possible. This test was performed three times. The total number of words remembered correctly was noted as the word memory score (maximum possible score was 30).

   In the picture memory test subjects were shown 10 common pictures instead of words on a computer screen. The total number of pictures correctly remembered was noted as the picture memory score.

b. Semantic Memory Test: Semantic memory was assessed using verbal fluency test (35, 36) Subjects were asked to close their eyes and to think of as many animal names as possible during a 30s period. Subsequently they were asked to open their eyes and name as many animals as possible for a period of one minute. The total number of animal names recalled was used as the verbal fluency score.

c. Attention Task Test: Digit span forward test was used to assess focused attention or attentional abilities (37, 38). A sequence of two numbers (one number per second) was read to the subject. The subject was asked to repeat them immediately. If the subject recalled these two digits, a sequence of three numbers was read to the subject. The test continued until either the subject could not recapitulate two consecutive sequences of the same length or the subject repeated the sequence of ten numbers. The score was determined by the length of the longest correctly repeated sequence, ranging from zero to nine numbers. This test probes immediate memory for digits, based on focused attention.

Statistical analysis

The statistical analysis was done using SPSS-20 Software. One-way analysis of variance (ANOVA) followed by Bonferroni's post hoc test for multiple pair-wise comparisons of MMSE, working memory (word memory and picture memory) and Kruskal–Wallis test was used to compare CDR & Semantic Memory among the groups.

Pearson/spearman's correlation was done between MMSE & CDR with all cognitive function testing scores. It represented linear changes among the three groups. Statistical significance was accepted for p value of <0.05.

Results

The mean MMSE and CDR scores followed a hierarchical pattern, which was Control>MCI>AD for MMSE and Control<MCI<AD for CDR.

MMSE and CDR scores were significantly lower in MCI and AD compared to control and in AD compared to MCI (Table I).

Further, a significant negative correlation between CDR and MMSE scores was observed in control

[r=-0.41, p=0.05] and AD [r=-0.49, p=0.013]. However, MCI, didn't show any correlation between the CDR and MMSE scores (Fig 1).

Working/Semantic Memory scores

Working memory test revealed an overall group effect. The working memory scores (for both word and picture memory) were significantly higher in control compared to MCI and AD and MCI compared to AD (Table II).

Word memory scores correlated positively with MMSE score in control [r=0.45, p=0.05] and AD [r=0.64, p=0.001] & [Fig. 2a]. Picture memory scores correlated positively with MMSE only in AD [r=0.051, p=0.01] & [Fig. 2b]. In MCI no correlation was observed between the MMSE and working memory scores. Semantic memory scores showed a different pattern. MCI patients had scores comparable to control as well as AD, while AD had significantly lower scores compared to control (Table II). In other words MCI group could not be distinguished on the basis of semantic memory scores. Within MCI, however, MMSE and semantic memory scores showed positive correlation [r=0.48, p=0.029] & [Fig. 2c].

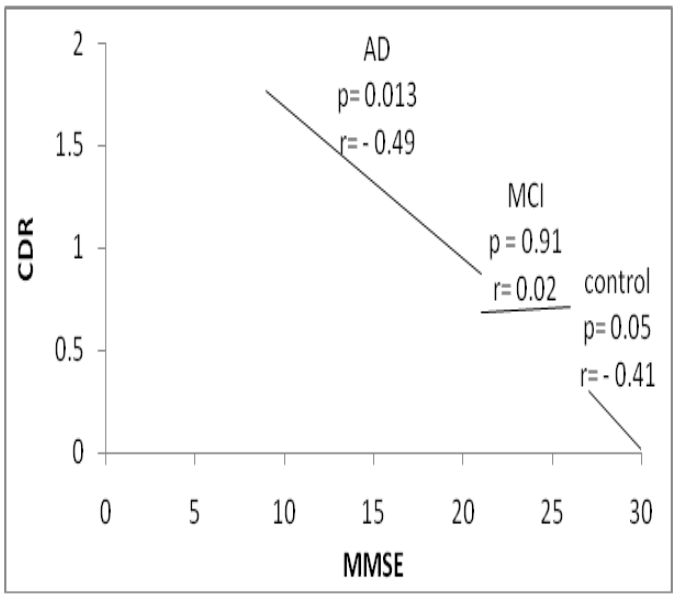

Fig. 1: Correlation between MMSE and CDR scores in all three groups.

Focused Attention Test (AT)

Digit span forward test revealed significant intergroup differences. MCI and control had comparable scores, while AD had significantly lower scores compared to control as well as MCI [Table II]. Scores of focused

TABLE I: MMSE and CDR scores in Control, MCI and AD.

