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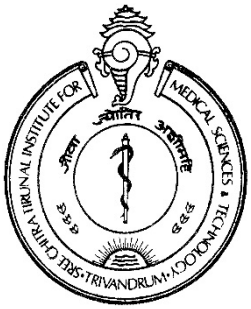

A Comparison of Cognitive Profiles and Structural Correlates in Vascular and Non Vascular Mild Cognitive Impairment

Thesis submitted in partial fulfillment of the rules and regulations for

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By

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Department of Neurology

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CERTIFICATE

I, **Dr Divya K P,** hereby declare that this project was undertaken by me under the supervision of the faculty, Department of Neurology, Sree ChitraTirunal Institute for Medical Sciences and Technology.

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The candidate, Dr Divya K P, has completed the project under my guidance.

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Introduction

As people live longer, the burden of cognitive impairment in society becomes increasingly important. Mild cognitive impairment (MCI) represents an intermediate state of cognitive function between the changes seen in aging and those fulfilling the criteria for dementia.[1] Most people undergo a gradual cognitive decline, typically with regard to memory, over their life span; the decline is usually minor, and does not compromise the ability to function. Known as "mild cognitive impairment," this entity has been receiving considerable attention in clinical practice and research settings.[2,3,4]

There are different aetiologies causing MCI including degenerative, vascular, psychiatric and traumatic causes [5] Although Alzheimer disease is the most commonly diagnosed cause of cognitive dysfunction among the aged, cognitive impairment caused by vascular disease, including subclinical brain injury, silent brain infarction, and clinically overt stroke are important as independent causes and contributors to cognitive dysfunction. There are challenges in interpreting the literature because of nosology, criteria, and measurement issues, but the construct of vascular contributions to cognitive impairment and dementia is sufficiently important. Most studies on MCI have focused on MCI as prodromal Alzheimer's Disease , but studies on MCI preceding other possible dementia disorders, such as vascular dementia (VaD), have been few.

The prodromal stage of VaD is called vascular mild cognitive impairment (VaMCI) . Vascular cognitive impairment (VCI) refers to cognitive impairment caused by cerebrovascular disease and covers a whole spectrum of disorders, from minimally objectively identifiable deficits to VaD [6]. And because vascular risk factors are treatable, it should be possible to prevent, postpone, or mitigate VCI.

There is very little agreement about the clinical picture of vascular mild cognitive impairment (VaMCI) and studies about the pattern of cognitive impairment in VaMCI from India are lacking. This prospective study was conceptualized to assess the pattern of cognitive profiles in patients with mild cognitive impairment due to a vascular etiology and to compare how it is different from that of the mild cognitive impairment of a non vascular etiology. The study also describes the neuroimaging findings in patients with MCI due to vascular etiology.

Review of Literature

Mild Cognitive Impairment (MCI)

Mild cognitive impairment is classified into two subtypes: amnestic and nonamnestic.[3] Amnestic mild cognitive impairment is clinically significant memory impairment that does not meet the criteria for dementia. Non-amnestic mild cognitive impairment is characterized by a subtle decline in functions not related to memory, affecting attention, use of language, or visuospatial skills . The estimated prevalence of mild cognitive impairment in population-based studies ranges from 10 to 20% in persons older than 65 years of age.[5,7-10] Several longitudinal studies have shown that most persons with mild cognitive impairment are at increased risk for the development of dementia.[5,8-10] The patient's history typically raises the suspicion of a decline in cognition, usually memory, and neuropsychological testing may be necessary to corroborate the decline, especially for cases in which the deficits are particularly subtle. Neuropsychological testing may be helpful to distinguish particularly mild cases from normal aging, but testing is not routinely needed to make the clinical diagnosis.

In 2004 the International Working Group on Mild Cognitive Impairment published a consensus report in which the following criteria were proposed for MCI: (i) the person is neither normal nor demented; (ii) there is evidence of cognitive deterioration shown by either objectively measured decline over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits; and (iii) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired [11] In accordance with the increasing heterogeneity of the concept, the MCI subgroups increased , subjects can now be

designated to one of four subgroups: amnestic; amnestic with multiple domains impaired: non- amnestic multiple domains impaired; non-amnestic single domain impaired[12].

The concept of different aetiologies causing MCI was also introduced: degenerative, vascular, psychiatric and traumatic [5]. A model with MCI subtypes of different aetiologies representing different prodromal dementia disorders was put forward. Amnestic MCI (aMCI) of degenerative aetiology was suggested to represent prodromal AD; amnestic MCI with multiple domains impaired (maMCI) of degenerative aetiology would also represent prodromal AD; maMCI of vascular aetiology would represent vascular dementia (VaD); non- amnestic MCI with multiple domains impaired (mdMCI) of degenerative aetiology dementia was suggested to be prodromal dementia with Lewy bodies (DLB); mdMCI of vascular aetiology VaD; non-amnestic MCI with single domain impaired would be prodromal frontotemporal dementia (FTD) or DLB. Thus, it was suggested that a combination of clinical subtypes and aetiologies would be useful in predicting the specific dementia disorder that a person with MCI would progress to [5].

Vascular Cognitive Impairment

Cognitive impairment due to cerebrovascular disease is termed "Vascular Cognitive Impairment" (VCI) and forms a spectrum that includes Vascular Dementia (VaD) and milder forms of cognitive impairment referred to as Vascular Mild Cognitive Impairment (VaMCI).[13] While VaD is the second most common cause of dementia, the milder form VaMCI is much more common. Nearly half of individuals with VaMCI convert to dementia after five years.[14] Vascular cognitive disorders are poised to become

the silent epidemic of the 21st century and contribute significantly to mortality, disability, and decreased quality of life.[15]

It is now clear that VCI is not a single entity, but represents a complex neurological disorder that occurs as a result of interaction between vascular risk factors such as hypertension, diabetes, obesity, dyslipidemia, and brain parenchymal changes such as macro and micro infarcts, haemorrhages, white matter changes, and brain atrophy occurring in an ageing brain. Factors that determine progression of milder form VaMCI to dementia are not well understood. Since VCI is amenable to prevention and treatment, there is a pressing need to identify factors that protect or predispose to it.[16]

Vascular Dementia

Vascular dementia (VaD) is the second most common cause of dementia after Alzheimer disease (AD), and in some Asian countries, it is the most common cause.[17,18,19] Definition of VaD has undergone many modifications in the past and several diagnostic criteria exist, but in its most constructive use, the term refers to "dementia due to cerebrovascular disease". While it is very heterogeneous in its causation, clinical course, imaging, and pathology–common factors operating are brain injury caused by vascular disease leading to cognitive impairment severe enough to cause functional impairment.

Three clinicoradiologic subtypes are recognizable in clinical practice: Multi infarct dementia is characterized by recurrent stroke, stepwise course, focal neurological symptoms and signs, and multiple cerebral infarcts on brain imaging. Strategic infarct dementia is characterized by an abrupt onset of memory impairment or behavioural change in association with a single, strategically placed infarct. Sites associated with dementia include basal forebrain, medial temporal, thalamic or parieto-occipital infarcts.

Subcortical vascular dementia is increasingly recognized as a frequent cause of VaD. The condition is usually the consequence of hypertension and diabetes causing small-vessel disease, which leads to white matter and deep subcortical gray and white matter demyelination and lacunar infarcts.[20]

A uniform clear profile of cognitive syndrome typical of VaD has not been identified. The reasons are probably related to heterogeneity of patient groups in neuropsychological studies. In comparison to AD, there is a general consensus that episodic memory is more impaired in AD, and that executive/attentional processing is more impaired in vascular dementia, especially in patients with subcortical VaD.[21] Patients with VaD also showed greater impairment in both semantic memory and visuospatial/perceptual function than the patients with AD.[22]

Concept of Vascular Cognitive Impairment

There is increasing evidence that patients with clinically significant cognitive impairment in association with cerebrovascular disease frequently do not fulfil the traditional criteria of dementia.[23] This lead Hachinski *et al*. to propose the term "Vascular Cognitive Impairment" (VCI) to refer to the spectrum of cognitive impairment that is caused by or associated with vascular factors.[13] To corroborate this entity, there is also evidence that VaD is preceded by a state of mild cognitive impairment (MCI), similar to AD.[24] Nearly half of elderly with mild cognitive problems due to vascular disease converted to dementia after five years in the Canadian Study of Health and Aging.[14] Both Amnestic MCI characterized by memory loss and MCI with multiple cognitive deficits (mcd- MCI) appear to be prodromal for VaD.[25,26] Independent of MCI subtype, a study demonstrated that risk of conversion to dementia was associated with presence of potentially treatable vascular risk factors.[25]

VCI encompasses all cases of cognitive impairment of cerebrovascular origin without requirement for dementia and not requiring prominent memory loss.[13] VCI forms a spectrum that includes VaD, mixed AD with a vascular component, and VCI that does not meet dementia criteria (VaMCI). Vascular cognitive impairment without dementia was the most prevalent form of vascular cognitive impairment among those aged 65 to 84 years in the Canadian Study of Health and Aging.[27] Of 270 patients with TIA/ nondisabling stroke, 56% were found to be cognitively intact, 40% had cognitive impairment no dementia (CIND) and 4% had dementia.[28] Poststroke cognitive impairment of varying severity was observed in half of patients with stroke associated with small artery disease 3 months later.[29] As the condition is preventable to a large extent, it is important to identify patients at early stages of cognitive impairment, to treat appropriately, and prevent progression to frank dementia.[13]

Cerebrovascular Disease- Dementia Interface

Postmortem pathological studies indicate that up to 34% of dementia cases show significant vascular pathology. Mixed degenerative and vascular pathologies are increasingly being recognised and hospital-based series from developed countries report mixed dementia in one-third of patients.[30,31] Further, both small-vessel disease and AD pathology have been found to be linked to loss of neurons in the CA 1 area of the hippocampus.[32] An interaction between the two pathologies was demonstrated in the Nun study, where lacunar strokes were found to magnify the effects of any given load of AD pathology, and vice versa. The odds ratio for a clinically probable AD diagnosis was 4.7 in the presence of AD pathology alone, but it increased to 16.2 in the presence of a combination of AD pathology.[33] The two pathologies are also found to influence each

other's outcome. Incident stroke was a risk factor significantly associated with increased rate of cognitive impairment in AD.[34]

