CHAPTER 5
NEUROPSYCHOLOGICAL PROFILE OF ALZHEIMER’S DISEASE

5.1 GENERAL BACKGROUND

Neuropsychological assessment plays a crucial role in the assessment of cognitive decline in older age. In India, there is a dearth of culturally appropriate standardized measure to assess cognitive functions in early dementia. The main objectives of this study was to examine clinical validity of neuropsychological analysis for elderly in identifying early dementia and to evaluate the conversion rates to AD in subtypes of MCI and to identify neuropsychological measures most predictive of the time to conversion. Finally, we sought to identify which baseline neuropsychological measures from the comprehensive battery were the most predictive of time to AD conversion.

The neuropsychological tests have been proved to be a useful marker for early diagnosis AD and discriminate the patients and controls. Most of the neuropsychological tests have been in regular use in the memory clinic at SCTIMST for more than 10 years. The proposed study is expected to identify neuropsychological analysis in the South Indian population that may serve as potential predictors of cognitive impairment or dementia in the elderly population in India. With the expected rise in the population at risk for dementia in the coming years in the country and the devastating nature of the disease for the patient as well as the family, ability to make early diagnosis or preclinical diagnosis will provide an enormous potential for disease modifying intervention, which is perhaps one of the most intensely researched areas that is making rapid progress internationally.

5.2 NEUROPSYCHOLOGICAL EVALUATION

The neuropsychological test battery included measures of learning and memory, orientation abstract reasoning, language, attention, and visuospatial ability. Neuropsychiatric inventory test assesses 12 behavioral problems that commonly occur in people with dementias, including agitation, anxiety, apathy, delusions (fixed, false beliefs), hallucinations (sensing things that are not really there), euphoria (i.e.; extreme happiness or elation), dysphoria (i.e.; the opposite of euphoria), eating difficulties, loss of inhibition (the ability to hold back an extreme
emotion or behavior), irritability, irregular motor behavior (e.g.; shaking or trembling in just the hands or another body part), and sleeping disturbances [116].

All participants were invited to SCTIMST for the neuropsychological and neuroimaging tests on a mutually convenient appointment. All neuropsychological testing were carried out in the Neuropsychological testing rooms of the Cognition and Behavioural Neurology Section (CBNS) of the department of neurology. A qualified neurologist carried out all clinical assessments. All patients deemed requiring psychiatry consultation will be referred to the psychiatrist supporting the memory clinic at SCTIMST and as per the established procedure of this memory clinic. All neuropsychological evaluations will be carried out by a qualified, neuropsychology-trained and experienced psychologist who will be blinded to the clinical diagnosis of the subjects.

All participants, after informed consent, will be subjected to clinical examination, which will consist of brief structured history for cognitive, and other neurological symptoms and risk factors and a detailed neurological examination at baseline, after 1 year (Visit-1) and after 2 years (Visit-2). They will also be subjected to a structured neuropsychological tests and radiological investigation at baseline, Visit-1 and Visit-2. When a subject receives a diagnostic categorization of DEM, he/she will transfer into the AD category. Clinical evaluation by a clinician using a brief structured standardized medical history examination and a bedside mental status examination. Qualified psychologists administered a battery of neuropsychological tests.

Neuropsychological testing and interpretation of results in early diagnosis are more difficult. Each patient will undergo a brief cognitive screening battery Mini Mental State Examination (MMSE) and Addenbrooke's Cognitive Examination (ACE) to exclude undiagnosed cases of cognitive impairment. ACE assesses memory, concentration, and other cognitive skills [117][118]. The most frequently used mental status exam is called the Mini-Mental State Exam, a research-based set of questions that results in a score representing a person's general level of cognitive functioning. The maximum score on the MMSE is 30. In general, scores of 24 or more are considered within the normal range of cognitive functioning; scores between 20 and 23 are suggestive of mild cognitive impairment or possible early-stage Alzheimer's disease scores between 10 and 19 are associated with middle-stage Alzheimer's; and a score of 9 or less is considered consistent with severe or late-stage
Alzheimer's disease. The MMSE is generally a reliable and valid indicator of cognitive impairment that can correctly distinguish between individuals with dementia, individuals with pseudo dementia due to depression, and individuals with depression and no cognitive impairment [119]. However, the test must be used with caution in certain groups of people. Another commonly used scale for evaluation of the staging severity of dementia is Clinical Dementia Rating (CDR) scale. It was developed primarily for use in persons with dementia of the Alzheimer type (the equivalent of probable AD) and it can also be used to stage dementia in other illnesses as well. It assesses six domains: memory, orientation, judgment and problem-solving, community affairs, home and hobbies and personal care [120]. The global CDR score is the weighted average of the category ratings. The ratings are 0 for healthy people, 0.5 for questionable dementia and 1, 2 and 3 for mild, moderate and severe dementia as defined in the CDR scale. The ‘sum of boxes’ scores (CDR-sb) are the sum of the category ratings [121].