Parameters	*Control*	*MCI*	*AD*	*Overall p value*	*Post-hoc analysis p value*		
					Control vs. MCI	*Control vs. AD*	*MCI vs. AD*
MMSE	28.22±1.10	24.2±1.60	16.54±3.68	0.001	0.001***	0.001***	0.001***
CDR	0 (0-0.5)	0.5 (0.5-1)	2 (0.5-2)	0.001	0.001***	0.001***	0.001***

MCI, Mild Cognitive Impairment; AD, Alzheimer disease; MMSE, Mini-Mental Status Examination; CDR, Clinical Dementia Rating. Data are presented as mean (±SD) for normally distributed variables and median range for non-normally distributed variables. (a) ANOVA followed by Bonferroni's post-hoc test. (b) Kruskal–Wallis test followed by Bonferroni's post-hoc test. Levels of significance (p=0.001)***

TABLE II: Cognitive decline during cognitive function tests in Control, MCI and AD.

Parameters	*Control*	*MCI*	*AD*	*Overall p value*	*Post-hoc analysis p value*		
					Control vs. MCI	*Control vs. AD*	*MCI vs. AD*
Word memory	14.95±3.59	11.65±4.68	6.41±4.08	0.001	0.035**	0.001***	0.001***
Picture memory	15.81±5.10	11.55±3.54	5.29±3.81	0.001	0.005**	0.001***	0.001***
Semantic memory	8.5 (2-22)	6.5 (2-13	6 (0-25)	0.020	0.145	0.008**	0.130
Attention task	6.04±1.55	6.31±1.45	4.45±1.38	0.001	1.000	0.002**	0.001***

MCI, Mild Cognitive Impairment; AD, Alzheimer disease; MMSE.
Data are presented as mean (±SD) for normally distributed variables and median range) for non-normally distributed variables. (a) ANOVA followed by Bonferroni's post-hoc test. (b) Kruskal–Wallis test followed by Bonferroni's post-hoc test. Level of significance is: **(p=0.01) & ***(p=0.001)