Vascular Risk Factors and the Brain

There is also strong evidence that cardiovascular risk factors such as hypertension, diabetes, metabolic syndrome, midlife obesity, and hyperlipidemia are independently associated with an increased risk of cognitive decline and dementia.[18,35] The Cardiovascular Health Cognition Study developed a late-life dementia risk index that included older age, worse cognitive test performance, lower body mass index (BMI), APOE 4 allele, MRI findings of white matter disease or ventricular enlargement, internal carotid artery thickening on ultrasound, history of bypass surgery, slower physical performance, and lack of alcohol consumption. Dementia risk within 6 years was 4% in those with low scores and 56% in those with high scores.[36] In the elderly, the Rotterdam scan study demonstrated that higher age, small vessel disease, and cardiovascular risk factors are associated with smaller brain volume, especially white matter volume.[37]

Recently, studies have also revealed the importance of silent strokes as risk factors for dementia in the elderly. Silent brain infarcts, i.e., infarcts in individuals without clinical manifestation of stroke are detected in 20% of healthy elderly people and up to 50% of patients in selected series.[38,39] They are associated with subtle deficits in physical and cognitive function that commonly go unnoticed. Moreover, the presence of silent infarcts more than doubles the risk of subsequent stroke and dementia.[40]

Indian Perspective

Vascular cognitive impairment is a problem of special concern for developing countries including India. Developing countries have a rapidly ageing population and it is projected that 71% of dementia cases will be in the developing world. VaD is the second most common cause of dementia accounting for 39% of cases,[41] and hence, absolute numbers of VaD, is high in India.[42]

Cardiovascular disease burden is high in developing countries including India and has been attributed to the increasing incidence of atherosclerotic diseases, perhaps due to urbanization, epidemiologic transition and higher risk factor levels, the relatively early age at which they manifest, the large sizes of the population, and the high proportion of individuals who are young adults or middle-aged in these countries.[43] Vascular risk factors has been demonstrated to be strongly associated with MCI in an epidemiologic study from Kolkata.[35] Higher prevalence of vascular risk factors in India is likely to increase burden of VaD and VaMCI.

Stroke, the overt manifestation of cerebrovascular disease is one of the most important risk factors for VaD. Stroke burden is increasing rapidly in developing countries. Studies have consistently shown that up to 64% of persons who have experienced a stroke have some degree of cognitive impairment[44] with up to a third developing frank dementia.[45] In a hospital-based study from Hyderabad, of 123 consecutive patients from the Stroke registry evaluated a minimum of 3 months after stroke, 91 (74%) were found to have cognitive impairment- 31% with VaD and 43% with VaMCI. A longitudinal follow-up of 50% of the group over a mean period of 13 months demonstrated that all patients with dementia at baseline continued to have dementia at follow-up and none of the cognitively normal patients worsened. Course of

VaMCI was variable-seven patients reverted to normal and one patient progressed to dementia.[46] Inadequate resources and low awareness coupled with growing numbers of patients with VaMCI make it a problem that needs urgent attention on a priority basis.

Neuropathology of Vascular Cognitive Impairment

A variety of vascular events may be responsible for VCI, but generally, its origin can be classified secondary to large vessel disease, small vessel disease, or a combination of the two. Large vessel disease, or stroke, is more likely to lead to significant cognitive impairment and dementia if it is progressive.[47] In contrast, cerebral small vessel disease may be the most common cause of vascular pathology leading to VaMCI.[48,49] Cerebral small vessel disease (CSVD) refers to a variety of pathological processes that affect small penetrating arteries, arterioles, capillaries, and even small veins in the brain, and is one of the most prevalent neurological conditions.[50]

Current brain imaging methods reveal resultant neuropathology in the form of white matter lesions (often termed leukoaraiosis or rarefaction of white matter), lacunar infarcts (small covert ischaemic lesions 0.2–15 mm^3 in size), and cerebral microbleeds (small covert haemorrhagic lesions). Despite possible differences in the origin of vascular abnormalities, the deterioration of these small vessels commonly leads to neuronal damage of subcortical brain structures and corresponding cognitive impairment.

A disruption to fronto-subcortical pathways is thought to be one of the main contributions to cognitive dysfunction in CSVD [51]. Damage to the fronto-subcortical network can occur in the form of white matter lesions or microbleeds affecting long association fibres, or those pathways that connect cortical and subcortical regions. The network may also be damaged by lacunes or microbleeds at subcortical nodes of these networks, which are also dependent on small vessels for blood supply. They include such

structures as the pons, thalamus and basal ganglia. A localized disturbance to this network may cause differing effects, depending on the size and site of the lesion. However, the general cognitive presentation of CSVD is thought to be more consistent.[58]

Diagnosis of Vascular Cognitive Impairment

The diagnosis of vascular cognitive impairment requires establishing the presence of cognitive impairment and its association with cerebrovascular disease. Identifying the presence and impact of cognitive impairment involves the following steps: reporting of subjective symptoms, objective confirmation by neuropsychological and behavioural assessment, determination of severity of cognitive decline, and its functional impact on ADL. A practical approach for diagnosing and classifying Vascular cognitive impairment has been provided in a statement of the American Heart Association/ American Stroke Association [54].

Cerebrovascular disease can be established by the clinical history of a stroke and the presence of focal neurological deficits corroborated by brain imaging. The mechanism underlying the stroke can be identified by the use of appropriate investigations, including ECG, 2D ECHO, extracranial and intracranial vascular imaging, and hematological investigations. The association between stroke and cognitive impairment is thought to be substantiated by a temporal relationship between the two and location of infarct in a region appropriate for cognitive impairment.

In an attempt to harmonise methodology to identify and describe individuals with VCI, particularly in the early stages, the National Institute for Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN) developed common standards in clinical diagnosis, epidemiology, brain imaging, neuropathology, experimental models, genetics, and clinical trials to recommend minimum, common,

clinical, and research standards for the description and study of vascular cognitive impairment.[59] Using the same standards was thought to help identify individuals in the early stages of cognitive impairment, make studies comparable, and integrate knowledge, thereby accelerating the pace of progress understanding, preventing and treating VCI.

A practical approach for diagnosing and classifying Vascular cognitive impairment[54] :

1. The term VCI characterizes all forms of cognitive deficits from VaD to MCI of vascular origin.
2. These criteria cannot be used for subjects who have an active diagnosis of drug or alcohol abuse/dependence. Subjects must be free of any type of substance for at least 3 months.
3. These criteria cannot be used for subjects with delirium.

Dementia

1. The diagnosis of dementia should be based on a decline in cognitive function from a prior baseline and a deficit in performance in _2 cognitive domains that are of sufficient severity to affect the subject's activities of daily living.
2. The diagnosis of dementia must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions.
3. The deficits in activities of daily living are independent of the motor/sensory sequelae of the vascular event.

Probable VaD

1. There is cognitive impairment and imaging evidence of cerebrovascular disease and
    a. There is a clear temporal relationship between a vascular event (eg, clinical stroke) and onset of cognitive deficits, or
    b. There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (eg, as in CADASIL).
2. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder.

Possible VaD

There is cognitive impairment and imaging evidence of cerebrovascular disease but

1. There is no clear relationship (temporal, severity, or cognitive pattern) between the vascular disease (eg, silent infarcts, subcortical small-vessel disease) and the cognitive impairment.
2. There is insufficient information for the diagnosis of VaD (eg, clinical symptoms suggest the presence of vascular disease, but no CT/MRI studies are available).
3. Severity of aphasia precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (eg, annual cognitive evaluations) before the clinical event that caused aphasia could be classified as having probable VaD.

4. There is evidence of other neurodegenerative diseases or conditions in addition to cerebrovascular disease that may affect cognition, such as
    a. A history of other neurodegenerative disorders (eg, Parkinson disease, progressive supranuclear palsy, dementia with Lewy bodies);
    b. The presence of Alzheimer disease biology is confirmed by biomarkers (eg, PET, CSF, amyloid ligands) or genetic studies (eg, PS1 mutation); or
    c. A history of active cancer or psychiatric or metabolic disorders that may affect cognitive function.

VaMCI

1. VaMCI includes the 4 subtypes proposed for the classification of MCI: amnestic, amnestic plus other domains, nonamnestic single domain, and nonamnestic multiple domain.
2. The classification of VaMCI must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions. The classification should be based on an assumption of decline in cognitive function from a prior baseline and impairment in at least 1 cognitive domain.
3. Instrumental activities of daily living could be normal or mildly impaired, independent of the presence of motor/sensory symptoms.

Probable VaMCI

1. There is cognitive impairment and imaging evidence of cerebrovascular disease and
    a. There is a clear temporal relationship between a vascular event (eg, clinical stroke) and onset of cognitive deficits, or

b. There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (eg, as in CADASIL).

2. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder.

Possible VaMCI

There is cognitive impairment and imaging evidence of cerebrovascular disease but

1. There is no clear relationship (temporal, severity, or cognitive pattern) between the vascular disease (eg, silent infarcts, subcortical small-vessel disease) and onset of cognitive deficits.
2. There is insufficient information for the diagnosis of VaMCI (eg, clinical symptoms suggest the presence of vascular disease, but no CT/MRI studies are available).
3. Severity of aphasia precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (eg, annual cognitive evaluations) before the clinical event that caused aphasia could be classified as having probable VaMCI.
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b. The presence of Alzheimer disease biology is confirmed by biomarkers (eg, PET, CSF, amyloid ligands) or genetic studies (eg, PS1 mutation); or
c. A history of active cancer or psychiatric or metabolic disorders that may affect cognitive function.

Unstable VaMCI

1. Subjects with the diagnosis of probable or possible VaMCI whose symptoms revert to normal should be classified as having "unstable VaMCI."
2. VCI indicates vascular cognitive impairment; VaD, vascular dementia; MCI, mild cognitive impairment; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CT/MRI, computed tomography/magnetic resonance imaging; PET, positron emission tomography; CSF, cerebrospinal fluid; and VaMCI, vascular mild cognitive impairment.

Definition of Vascular Mild Cognitive Impairment

The operational definition for vascular mild cognitive impairment to be applied in research studies have been laid down in the AHA/ASA. Vascular MCI includes the 4 subtypes proposed for the classification of MCI: amnestic, amnestic plus other domains, nonamnestic single domain, and nonamnestic multiple domain. The classification of VaMCI must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions. The classification should be based on an assumption of decline in cognitive function from a prior baseline and impairment in at least 1 cognitive domain. Instrumental activities of daily living could be normal or mildly impaired, independent of the presence of motor/sensory symptoms.[66]

Neuropsychological Assessments of VCI

The 2006 NINDS–Canadian Stroke Council VCI harmonization standards suggested different neuropsychological protocols for use in patients with suspected VCI[59]. The neuropsychological assessment of patients with suspected VCI requires a comprehensive cognitive battery.