5.3 LONGITUDINAL AND CROSS-SECTIONAL ANALYSIS

5.3.1 Demographic Clinical Features and Neuropsychological Performance

Demographic details of the incident cohort are shown in Table.3.1. The 49 MCI and 41 AD patients who presented with memory problems to a memory clinic at SCTIMST. Among the 23 MCI subjects participated in a longitudinal study of putative early markers of AD. Twenty three healthy control subjects, recruited were examined annually met the same inclusion/exclusion criteria and completed the same neuropsychological test battery. The institutional ethics committee reviewed and approved the research protocol, and written informed consent was obtained from each participant. The mean (SD) age of the incidence MCI cohort was 65.77 (11.97) years and education was 12.08 (3.96) at study entry. The 23 MCI subjects who completed cognitive testing on the ACE (79.82±11.02) and the MMSE (26.57±2.67) at baseline and (69±11.14) on the ACE and (25.5±1.98) on the MMSE at follow-up. The mean (SD) age of the incidence NCI cohort was 61.87 (6.62) years and education was 14.52 (4.19) at study entry. The 23 NCI subjects who completed cognitive testing on the ACE (93.87±4.74) and the MMSE (28.70±0.97) at baseline and (92.95±3.94) on the ACE and (28.02±0.87) and the MMSE at follow-up. The mean (SD) age of the incidence AD cohort was 69.88±09.08 years and education was
10.92 (3.92) at study entry. The 41 AD subjects who completed cognitive testing on the ACE (56.32±24.32) and the MMSE (17.68±6.93) at baseline.

5.3.2 Neuropsychological Prediction of Conversion to AD in Patients with MCI

We investigated the earliest neuropsychological changes in Alzheimer’s disease by comparing the baseline performance of 23 individuals who subsequently developed AD within an average of 2-3 years with 23 pair wise matched individuals who remained cognitively healthy (NCI). The patients with AD had significantly lower MMSE (p<0.000) and ACE scores (p<0.000) when compared to control subjects. Cognitive and functional ability screening were done at baseline and 24-36 month follow-up assessments, among the 23 eligible participants who were mild cognitive impairment at baseline, 6 patients developed dementia after the 18 months follow-up duration and 17 patients were continue the stable state over a follow-up period average of 18 months.

Participants with AD showed significantly poorer performance on every test including memory and non memory domains. However, tests of episodic and semantic memory were particularly sensitive in discriminating between normal and AD groups. At baseline, 49 MCI subjects aged greater than 55 years underwent cognitive and functional screening. Among the 49 subjects, 23 MCI subjects completed all of the incidence phase screening and evaluation procedures thus forming the incidence cohort. This longitudinal study included one subject, who had died after the first follow-up screening, the duration of follow-up of the incidence cohort ranged from 2 to 3 years.

Both AD and MCI subjects were matched for age and gender. The mean education in the AD was 10.92+3.92 and in MCI was 12.08+ 3.96. When the neuropsychological performance of the two groups was compared it was seen that the AD performed significantly poorer than the MCI on 9 subcomponents in ACE and also on MMSE, RAVLT and Trail Making tests. On complex frontal executive tasks also the performance of AD was significantly impaired when compared to MCI [122]. Results indicate that on the ACE, MCI in comparison with NCI performed significantly poorer only in memory subtests. However AD on comparison to MCI showed impairment also on other cognitive sub tests too. On the MMSE, there was significant difference between MCI and NCI, whereas, AD patients scored significantly lower than MCI. On Semantic Battery, MCI showed significant
impairment in category fluency, while AD patients showed significant impairment in both category and letter fluency. On Trial making test, MCI was not seen to differ from NCI. Comparison of AD with MCI showed significantly more errors for AD in both Trail A and B. For Trail A, AD patients took more time to complete the task compared to MCI. Our results show that, neuropsychological the MCI when compared to NCI showed impairment only on tests involving memory but was comparable on all other cognitive tests. From our results we find that tests such as ACE, MMSE, SB and Trail making are able to pick up the transition from MCI to AD.