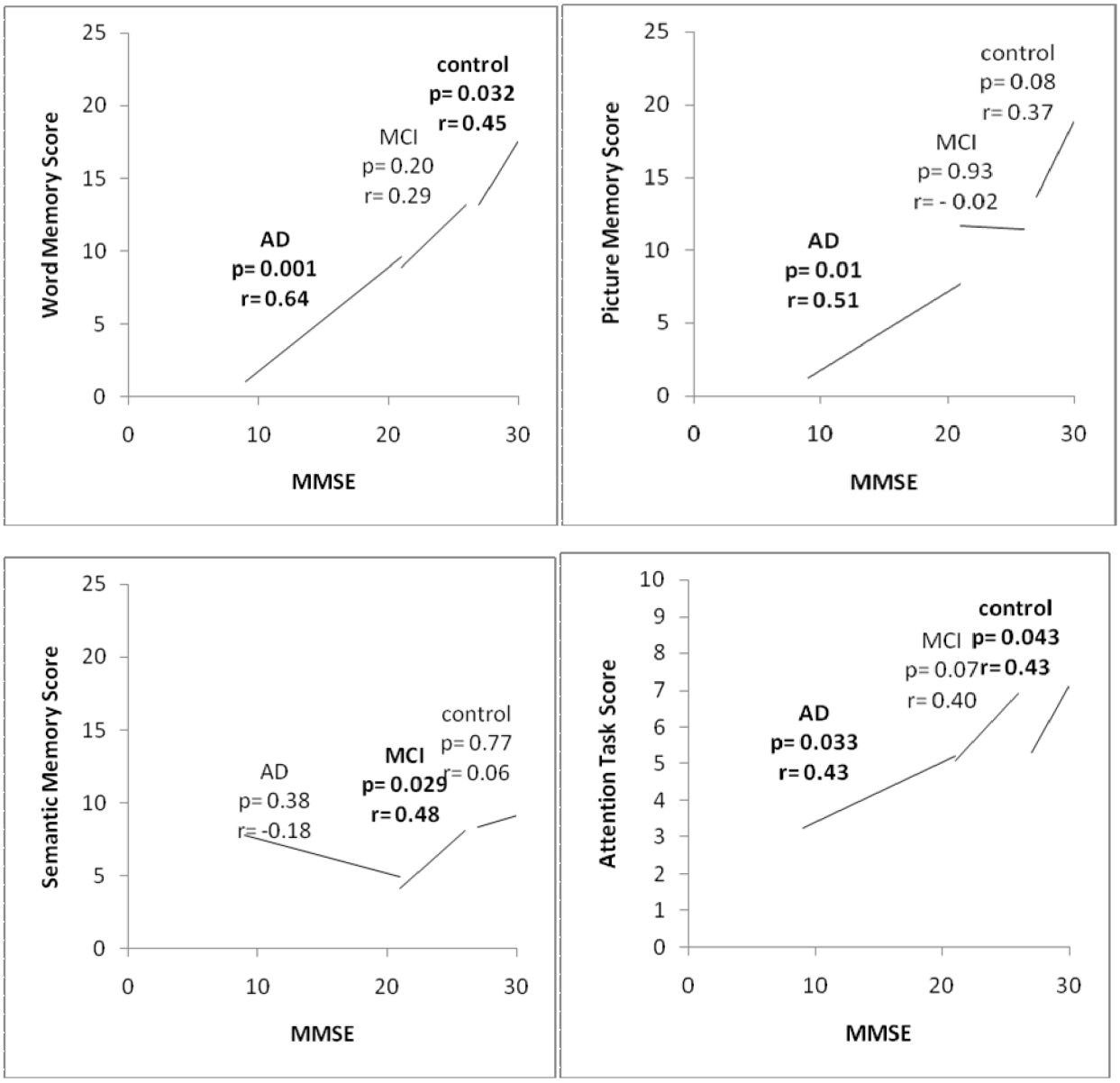

Fig. 2: Correlation between MMSE and cognitive function scores in all three groups
(a) Correlation between MMSE and Word Memory Score
(b) Correlation between MMSE and Picture Memory Score
(c) Correlation between MMSE and Semantic Memory Score
(d) Correlation between MMSE and Attention Test Score

attention correlated positively with MMSE in control [r=0.43, p=0.043] and AD [r=0.43, p=0.003] & [Fig. 2d]. However, MCI didn't show any correlation between the MMSE and attention test scores.

Correlation of various cognitive function scores with CDR did not show significance (except with word memory scores in AD) [Fig. 3a].

Thus to conclude, AD patients had deficit in working & semantic memory and attention, while MCI had preserved semantic memory and attention capacity.

Discussion

This systematic, cross sectional investigation demonstrates deficits in working memory, semantic memory and attention in patients of MCI & AD compared with healthy controls. MCI had scores