The pattern of VCI cognitive deficits may include all cognitive domains, but there is likely to be a preponderance of so-called "executive" dysfunction, such as slowed information processing, impairments in the ability to shift from one task to another, and deficits in the ability to hold and manipulate information (ie, working memory). Neuropsychological protocols must therefore be both sensitive to a wide range of abilities and especially attuned to the assessment of executive function. Timed executive function tests may be especially sensitive to VCI-related impairment because of the slowed information processing noted in this patient sample. The protocol contains recommended tests in 4 domains: executive/ activation, language, visuospatial, and memory. In addition, tests were selected to examine neurobehavioral change and mood. High priority was given to executive control, activation state and processing speed, word retrieval and episodic memory, to help differentiate VCI from AD and to target the executive domain. Operational definitions of cognitive impairment is taken as 1.5 standard deviations below that of an appropriate comparison group are preferred over qualitative descriptions of cognitive symptoms.

The protocol[59] includes tests in the following domains :

a. Executive /Activation

The functional domains within the frontal lobes can be fractionated into a dorsal (executive-cognitive) and a ventral (emotional-self regulatory) trend. To assess these domains , category (semantic) and a letter (phonemic) fluency test [61,62,63] was proposed. Digit Symbol-Coding subtest from the Wechsler Adult Intelligence Scale [58] can be used ,in addition , as this task provides a direct measure of processing speed and activation.The Trail making Test was also chosen to provide an additional measure of information processing speed and set shifting. Additional scoring option of Verbal Learning Test (RAVLT) can provide measures of strategic learning reflecting dorsolateral frontal function.

b. Visuospatial

The working group selected the Rey-Osterreith Complex Figure copy condition as the primary visuospatial test. The memory condition of the test was selected as a supplemental measure. This well-known, untimed spatial task requires both organizational and visuo-perceptual skill. Multiple scoring systems are available, including a standard 36-point method of determining accuracy of the final product [59] and more qualitatively based systems that include a study of subject's organizational ability.

c. Language/Lexical Retrieval

The short Form (15 item) of the Boston Naming Test (BNT) animal fluency can serve as a less structured lexical retrieval task as well as that of a test of executive function. Verbal fluency tasks have been widely used for many decades with some

discriminative value in differentiating cognitive impairment and dementia from normal aging as well as VCI from AD.

d. Memory/Learning

The working group preferred a list-learning test or a paired association–learning test because list-learning tests can generate acquisition scores initially and with repeated administration, as well as a short and long-delayed recall. RAVLT was chosen as the list learning test in the protocol

e. Neuropsychiatric/Depressive Symptoms

The working group recommended a Neuropsychiatric inventory [60] to be included in the protocol. This can be completed by a caregiver without the need for an interviewer The Mini-Mental State Examination (MMSE[61]) is widely used in all dementia studies and would be a sensible supplement to the above protocol.

Neuroimaging in Vascular Mild cognitive Impairment

The main role of neuroimaging in the study of VCI so far has been to describe the brain, not diagnose it. Thus, neuroimaging plays a fundamentally different role in the study of VCI than it does in other conditions.This focus on description rather than diagnosis results from the facts that (1) vascular and degenerative pathology frequently coexist, and (2) there are no pathognomonic radiological features of VCI. Prospective studies of VCI must include measures of ischemic brain injury as well as AD-type pathology, a prevalent confounder of brain-behavior relationships in VCI.

MRI is the ideal imaging tool for cognitive disorders because it is the most sensitive modality, and it offers the greatest amount of reliable data[59]. The minimally

acceptable field strength is 1.0 T, but 1.5 T or greater is preferred. The following sequences are required: 3D T1-weighted, T2-weighted, fluid-attenuated inversion recovery, and gradient echo.The first 3 sequences provide information on the anatomy and presence of infarction and other pathology, whereas the latter detects large and small, acute and chronic haemorrhages. In addition, diffusion-weighted images, and quantification of the apparent diffusion coefficient is encouraged because it gives information about acute strokes and integrity of the white matter fibers [47].

White matter lesions (WMLs) have been associated with declining scores in the modified MMSE and the Digit Symbol Substitution Test as well as with incident MCI, dementia,and death [60]. White matter hyperintensities are graded according to Fazeka's scale[61] as follows:

Fazekas et al (Total Score Minimum, 0; Maximum, 6)

Periventricular and deep WMCs are rated separately. A total score is obtainable by summing the 2 partial scores.

Periventricular Hyperintensities

Scores are as follows: 0-absence, 1-"caps" or pencil-thin lining,2-smooth "halo," and 3-irregular periventricular hyperintensities extending into the deep white matter.

Deep White Matter Hyperintense Signals

Scores are as follows: 0-absence, 1-punctuate foci, 2-beginning confluence of foci, and 3-large confluent areas.

Cerebral microbleeds are a useful biomarker for pathologic damage to small vessels. CMBs, characterized by foci of signal loss on T2*-weighted gradient-echo MRI, have

been histopathologically confirmed as hemorrhagic microvascular lesions or microangiopathy in the brain. Their role in contribution to cognitive impairment remains uncertain , though few studies have shown a correlation of the presence of microbleeds with cognitive decline [62].

Aims and Objectives

1. To study the detailed cognitive profile in patients with mild cognitive impairment due to vascular etiology (VaMCI)
2. To compare the pattern of cognitive impairment in patients with Vascular mild cognitive impairment with those of a pre-existing cohort of mild cognitive impairment due to non vascular etiology
3. To study the MRI characteristics in patients with mild cognitive impairment due to vascular etiology (VaMCI) in correlation with neuropsychological profiles.
4. To compare the MRI characteristics of patients with VaMCI and with those of patients with mild cognitive impairment due to non vascular etiology

Materials and Methods

Study design:

The study is a hospital based prospective case-control study to assess the profile of mild cognitive impairment in patients who complain of subjective cognitive symptoms after a minor stroke or transient ischemic attack (TIA) , i.e; vascular mild cognitive impairment (VaMCI) and to compare them with the pattern of cognitive dysfunction in patients with mild cognitive impairment (MCI) due to non vascular etiology who are taken from a previos study cohort. Also these patients are compared against a cognitively normal healthy control group. The MRI characteristics of the patients in the VaMCI and MCI are also compared.

Study period:

The study was conducted over a period of 24 months from January 2013 to December 2014.

Methodology:

The patients with VaMCI were identified from out-patients attending the Neurology/Stroke OPD or inpatients admitted in the Neurology / Stroke ward of Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Thiruvananthapuram. This cohort was identified from about 150 patients with subjective memory complaints (SMC) after a minor stroke / TIA who were screened with Addenbrooke's Cognitive Examination –Malayalam (M-ACE). SMC were addressed using the Malayalam version of Instrumental Activities of Daily Living (ADL) scale (Appendix attached). The patients with a transient ischemic attack or minor stroke with a

National Institute of Health Stroke Scale (NIHSS) of ≤ 5 were taken for the ease of follow up and neuropsychological evaluation at review for cognitive dysfunction. Patients with major strokes and strategic infarcts involving the language domain were excluded as the deficits could potentially interfere with neuropsychology testing. Patients underwent neuropsychology evaluation at 3 month follow up after the index stroke.

Inclusion criteria is as under:

a) History of transient ischemic attack or minor stroke with NIHSS of ≤5

b) Subjective cognitive impairment with CDR<1

c) Objective evidence of cognitive impairment on neuropsychological testing defined based on test score <1.5SD from the mean value for a particular test (Addenbrooke's cognitive examination-malayalam) derived from normative control data [59,63]

d) Absence of clinically significant anxiety/ depression

e) No prior history of subjective memory complaints (SMC) before the stroke.

Exclusion criteria: were

a) CDR of ≥ 1
b) Major stroke / prominent neuropsychiatric symptoms / gait disorder
c) Patient with recurrent TIA or minor stroke

Thirty-six patients with MCI of non vascular etiology from a pre-existing study cohort were taken for comparison of the pattern of cognitive impairment. They were recruited from the memory clinic of Sree Chitra Tirunal Institute for Medical Science

and Technology and diagnosed based on Petersen's criteria[3] (which is similar to the NINDS criteria for VaMCI except that the latter includes the history of an antecedent stroke). The cognitively normal healthy controls (CNHC) were selected from the hospital staff, friends and relatives of hospital staff and visitors of the patients in the hospital who agreed to participate.

Inclusion criteria (for patients with MCI):

1. Age >55 years
2. Diagnosis of MCI, as per standard diagnostic criteria (Petersen et al, 2001)
3. Ability to read, understand and write Malayalam well.
4. Ability to provide written informed consent.

Inclusion criteria (for Controls)

1. No known neurological or psychiatric disorders
2. Normal neurologic examination (except for assessment of higher functions)
3. Age, gender and level of education matched with patients.
4. Ability to read, understand and write Malayalam well.
5. Ability to provide written informed consent.

Exclusion criteria (for MCI patients and Controls)

1. Clinically significant anxiety/depression (based on HADS)
2. Patients on psychiatry medications

3. Any significant neurological, psychiatric or medical co-morbidity interfering with cognitive testing or affecting cognitive functions in the judgement of the investigators.

Voluntary informed consent was obtained from each subject prior to enrollment in the study. Each subject ,was given both verbal and written information describing the nature of the study, need for participating in the study and potential benefits and risks of the study. The informed consent process took place under conditions where the subject had sufficient time to consider the risks and benefits associated with participation in the study. He/she was also informed that the participation in the study was voluntary and that he/she may refuse to participate or withdraw from the trial, at any time, without affecting their care.

Assessment of cases:

All the subjects selected were interviewed based on a structured proforma. The details included the following:

History

The demographic profile of the person ; name, age, sex, occupation, educational status. Details of the stroke / TIA , risk factors , duration of risk factors , TOAST classification for stroke aetiology, infarct location were collected.

Physical examination

A detailed neurological examination of the cases was done at 3months after the index event to identify the stroke severity and NIHSS.

Assessment of Controls

The controls also underwent neurological examination to ensure that they have no neurological disorders.

Investigations

Neuropsychological assessment

A detailed neuropsychology evaluation was done in all the patients with subjective cognitive symptoms temporally related to the TIA/minor stroke and those patients diagnosed to have mild cognitive impairment based on the cut-off scores on neuropsychology evaluation as diagnosed by score <1.5 times the standard deviation and healthy controls. The neuropsychologic evaluation was done by the a qualified Neuropsychologist of the Institute.