Using Mann-Whitney tests we compared the performance of MMSE and ACE score on patients with controls. The MCI patients who converted to AD on follow-up evaluation with MCI patients who did not, hereafter referred to as MCI converters and MCI non converters or Progressive MCI and Stable MCI respectively. Using Mann-Whitney test we compared the performance of MCI and NCI at Visit 1 and also the difference between MCI at visit1 and AD. Results indicated in Table.5.1. Neuropsychological markers prove useful in the early identification of subjects at risk for conversion to dementia. Fig.5.1 shows the graphical representation of performance on MMSE and ACE across visit 1 and 2.

Table.5.1. Longitudinal and discriminating study of MMSE and ACE

<table>
<thead>
<tr>
<th>NPI</th>
<th>NCI</th>
<th>MCI</th>
<th>AD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28.70±00.97</td>
<td>26.57±02.64</td>
<td>17.68±02.64</td>
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</tr>
<tr>
<td>MMSE</td>
<td>93.87±04.74</td>
<td>79.82±11.02</td>
<td>56.32±24.32</td>
<td>0.000</td>
</tr>
<tr>
<td>ACE</td>
<td></td>
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Fig.5.1 demonstrates the graphical representation of MMSE and ACE score at baseline and follow-up data of MCI patients. The follow-up MMSE and ACE have decreased compared to baseline evaluation.
5.4 DISCUSSION

Using Mann-whitney test we compared the performance of MCI and NCI at Visit 1 and also the difference between MCI at visit1 (baseline) and MCI at visit 2. Results indicated in Table.5.1. This results indicates that at visit1 the MCI had significant impairment on MMSE (p<0.001) and ACE (p<0.000) tests of memory compared to NCI. In addition the NCI to AD was also significantly more than the NCI to MCI group. The mean education of AD was lower than MCI and NCI, while that of MCI and NCI were comparable. MCI and AD groups were comparable on age and NCI were younger. Results indicate that on the ACE, MCI on comparison with NCI performed significantly poorer only in memory subtests. However AD on comparison to MCI showed impairment also on other sub tests.

Neuropsychology has contributed importantly to the characterization of the dementia associated with the neuropathology of AD, its differentiation from cognitive changes accompanying normal aging, and its distinction from dementias associated with other types of neuropathology. Obviously, diagnosing Alzheimer's is a complex process because the physician or team of health care professionals has a great deal of information to sort through. If a diagnosis of Alzheimer's is made, the next step is to then begin treating the disease and symptoms. As previously explained, there is no cure for AD. However, there are some treatments and approaches that can sometimes improve symptoms and/or quality of life. The first
stage of treatment is typically to address the person's cognitive symptoms with one or more of the medications described below. Although these drugs can be helpful, they cannot stop or reverse the disease, and eventually, the brain damage. The second stage of treatment is to address the person's environment or surroundings in order to maximize the person's functioning.

The comparison of normal controls and AD groups indicated that normal controls consistently scored higher on neuropsychological tests. This indicates that neuropsychological battery can differentiate between the normal and clinical groups. The MCI converters were older and scored lower on the MMSE at baseline. During the 3-year follow-up, compared with MCI non-converters, converters had greater decline on MMSE scores. MCI converters scored lower than non-converters on all measures of verbal and nonverbal memory and executive function abilities. In this study, 6 MCI patients converted to AD during a mean follow-up of 18 months, remaining the 17 were classified at baseline and follow-up as stable MCI and one pure amnestic patient (aMCI) converted to AD on these follow up duration.

5.5 SUMMARY

This chapter discusses and displays the analysis of different neuropsychological tests for the early diagnosis of AD and the longitudinal and cross sectional analysis result for discriminate the AD patients from controls.