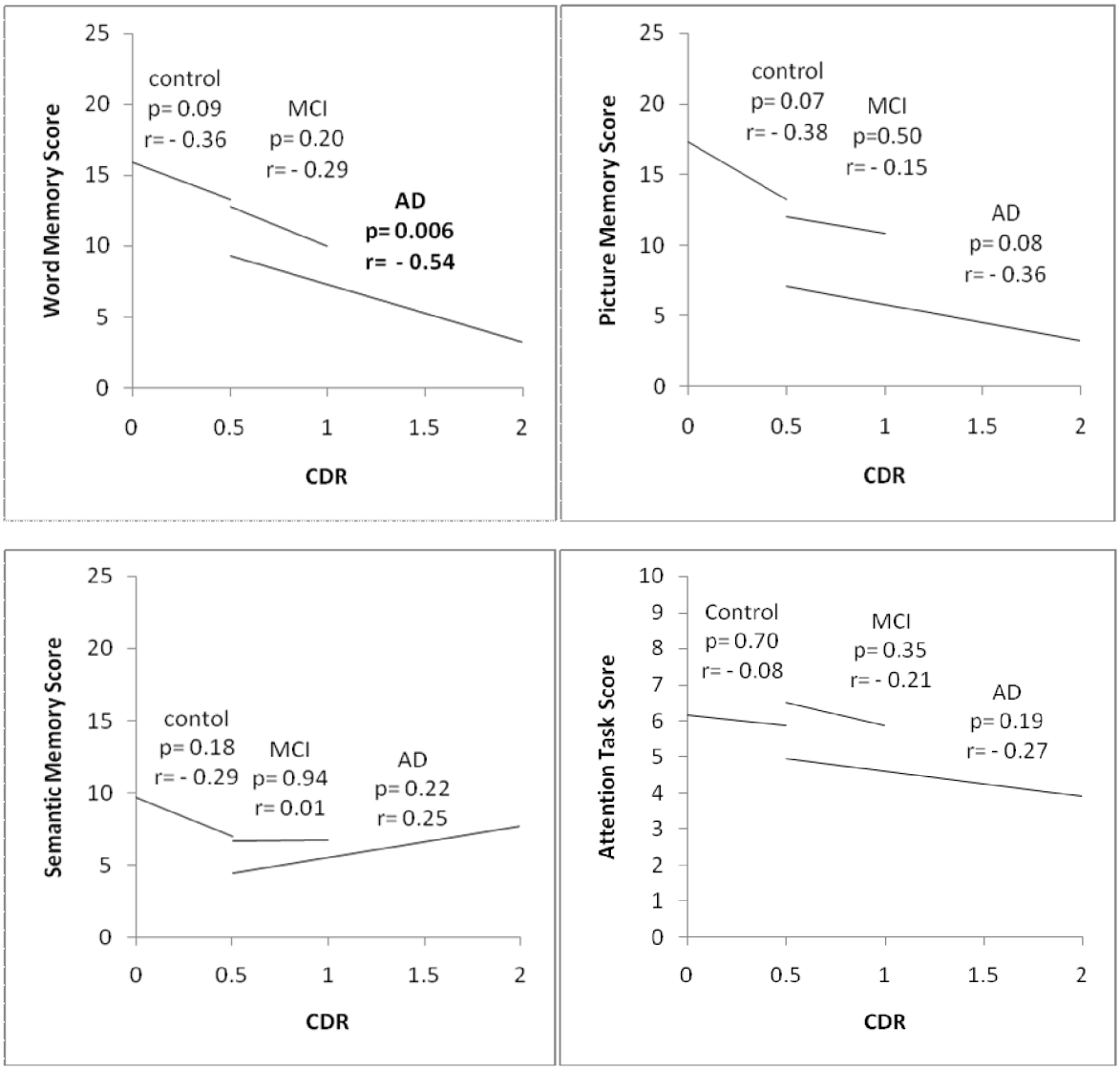

Fig. 3 : Correlation between CDR and cognitive function scores in all three groups
(a) Correlation between CDR and Word Memory Score
(b) Correlation between CDR and Picture Memory Score
(c) Correlation between CDR and Semantic Memory Score
(d) Correlation between CDR and Attention Test Score

between control and AD that were significantly different for word and picture memory but not for semantic memory. MCI attention scores were comparable to control and better than AD scores. In other words, AD had significant deficits compared to control in all the three cognitive domains tested but MCI had deficits only in working memory compared to control. It is suggested from these results that deficit in working memory could be the first domain of cognition to get affected in MCI, although scores of working memory did not show correlation with MMSE scores within this group. Semantic memory and attention remained preserved in MCI. The relationship between MMSE scores and working memory was apparent in correlation analysis in control and AD. MCI group showed significant correlation between MMSE and semantic memory only.

Working memory deficits have been documented in AD as well as the earliest stages of the disease (39-42). In the present study AD group was significantly impaired on both word (verbal) and picture (recognition+verbal) memory tests; this impairment in AD may be because of expansion of

pathology to temporal lobe as well as outside the medial temporal lobe including the parietal and antero-lateral aspects of the temporal lobe (43). Initiation of these degenerative changes in MCI could have resulted in working memory impairment in this group. Preservation of semantic memory could be related to preservation of anterior temporal lobe, which plays an important role in semantic processing (44, 45). Deficits in semantic memory that are related to temporal-parietal regions of the lateral temporal lobe has been reported (46). The failure of semantic cognition in MCI and AD could be associated with either loss of amodal semantic representations modulated by the anterior temporal lobe or loss of semantic control mediated by the temporo-parietal regions which is found to be hypometabolic in the case of AD and MCI (43). Similar trend in working and semantic memory deficits has been reported by Hiele et al, that MCI patients performed significantly worse on the word memory and picture memory tests, while animal fluency scores did not differ from control (34).

Deficit in focused attention in AD compared to both control and MCI in the present study is corroborated by earlier studies reporting difficulties in all types of attention, with greatest difficulty in switching attentional focus that AD patients experience (47). This could be related to the significant cholinergic dysfunction in AD (48). We observed that MCI didn't show significant difference in attention task scores compared to control and this may be because of preserved cholinergic function in MCI compared to control (49-51).

In this study, a significant correlation between various cognitive scores and MMSE (and no correlation with CDR) supports the notion that MMSE could be used as a better measure of dementia in AD.

In conclusion, working memory deficits in absence of semantic memory and attention deficits could be the characteristic features of MCI. Appearance of attention deficits could be a sign of progression to AD, while a deficit in working memory; semantic memory and attention could be a feature of AD compared to control.

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