All the subjects (patients and controls) underwent standard neuropsychological assessment with an MCI battery which includes the following components:

a) Addenbrooke's Cognitive Examination

b) Weschler Memory Scale (WMS)- verbal and visual

c) Rey Auditory Verbal Learning Test (RAVLT)

d) Attention span (forward and backward digit)

e) Trail making test A & B

f) Wisconsin card sorting test (WCST)

g) Delayed Matching to Sample 48 (DMS48)

h) Hospital Anxiety and Depression Scale (HADS)

i) Scale for the Instrumental Activities of Daily Living (IADL)

ACE was used as a general screening tool ,Weschler Memory Scale (WMS)-verbal and visual as a tool to assess working and short term memory in the verbal and visual domains, RAVLT for testing new learning and retrieval, Trail making test A for sustained attention , Trail making test B for attention , executive function and set shifting , Wisconsin card sorting test for executive functions and DMS 48 was used for visual recognition memory. Visuo-spatial abilities and perception were studied from the sub-components of ACE in addition to WMS-visual subsets.

ACE (Addenbrooke's Cognitive Examination)

ACE is a brief bedside cognitive screening instrument and used as a scrrening tool . It is easy to use and has excellent sensitivity and diagnostic accuracy. ACE encompasses test of attention, orientation, memory, language, visuo-spatial skills and executive function with a total score of 100. The design of the ACE allows sensitivity to the early stages of AD and FTD. The excellent performance of ACE has prompted its translation into a number of languages. These translation has facilitated the examination of ACE performance in a large number of independent patient cohorts. Malayalam versions of ACE has been validated previously for population-based screening for dementia in the community and amnestic MCI along with other neuropsychological tests [63,64] 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), remote memory, and language.

Registration/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

Wechsler Memory Scale (WMS)

The Wechsler Memory Scale is a neuropsychological test that can be used with people from age 16 to 90. 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 minutes, 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.

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 minutes.

Rey Auditory Verbal Learning Test (RAVLT)

The Rey Auditory Verbal Learning Test (RAVLT) is an efficient neuropsychological instrument for evaluating episodic declarative memory. It provides scores for assessing immediate memory, new verbal learning, susceptibility to interference (proactive and retroactive), retention of information after a period of time,

and memory recognition. The test is designed as a list-learning paradigm in which the patient hears a list of 15 nouns and is asked to recall as many words from the list as possible. After five repetitions of free-recall, a second “interference” list (List B) is presented in the same manner, and the participant is asked to recall as many words from List B as possible. After the interference trial, the participant is immediately asked to recall the words from List A, which she or he heard five times previously. After a 20 min delay, the participant is asked to again recall the words from List A. After this “delayed recall” task, a list of 50 words is presented containing all of the words.

Digit-span task

Digit-span task is used to assess both attention and short-term memory (forward digit span) and working memory (backward digit span). Participants are presented with a series of digits (e.g., '8, 2, 4') and must immediately repeat them back. If they do this successfully, they are given a longer list (e.g., '9, 2, 4, 1'). The length of the longest list a person can remember is that person's digit span. While the participant is asked to enter the digits in the given order in the forward digit-span task, in the backward digit-span task the participant needs to reverse the order of the numbers.

Trail Making Test (TMT)

The Trail Making Test (TMT) is among the most commonly used neuropsychological tests in clinical practice because it is among the instruments most sensitive to brain damage .The test assesses executive functioning, psychomotor speed and visual scanning. The task requires a subject to 'connect-the-dots' of 20 consecutive targets on a sheet of paper There are two parts to the test: A, in which the targets are all numbers (1,2,3, etc.) and the test taker needs to connect them in sequential order, and B, in which the subject alternates between numbers and letters (1, A, 2, B, etc.).

Wisconsin card sorting test (WCST)

WCST is considered a measure of executive function because of its reported sensitivity to frontal lobe dysfunction, Used primarily to assess perseveration and abstract thinking, As such, the WCST allows to assess strategic planning; organized searching; and ability to utilize environmental feedback to shift cognitive sets, direct behavior toward achieving a goal, and modulate impulsive responding . Test structure includes, Four stimulus cards incorporate three stimulus parameters (color, form, and number). Respondents are required to sort numbered response cards according to different principles and to alter their approach during test administration. To complete the task, clients should have normal or corrected vision and hearing sufficient to adequately comprehend the instructions and to visually discriminate the stimulus parameters.

Delayed Matching to Sample 48 (DMS48)

The DMS48 is a test of visual recognition memory test . DMS assesses forced choice recognition memory for non verbalisable patterns, testing both simultaneous matching and short term visual memory. With Delayed Matching to Sample (DMS), memory and forced decision-making were tested. DMS is reported to be a test for both immediate matching to sample, delayed matching to sample and forced choice recognition memory. This test may be sensitive to damages mainly in the medial temporal lobe with some input from the frontal lobe. Patients were asked to remember 48 non-figurative objects, recall them and distinguish them from other similar patterns after a delay of 0, 4 or 12 seconds. The DMS-48 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.

MRI:

As part of the routine stroke evaluation on admission or first OPD visit, patients of VaMCI underwent CT scan of the brain with CT angiogram followed by limited sequences of magnetic resonance imaging (MRI) of the Brain which includes FLAIR axial, coronal/SWI/Diffusion-ADC Maps as part of the standard evaluation.

Presence of white-matter hyperintensities was graded according to Fazekas grading [61] including the periventricular and deep locations and the presence of global cerebral atrophy was graded as mild , moderate and severe based on qualitative subjective analysis by an experienced Radiologist familiar with the rating scales. The presence of Cerebral Micro bleeds (CMB) was noted and the number and location was noted. These MRI characteristics were correlated with neuropsychology test domains and comparisons was done with identical sequences of patients with MCI due to non vascular etiology.

The periventricular and deep white matter hyperintensities were graded according to the Fazekas grading as given below :

Total Score Minimum, 0; Maximum, 6

Periventricular and deep WMCs are rated separately. A total score is obtainable by summing the 2 partial scores.

Periventricular Hyperintensities

Scores are as follows: 0-absence, 1-“caps” or pencil-thin lining,2-smooth “halo,” and 3-irregular periventricular hyperintensities extending into the deep white matter.

Deep White Matter Hyperintense Signals

Scores are as follows: 0-absence, 1-punctuate foci, 2-beginning confluence of foci, and 3-large confluent areas.

Global cerebral atrophy was graded qualitatively as mild, moderate and severe which has been found to have good reliability when used by a single rater. [65]

Ethical considerations:

The study was approved by the Institute Ethical Committee. Written informed consent was obtained from all the subjects participating in the study. The informed consent procedure was done according to the guidelines provided in the Declaration of Helsinki and the ICH E6 Guideline for Good Clinical Practice.

Statistical analysis

The baseline variables like age , sex and education of the three groups, namely VaMCI , MCI and controls were compared by ANOVA. The tests of normality were done using the Shapiro – Wilk test to identify normal and non normal distributions. Non parametric tests were used wherever group specific normality tests did not show a normal distribution. The significant difference in means between VaMCI , MCI and controls were calculated by ANOVA for normal distributions and using Kruskall Wallis test and Median tests for the non normal distributions. Linear regression analysis was done after adjusting for age and sex. Those parameters which were found significant on bivariate analysis were further analysed by logistic regression after adjusting for age and sex. Chi square test was used to compare the difference in the cognitive functions between patients with VaMCI and MCI and MCI and controls for categorical variables. Means of numeric variables were compared between groups by Students t-test. Proportions were compared by Chi-square test or Fisher's Exact test.

The cut off for these variables was mean -1.5 SD from the control values. Data analysis was done using the statistical software, SPSS v16 under the guidance of a statistician. p values of ≤ 0.05 were taken as statistically significant.

Results

256 patients with minor stoke (NIHSS≤5) or TIA were interviewed for subjective cognitive symptoms at three months after index event. Of these sixty five patients (25.3%) had subjective cognitive symptoms following the stroke as per the memory components of IADL scale and underwent neuropsychological evaluation with the standard neuropsychological test battery mentioned above. Of these fifty patients satisfying the inclusion criteria for the study formed the VaMCI study cohort. The clinical and demographic characteristics of the VaMCI cohort has been shown in table 1. Median interval between stroke and neuropsychological testing was twelve weeks.

Table 1. Clinical and demographic characteristics of the VaMCI cohort

Variable	**n= 50**
Age (in years) (SD)	64.98(9.29)
Male: Female	4.5:1
Education	10.4 (3.4)
Diabetes	55.6%
Hypertension	88.9%
Dyslipidemia	48.1%
Smoking	36.8%
TOAST Classification Large vessel atherosclerosis Cardioembolic Lacunar Others	 25.9% 7.4% 37.2% 29.6%

Comparison of Baseline characteristics between VaMCI , MCI and controls

The cognitive profile of in the VaMCI group was compared against that of a group of thirty six patients with mild cognitive impairment of non vascular etiology (MCI). There were twenty seven patients in the control group.

The mean age of the VaMCI cohort was comparable with the controls. However the patients in the VaMCI cohort were younger as compared to those in the MCI cohort though this difference was not significant. The persons in the MCI cohort were significantly older as compared to the controls. (tables 2). The same has been depicted in figure 1.

Table 2. Comparison of age among the three cognitive groups

	N	Mean	Std. Deviation	ANOVA p
Control	27	63.96	7.330	**0.020***
MCI	36	69.06	5.855	
VaMCI	50	64.98	9.290	
Total	113	66.04	8.088	

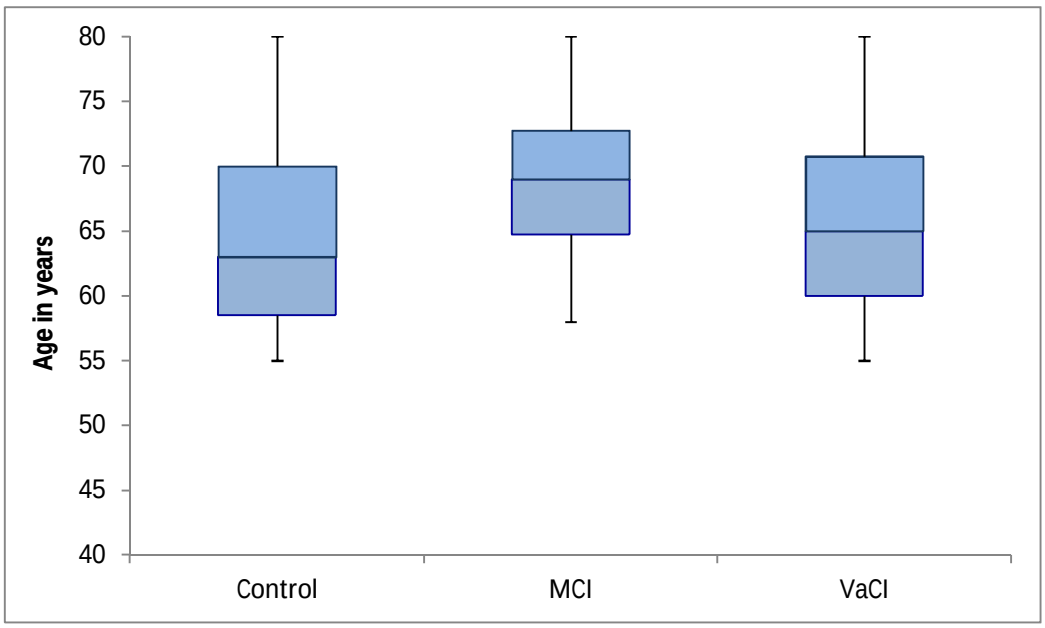
* - p value significant at <0.05

Post-hoc - Bonferonni

	Control	MCI	VaMCI
Control	-	**0.038***	1
MCI	**0.038***	-	0.059

* - p value significant at <0.05

Figure 1 . Box plot showing the comparison of age among the three cognitive groups



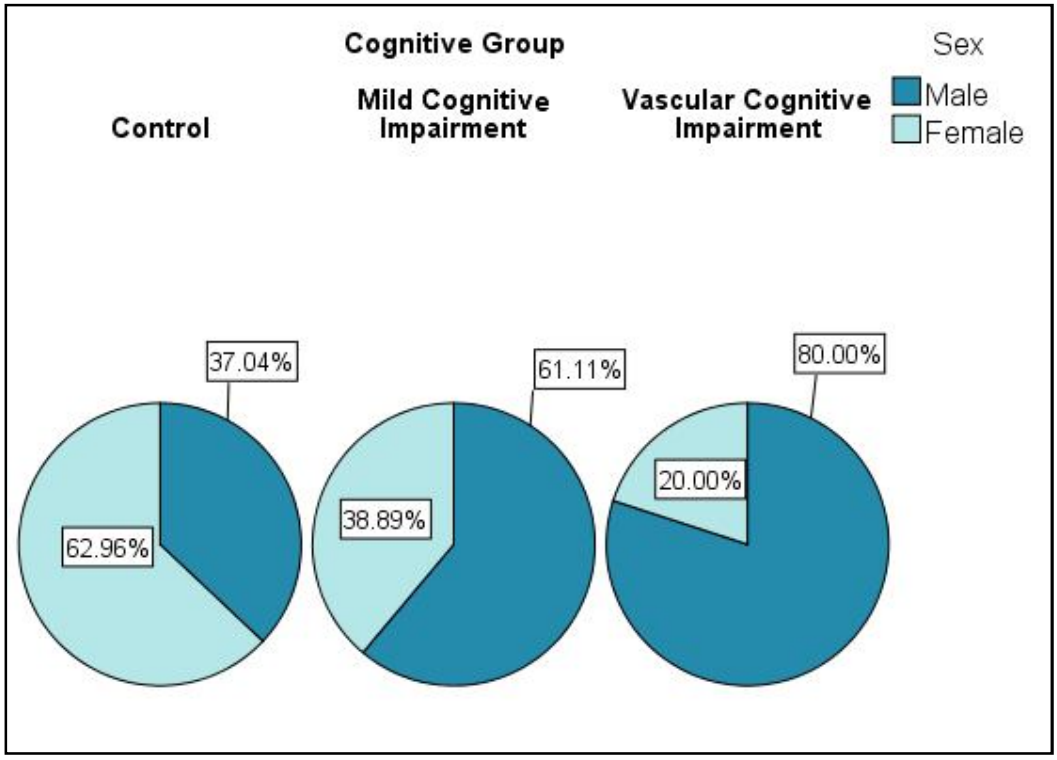
The males were significantly higher in the VaMCI and MCI cohort as compared to the control group as shown in table 3 and figure 2.

Table 3. Gender-wise distribution in the three cognitive groups.

		Cognitive groups			Total
		Control	MCI	VaMCI	
Sex	Male	10	22	40	72
		37.0%	61.1%	80.0%	63.7%
	Female	17	14	10	41
		63.0%	38.9%	20.0%	36.3%
Total		27	36	50	113
		100.0%	100.0%	100.0%	100.0%

Chi square p value = **0.001***

Figure 2. Gender-wise distribution in the three cognitive groups

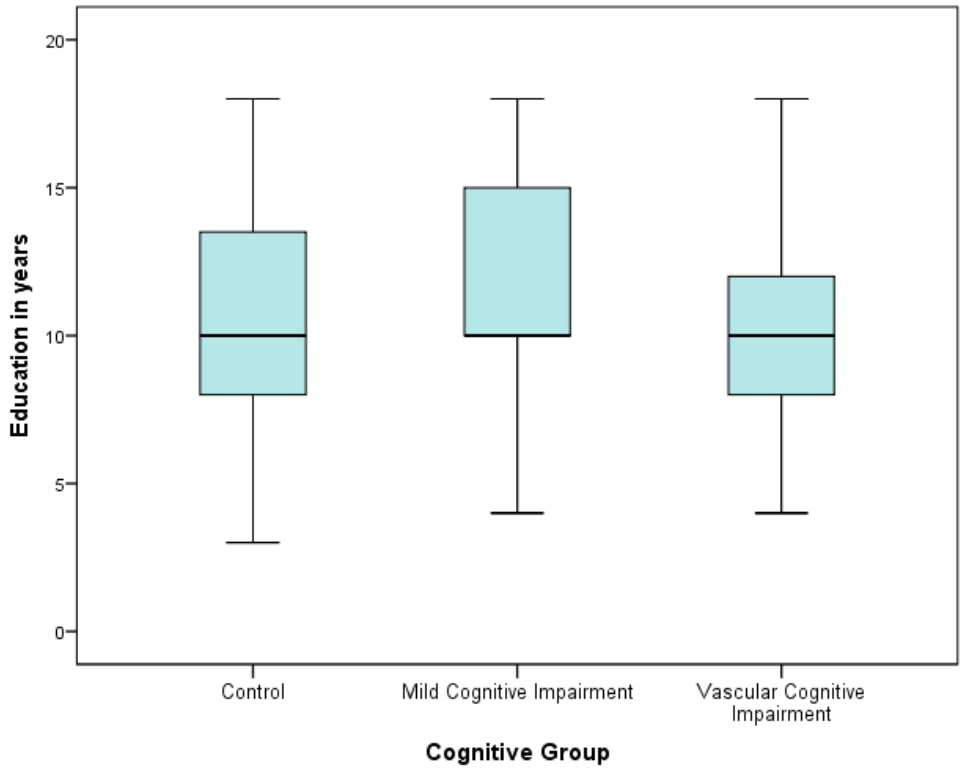


There was no significant difference in the mean educational status of the persons in the three groups (table 4 , fig 3)

Table 4. Comparison of educational status among the three cognitive groups

	N	Mean	Std. Deviation	ANOVA p
Control	27	10.48	3.807	0.436
MCI	36	11.33	3.521	
VaMCI	50	10.38	3.380	
Total	113	10.71	3.525	

Figure 3. Box Plot depicting the comparison of educational status among the three cognitive groups



Comparison of Neuropsychological Battery tests components between persons with VaMCI, MCI and controls

The neuropsychological battery test components were compared between persons in the VaMCI , MCI and control groups. Non parametric tests were used wherever group specific normality tests did not show a normal distribution . The groups were not comparable for age and sex and hence adjustments for the same was done. Multivariate analysis was done when a significant difference in bivariate analysis was found.

Table 5. Comparison of Neuropsychological Battery tests components between the three groups

		N	Mean	Std. Deviation	Minimum	Maximum	ANOVA p value	Kruskall Wallis test p	Median test p value	Linear regression † p value
MMSE	Control	27	28.33	1.330	25	30	0.228	0.339	0.591	
	MCI	36	27.86	1.570	23	30				
	VaMCI	50	27.64	1.903	22	30				
	Total	113	27.88	1.686	22	30				
ACE	Control	27	85.41	8.924	70	99	**0.048***	0.100	0.102	**0.004***
	MCI	36	81.64	7.208	64	96				
	VaMCI	50	79.66	11.331	49	98				
	Total	113	81.66	9.801	49	99				
PHONEMIC FLUENCY	Control	27	10.26	3.230	2	18	**0.012***	**0.009***	**0.006***	0.070
	MCI	36	7.94	3.553	3	16				
	VaMCI	50	8.14	3.130	2	16				
	Total	113	8.58	3.398	2	18				
ANIMAL FLUENCY	Control	27	12.30	2.216	8	17	**0.000***	**0.001***	**0.007***	**0.027***
	MCI	36	9.14	3.595	2	15				
	VaMCI	50	10.92	3.016	5	17				
	Total	113	10.68	3.252	2	17				
WMSLM (Immediate recall story 1)	Control	27	9.22	3.250	2	16	0.150	0.198	0.841	
	MCI	36	7.28	5.006	0	17				
	VaMCI	50	9.02	4.872	0	19				
	Total	113	8.51	4.625	0	19				
WMSD1 (Delayed recall story 1)	Control	27	5.26	3.426	0	12	0.095	0.118	**0.032***	0.165
	MCI	36	3.94	3.779	0	14				
	VaMCI	50	5.92	4.685	0	16				
	Total	113	5.13	4.187	0	16				
WMSLMII (Immediate recall story 2)	Control	27	7.19	3.363	1	16	0.243	0.270	0.273	
	MCI	36	5.78	2.850	1	12				
	VaMCI	50	6.66	3.723	0	13				
	Total	113	6.50	3.394	0	16				
WMSD2 (Delayed recall story 2)	Control	27	4.48	3.251	0	11	0.180	0.219	**0.029***	0.679
	MCI	36	3.14	2.486	0	9				
	VaMCI	50	4.26	3.635	0	11				
	Total	113	3.96	3.239	0	11				

Table 5. Continued…

		N	Mean	Std. Deviation	Minimum	Maximum	ANOVA p value	Kruskall Wallis test p	Median test p value	Linear regression † p value
WMS total IM	Control	27	16.41	5.766	6	28	0.135	0.151	0.186	
	MCI	36	13.00	7.337	1	28				
	VaMCI	50	15.74	8.233	0	32				
	Total	113	15.03	7.497	0	32				
WMS total Delay	Control	27	9.74	5.894	0	18	0.122	0.145	**0.019***	0.336
	MCI	36	7.08	5.623	0	20				
	VaMCI	50	10.06	8.080	0	26				
	Total	113	9.04	6.951	0	26				
WMS VISUAL (immediate recall)	Control	27	22.15	6.954	8	36	**0.020***	**0.031***	**0.044***	**0.000***
	MCI	36	19.78	7.914	7	34				
	VaMCI	49	17.14	7.430	4	31				
	Total	112	19.20	7.684	4	36				
WMS DIGIT FORWARD	Control	27	5.70	1.295	3	9	**0.043***	0.082	0.216	0.196
	MCI	36	6.19	1.600	3	10				
	VaMCI	50	5.34	1.611	2	10				
	Total	113	5.70	1.569	2	10				
WMS DIGIT BACK	Control	27	4.59	1.738	1	7	0.316	0.346	0.350	
	MCI	36	4.78	1.675	2	10				
	VaMCI	50	4.24	1.598	0	9				
	Total	113	4.50	1.659	0	10				
WMS VISUAL DELAYED	Control	27	15.26	8.891	2	35	**0.010***	**0.012***	0.102	**0.004***
	MCI	36	9.81	8.369	0	31				
	VaMCI	50	9.64	7.542	0	29				
	Total	113	11.04	8.413	0	35				

† Adjusted for age, sex (dummy variable: male=0, female=1)

* - p value significant at <0.05

Table 5. Continued…

		N	Mean	Std. Deviation	Minimum	Maximum	ANOVA p value	Kruskall Wallis test p	Median test p value	Linear regression† p value
RAVLT TOTAL Immediate recall score of 5 trials	Control	27	43.22	11.298	20	62	**.000***	**0.000***	**0.000***	**.000***
	MCI	35	37.97	10.548	14	56				
	VaMCI	49	31.27	8.038	12	53				
	Total	111	36.29	10.803	12	62				
20 min recall score	Control	27	8.70	4.778	0	19	**.000***	**0.000***	**0.006***	**.000***
	MCI	35	6.49	3.633	0	15				
	VaMCI	50	4.06	3.266	0	11				
	Total	112	5.94	4.201	0	19				
RAVLT RECOGNITION score	Control	27	13.30	1.958	8	15	**.001***	**0.001***	**0.003***	.174
	MCI	35	10.14	3.889	0	15				
	VaMCI	50	11.30	3.228	1	15				
	Total	112	11.42	3.392	0	15				
Omission error	Control	27	1.70	1.958	0	7	**.003***	**0.001***	**0.001***	.087
	MCI	32	4.22	3.250	0	12				
	VaMCI	50	3.84	3.190	0	14				
	Total	109	3.42	3.095	0	14				
Commission error	Control	27	4.22	4.200	0	14	**.000***	**0.000***	**0.000***	**.001***
	MCI	32	5.91	4.546	0	17				
	VaMCI	50	1.88	1.934	0	7				
	Total	109	3.64	3.862	0	17				
TRAILA time in minutes	Control	26	2.4654	1.82529	.10	9.70	.215	0.367	0.678	
	MCI	36	2.1650	1.09926	.50	5.32				
	VaMCI	48	4.4081	9.32105	1.00	50.00				
	Total	110	3.2148	6.30397	.10	50.00				
No. of ERRORs in Trail	Control	26	.92	3.969	0	20	.128	.424	.443	
	MCI	36	.03	.167	0	1				
	VaMCI	48	.04	.289	0	2				
	Total	110	.25	1.950	0	20				
TRAILB	Control	24	3.9987	2.04720	1.29	8.00	**.009***	**.013***	**.059**	**.008***
	MCI	36	5.4711	2.54920	2.17	13.36				
	VaMCI	47	6.0106	2.78876	2.21	18.21				
	Total	107	5.3778	2.65353	1.29	18.21				
ERRORB	Control	24	3.75	7.182	0	25	.073	.278	.434	
	MCI	36	1.86	4.752	0	20				
	VaMCI	47	6.28	11.278	0	32				
	Total	107	4.22	8.813	0	32				
WCST Categories passed	Control	25	4.84	1.908	1	6	**.042***	**0.031***	Not done	**.016***
	MCI	34	4.24	2.016	2	6				
	VaMCI	50	3.58	2.167	0	6				
	Total	109	4.07	2.107	0	6				
WCST ERRORS	Control	25	6.44	5.665	0	27	.081	**0.012***	0.072	.057
	MCI	34	6.38	4.979	1	24				
	VaMCI	50	8.62	4.814	0	23				
	Total	109	7.42	5.143	0	27				
WCST Perseveration score	Control	25	.92	.954	0	3	**.009***	**.006***	**.185**	**.033***
	MCI	33	1.36	1.084	0	4				
	VaMCI	50	.68	.891	0	3				
	Total	108	.94	1.003	0	4				

† Adjusted for age, sex

* - p value significant at <0.05

Table 5. Continued…

		N	Mean	Std. Deviation	Minimum	Maximum	ANOVA p value	Kruskall Wallis test p	Median test p value	Linear regression† p value
DMS Immediate total	Control	27	40.33	4.891	22	47	.082	.071	.095	.150
	MCI	36	36.44	9.849	11	48				
	VaMCI	48	36.75	6.459	22	48				
	Total	111	37.52	7.545	11	48				
DOUBLE Immediate	Control	27	13.15	1.703	9	16	.614	.569	.484	
	MCI	36	12.61	3.210	4	16				
	VaMCI	48	12.60	2.181	8	16				
	Total	111	12.74	2.460	4	16				
UNIQUE Immediate	Control	27	14.26	2.177	6	16	.461	.059	.092	.794
	MCI	36	13.17	6.144	1	41				
	VaMCI	48	13.15	2.441	7	19				
	Total	111	13.42	3.988	1	41				
ABSTRACT Immediate	Control	27	12.89	1.739	7	16	**.024***	**.017***	**.000***	**.006***
	MCI	36	11.44	3.443	4	16				
	VaMCI	48	11.00	2.866	4	16				
	Total	111	11.60	2.927	4	16				
DMS DELAY TOTAL	Control	27	41.44	3.945	31	47	**.005***	**.001***	**.040***	**.004***
	MCI	36	37.44	9.981	9	48				
	VaMCI	48	35.35	6.930	13	48				
	Total	111	37.51	7.857	9	48				
DOUBLE DELAYED	Control	27	13.19	1.882	10	16	.246	.267	.266	
	MCI	36	12.25	3.375	3	16				
	VaMCI	48	12.10	2.660	3	16				
	Total	111	12.41	2.772	3	16				
UNIQUE DELAYED	Control	27	14.74	1.403	11	16	**.007***	**.001***	**.005***	**.004***
	MCI	36	12.89	3.793	3	16				
	VaMCI	48	12.77	2.224	7	16				
	Total	111	13.29	2.801	3	16				
ABSTRACT DELAYED	Control	27	13.52	1.847	9	16	**.000***	**.000***	**.000***	**.000***
	MCI	36	12.06	3.633	1	16				
	VaMCI	48	10.38	3.153	2	16				
	Total	111	11.68	3.297	1	16				

† Adjusted for age, sex

* - p value significant at <0.05

Table 6. Comparison of Neuropsychological Battery tests components between the three groups by logistic regression

	Median of whole sample		N	>Median	%	Logistic regression† p value	Adjusted Odds Ratio	95% CI of Odds Ratio		Logistic regression† p value	Adjusted Odds Ratio	95% CI of Odds Ratio	
								Lower	Upper			Lower	Upper
ACE		Control	27	17	63	REFERENCE	REFERENCE			.062	2.704	.951	7.689
		MCI	36	14	38.9	.105	.408	.138	1.207	.835	1.103	.440	2.760
		VaMCI	50	20	40	.062	.370	.130	1.052	REFERENCE	REFERENCE		
PHONEMIC FLUENCY	7	Control	27	18	66.7	REFERENCE	REFERENCE			**.005***	**4.711**	1.602	13.859
		MCI	36	13	36.1	**.037***	**.309**	.103	.932	.439	1.457	.561	3.779
		VaMCI	50	15	30	**.005***	**.212**	.072	.624	REFERENCE	REFERENCE		
ANIMALS FLUENCY	10	Control	27	17	63	REFERENCE	REFERENCE			.062	2.781	.951	8.134
		MCI	36	9	25	**.030***	**.281**	.090	.882	.635	.782	.282	2.163
		VaMCI	50	17	34	.062	.360	.123	1.052	REFERENCE	REFERENCE		
WMSD1 (Delayed recall story 1)	5	Control	27	11	40.7	REFERENCE	REFERENCE			.104	.419	.147	1.194
		MCI	36	10	27.8	.498	.679	.222	2.078	**.011***	**.285**	**.108**	**.748**
		VaMCI	50	28	56.0	.104	2.385	.837	6.796	REFERENCE	REFERENCE		
WMSD2 (Delayed recall story 2)	4	Control	27	14	51.9	REFERENCE	REFERENCE			.990	.993	.333	2.965
		MCI	36	8	22.2	.181	.444	.135	1.459	.122	.441	.156	1.244
		VaMCI	50	23	46.0	.990	1.007	.337	3.006	REFERENCE	REFERENCE		
WMS total Delay	8	Control	27	17	63.0	REFERENCE	REFERENCE			.872	1.090	.383	3.107
		MCI	36	11	30.6	.063	.349	.115	1.058	**.045***	**.381**	**.148**	**.978**
		VaMCI	50	28	56.0	.872	.917	.322	2.614	REFERENCE	REFERENCE		
WMS VISUAL (immediate recall)	19	Control	27	18	66.7	REFERENCE	REFERENCE			**.003***	**6.136**	**1.836**	**20.506**
		MCI	36	17	47.2	.199	.463	.143	1.498	**.042***	**2.843**	**1.037**	**7.798**
		VaMCI	49	18	36.7	**.003***	**.163**	**.049**	**.545**	REFERENCE	REFERENCE		
WMSDIGITFORWARD	6	Control	27	6	22.2%	REFERENCE	REFERENCE			.591	2.399	.099	58.350
		MCI	36	13	36.1	.246	4.420	.358	54.532	.113	10.603	.574	196.006
		VaMCI	50	10	20.0	.591	.417	.017	10.137	REFERENCE	REFERENCE		
WMSVISUALDELAYED	11	Control	27	17	63.0	REFERENCE	REFERENCE			.208	2.031	.674	6.121
		MCI	36	14	38.9	.323	.566	.183	1.752	.766	1.149	.459	2.879
		VaMCI	50	20	40.0	.208	.492	.163	1.484	REFERENCE	REFERENCE		

† Adjusted for age, sex

* - p value significant at <0.05

Table 6 Continued…

	Median of whole sample		N	>Median	%	Logistic regression† p value	Adjusted Odds Ratio	95% CI of Odds Ratio		Logistic regression† p value	Adjusted Odds Ratio	95% CI of Odds Ratio	
								Lower	Upper			Lower	Upper
RAVLT TOTAL Immediate recall score of 5 trials	36.00	Control	27	18	66.7	REFERENCE	REFERENCE			**.023***	**3.685**	1.199	11.320
		MCI	35	22	62.9	.443	1.588	.487	5.182	**.001***	**5.852**	2.067	16.568
		VaMCI	50	13	26.5	.023	.271	.088	.834	REFERENCE	REFERENCE		
20 min recall score	5.50	Control	27	19	70.4	REFERENCE	REFERENCE			**.041***	**3.157**	1.047	9.519
		MCI	36	20	57.1	.943	.958	.300	3.064	**.026***	**3.026**	1.141	8.026
		VaMCI	50	17	34.0	.041	.317	.105	.955	REFERENCE	REFERENCE		
RAVLT RECOGNITION score	12.00	Control	27	19	70.4	REFERENCE	REFERENCE			**.022***	**3.499**	1.200	10.205
		MCI	36	11	31.4	**.014***	.242	.078	.754	.737	.846	.319	2.246
		VaMCI	50	17	34	**.022***	.286	.098	.833	REFERENCE	REFERENCE		
Omission error	3.00	Control	27	3	11.1	REFERENCE	REFERENCE			**.006***	**.148**	.038	.580
		MCI	36	15	46.9	**.022***	5.353	1.269	22.585	.635	.794	.307	2.056
		VaMCI	50	27	54.0	**.006***	6.741	1.723	26.369	REFERENCE	REFERENCE		
Commission error	3.00	Control	27	13	48.1	REFERENCE	REFERENCE			**.004***	**5.641**	1.755	18.131
		MCI	36	21	65.6	.618	1.345	.420	4.309	**.000***	**7.585**	2.598	22.145
		VaMCI	50	11	22.0	.004	.177	.055	.570	REFERENCE	REFERENCE		
TRAILB	5.059	Control	27	8	33.3	REFERENCE	REFERENCE			.056	.337	.110	1.028
		MCI	36	16	44.4	.785	1.171	.377	3.640	.057	.395	.151	1.029
		VaMCI	50	29	61.7	.056	2.967	.973	9.050	REFERENCE	REFERENCE		
WCST ERROR	7	Control	27	8	32	REFERENCE	REFERENCE			.171	.468	.158	1.387
		MCI	36	11	32.4	.682	.783	.243	2.527	**.040***	**.366**	.141	.954
		VaMCI	50	27	54	.171	2.136	.721	6.328	REFERENCE	REFERENCE		
WCST Perseveration score	1	Control	27	6	24.0	REFERENCE	REFERENCE			.217	2.253	.621	8.180
		MCI	36	11	33.3	.546	1.476	.416	5.235	**.036***	**3.326**	1.078	10.259
		VaMCI	50	8	16.0	.217	.444	.122	1.611	REFERENCE	REFERENCE		

† Adjusted for age, sex

* - p value significant at <0.05

Table 6 Continued…

	Median of whole sample		N	>Median	%	Logistic regression† p value	Adjusted Odds Ratio	95% CI of Odds Ratio		Logistic regression† p value	Adjusted Odds Ratio	95% CI of Odds Ratio	
								Lower	Upper			Lower	Upper
ABSTRACT Immediate	12	Control	27	19	70.3	REFERENCE	REFERENCE			**.000***	**10.822**	**3.204**	**36.555**
		MCI	36	19	52.8	.189	.464	.148	1.460	**.002***	**5.023**	**1.785**	**14.136**
		VaMCI	48	12	25	**.000**	**.092**	**.027**	**.312**	REFERENCE	REFERENCE		
DMS DELAY TOTAL	39	Control	27	17	62.9	REFERENCE	REFERENCE			.076	2.586	.904	7.399
		MCI	36	18	50	.614	.757	.257	2.230	.161	1.958	.766	5.007
		VaMCI	48	16	33.3	.076	.387	.135	1.106	REFERENCE	REFERENCE		
UNIQUE DELAY	14	Control	27	17	62.9	REFERENCE	REFERENCE			**.003***	**5.439**	**1.807**	**16.367**
		MCI	36	15	41.7	.126	.429	.145	1.269	.091	2.334	.875	6.227
		VaMCI	48	12	25	**.003***	**.184**	**.061**	**.553**	REFERENCE	REFERENCE		
ABSTRACT DELAY	12	Control	27	20	74	REFERENCE	REFERENCE			**.001***	**6.800**	**2.142**	**21.589**
		MCI	36	18	50	.264	.520	.165	1.636	**.014***	**3.537**	**1.287**	**9.725**
		VaMCI	48	12	25	**.001***	**.147**	**.046**	**.467**	REFERENCE	REFERENCE		

† Adjusted for age, sex

* - p value significant at <0.05

The various neuropsychological test components were compared between the three groups using non parametric tests as well as linear regression analysis. The variables which were found to be significantly different were further analyzed by logistic regression after adjusting for age and sex.

As compared to the control group, on bivariate analysis, the persons in VaMCI group had significantly lower scores on ACE, phonemic fluency, animal fluency, WMS visual memory immediate and delayed , RAVLT total list learning, 20 minute recall, recognition scores, , Trail B test, WCST categories passed, DMS 48 abstract delay (immediate and delayed), DMS 48 total delay and unique delay. The VaMCI group had higher omission errors on RAVLT and WCST errors. These were further tested by logistic regression analysis adjusting for age and sex and it was found that the persons in VaMCI group had significantly lower scores on Phonemic fluency (p=0.005,OR=0.212,CI=0.072-0.624) WMS- visual category immediate (p=0.003 ,OR=0.163, CI=0.049-0.545), RAVLT total (p=0.023 ,OR=0.271 , CI=0.088-0.834) as well as 20 minute recall (p=0.041,OR=0.32,CI=0.105-0.955), DMS-48 abstract immediate (p=0.000,OR=0.092,CI=0.27-0.312), unique (p=0.003,OR=0.184,CI=0.061-0.553) and abstract delay (p=0.001, OR=0.147,CI=0.046-0.467) and had higher number of omission (p=0.006 ,OR=6.74 , CI=1.72-26.34) on RAVLT.

As compared to the MCI group, the VaMCI cohort had significantly higher scores on Welscher's logical memory scale (verbal) total delay (p=0.045,OR=0.381, CI=0.148-0.978) which persisted after adjusting for age and sex. However, the VaMCI group had significantly lower scores on WMS- visual immediate recall (p=0.042,OR=2.843, CI=1.037-7.798) , RAVLT total (p= 0.001,OR=5.85, CI=2.067-16.56) and 20 minute recall (p=0.026 ,OR=3.026, CI=1.14-8.03) , DMS-48 abstract

immediate (p=0.002,OR=5.023,CI=1.785-14.136) and abstract delay (p=0.014,OR=3.537,CI=1.287-9.725). The persons in VaMCI cohort made significantly more errors on WCST (p=0.040,OR=0.366, CI=0.141-0.954) while the MCI group made significantly more commission errors (p=.000, OR=7.59 , CI=2.6-22.14) and WCST– Perseverative errors (p=0.036,OR=3.326, CI=1.09-10.26). These significant differences persisted on multivariate analysis after adjusting for age and sex. The VaMCI had impaired Trail B tests and DMS 48 total delay which was significant on bivariate analysis, however they did not attain absolute significance on multivariate analysis , though the p value was tending to be significant (p=0.056). On bivariate analysis , the WCST categories passed was significantly lower for patients in the VaMCI group as compared to the MCI group.

The distribution of the various neuropsychological test variables in the the three cognitive groups have been shown in figure 4.

There was no significant difference in the HADS score for depression or anxiety among the groups.

MRI characteristics

MRI features including cerebral atrophy , periventricular and deep white matter hyperintensities and the presence and number of microbleeds were assessed and compared between the persons in the VaMCI and MCI group. Table 7 shows the distribution of cerebral atrophy and its grading in the VaMCI and MCI cohort. There was significantly more persons with moderate and severe cerebral atrophy in the MCI cohort as compared to the VaMCI cohort (Fisher exact test, **p = 0.003**)

Table 7. Comparison of the distribution of cerebral atrophy in the VaMCI and MCI cohort

			Atrophy				Total
			No atrophy	Mild	Moderate	Severe	
Cognitive Group	Mild Cognitive Impairment	Count	3	14	14	5	36
		% within Cog_Grp	8.3%	38.9%	38.9%	13.9%	100.0%
	Vascular Cognitive Impairment	Count	5	35	10	0	50
		% within Cog_Grp	10.0%	70.0%	20.0%	0.0%	100.0%
	Total	Count	8	49	24	5	86
		% within Cog_Grp	9.3%	57.0%	27.9%	5.8%	100.0%

Table 8 and 9 shows the distribution of periventricular and deep white matter hyperintensities respectively in the VaMCI and MCI cohort. There were significantly more periventricular (p=0.0007) and deep white matter hyperintensities (p=0.003) in the VaMCI cohort as compared to the MCI cohort.

Table 8. Distribution of periventricular white matter hyperintensities in the VaMCI and MCI cohort

			Periventricular				Total
			No changes	Grade 1	Grade 2	Grade 3	
Cognitive Group	Mild Cognitive Impairment	Count	21	8	7	0	36
		% within Cog_Grp	58.3%	22.2%	19.4%	0.0%	100.0%
	Vascular Cognitive Impairment	Count	9	24	14	3	50
		% within Cog_Grp	18.0%	48.0%	28.0%	6.0%	100.0%
	Total	Count	30	32	21	3	86
		% within Cog_Grp	34.9%	37.2%	24.4%	3.5%	100.0%

Table 9. Distribution of deep white matter hyperintensities in the VaMCI and MCI cohort

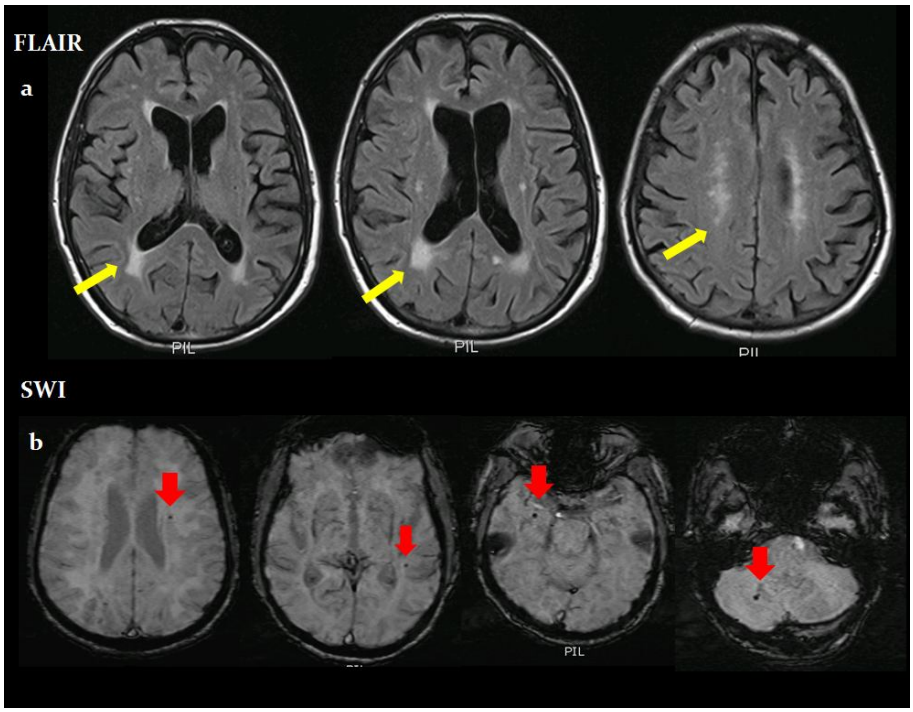
			Deep				Total
			No changes	Grade 1	Grade 2	Grade 3	
Cog_Grp	Mild Cognitive Impairment	Count	24	8	4	0	36
		% within Cog_Grp	66.7%	22.2%	11.1%	0.0%	100.0%
	Vascular Cognitive Impairment	Count	15	27	6	2	50
		% within Cog_Grp	30.0%	54.0%	12.0%	4.0%	100.0%
	Total	Count	39	35	10	2	86
		% within Cog_Grp	45.3%	40.7%	11.6%	2.3%	100.0%

Table 10 shows the presence of cerebral microbleeds in the MRI of persons in the VaMCI and the MCI groups. The presence of cerebral microbleeds was significantly more in the VaMCI group as compared to the MCI group (p=0.004). The representative images of periventricular hyperintensities and cerebral microbleeds has been shown in figure 5.

Table 10. Distribution of cerebral microbleeds in the VaMCI and MCI cohort

			MICROBLEEDS		Total
			Present	Absent	
Cognitive Group	Mild Cognitive Impairment	Count	11	25	36
		% within Cog_Grp	30.6%	69.4%	100.0%
	Vascular Cognitive Impairment	Count	31	19	50
		% within Cog_Grp	62.0%	38.0%	100.0%
	Total	Count	42	44	86
		% within Cog_Grp	48.8%	51.2%	100.0%

Figure 5. Representative MRI images (a) FLAIR images showing periventricular hyperintensities {Fazeka grade 2}(yellow arrows) and (b) SWI images showing cerebral microbleeds (red arrows)



Correlation of neuropsychological test results with MRI changes

Neuropsychological tests which had significant differences between the VaMCI and MCI groups were tested further for significant association with the grade of white matter hyperintensities and cerebral microbleeds in the VaMCI cohort. As there was smaller number of patients in the grades 2 and 3 white matter hyperintensities group, they were grouped together for analysis. It was found that there were significant differences in the RAVLT learning (p=0.012) and WMS delayed recall (p=0.014) between grade 1 (mild) and grade 2 and 3 (moderate to severe) deep white matter hyperintensities in patients in the VaMCI group. The patients with moderate to severe degree of deep white matter hyperintensities had lower scores on RAVLT list learning and delayed recall. There was no significant difference noted for the WMS visual

memory (immediate) component. The RAVLT list learning and WMS visual memory (immediate) showed significantly lower scores in the VaMCI cohort with moderate to severe grades of periventricular white matter hyperintensities on ANOVA however these were not reproducible on the Kruskall Wallis test. However no significant correlation was found between the neuropsychological tests with the presence of cerebral microbleeds within the VaMCI cohort. Correlation of the neuropsychological test results with the number of microbleeds was tested (table 14) , however no significant correlation was noted.

Table 11. Comparison of neuropsychological test results with severity of periventricular white matter hyperintensities

Neuropsychology test	**Periventricular WMH**	**N**	**Mean**	**Std. Deviation**	**Minimum**	**Maximum**	**ANOVA p value**	**Kruskall Wallis test**
RAVLT_TOTAL	No changes	9	34.00	7.053	26	46	**.027***	.079
	Grade 1	23	33.26	7.990	21	53		
	Grade 2 and 3	17	27.12	7.279	12	37		
	Total	49	31.27	8.038	12	53		
WMS total Delay	No changes	9	8.56	7.038	0	19	.959	.395
	Grade 1	24	11.71	7.981	0	26		
	Grade 2 and 3	17	8.53	8.704	0	23		
	Total	50	10.06	8.080	0	26		
WMSVISUAL (immediate)	No changes	8	17.75	7.479	8	26	**.036***	.992
	Grade 1	24	17.13	7.514	4	30		
	Grade 2 and 3	17	16.88	7.729	4	31		
	Total	49	17.14	7.430	4	31		

Table 12. Comparison of neuropsychological test results with severity of deep white matter hyperintensities

Neuropsychology test	Deep WMH	N	Mean	Std. Deviation	Minimum	Maximum	ANOVA p value	Kruskall Wallis test
RAVLT_TOTAL	No changes	15	36.53	7.809	26	53	**0.002***	**0.012***
	Grade 1	26	29.96	6.767	17	42		
	Grade 2 and 3	8	25.63	7.444	12	35		
	Total	49	31.27	8.038	12	53		
WMStotalDelay	No changes	15	11.53	7.615	0	26	**0.011***	**.014***
	Grade 1	27	11.52	8.126	0	23		
	Grade 2 and 3	8	2.38	3.926	0	11		
	Total	50	10.06	8.080	0	26		
WMSVISUAL (immediate)	No changes	14	17.50	7.633	8	30	.873	.905
	Grade 1	27	17.33	7.932	4	31		
	Grade 2 and 3	8	15.88	5.866	8	23		
	Total	49	17.14	7.430	4	31		

* - p value significant at <0.05

Table 13. Comparison of neuropsychological test results with presence of cerebral microbleeds

Neuropsychology test	Microbleeds	N	Mean	Std. Deviation	Minimum	Maximum	t test p value	Kruskall Wallis test
RAVLT_TOTAL	Present	30	30.43	7.104	12	44	.368	.465
	Absent	19	32.58	9.383	17	53		
	Total	49	31.27	8.038	12	53		
WMStotalDelay	Present	31	10.00	8.120	0	23	.947	.968
	Absent	19	10.16	8.235	0	26		
	Total	50	10.06	8.080	0	26		
WMSVISUAL	Present	31	17.16	7.067	4	30	.982	.893
	Absent	18	17.11	8.231	5	31		
	Total	49	17.14	7.430	4	31		

Table 14. Correlation between number of microbleeds and the neuropsychological tests

			NO OF MICROBLEEDS
Spearman's rho (non-parametric correlation coefficient))	RAVLT_TOTAL	Correlation Coefficient	-.153
		Sig. (2-tailed)	.295
		N	49
	WMStotalDelay	Correlation Coefficient	.025
		Sig. (2-tailed)	.864
		N	50
	WMSVISUAL	Correlation Coefficient	-.142
		Sig. (2-tailed)	.332
		N	49

Discussion

Though the entity of Vascular mild cognitive impairment has been well recognized in the recent years , there have been considerably fewer studies on the pattern of cognitive impairment in VaMCI. Few studies have compared the cognitive profiles in various types of mild cognitive impairment mainly into amnestic and non-amnestic domains. Most of these studies have been from the Western world and there is dearth of such studies from the Indian subcontinent especially in the light of the varied pattern of vascular risk factor profile in this area. Hence the current study was steered upon identifying the pattern of cognitive impairment in mild cognitive impairment due to vascular etiology as compared with that due to non vascular etiology and the impact of radiological findings on test performance.

Demographic characteristics

The patients in the VaMCI group were patients with subjective cognitive symptoms who were tested with the neuropsychological test battery at a median of 3 months after stroke. The mean age of this cohort was 64.9 years with a male preponderance. The mean age was comparable to that of the VaMCI studies by Nordlund et al.[66] The most common etiology of stroke in the VaMCI cohort was lacunar (37.2%) followed by large vessel atherosclerosis (25.9%). This is consistent with the observation that vascular mild cognitive impairment have been observed following silent brain infarcts and incident lacunes on MRI. In a study on post stroke cognitive impairment in the London stroke registry [67] a progressive trend of cognitive impairment was observed among patients with small vessel occlusion and lacunar infarction, as was seen in our study. In a study on the cognitive impairment after first ever ischemic stroke it was

found that in most patients with cognitive impairment was due to large artery atherosclerosis (23.8%) with only 13.7% of the strokes being due to lacunar infarcts.[68] This difference could be because we had excluded patients with strategic infarcts, major strokes as well as patients with cognitive impairment amounting more than just mild cognitive impairment. A study by Alladi S et al [74] from Hyderabad, India showed similar distribution of stroke etiology as in our study ,with small artery disease (42.9%) being the most commonest followed by large artery atherosclerosis (16.7%).

Comparison of cognitive profile of VaMCI vs cognitively normal healthy controls

Fifty patients who satisfied the criteria for VaMCI underwent detailed neuropsychological evaluation with a standard neuropsychological test battery. These results were compared against twenty seven cognitively normal healthy controls and thirty six patients with mild cognitive impairment due to non vascular etiology. As compared to the control group, on bivariate analysis, the persons in VaMCI group had significantly lower scores on ACE, phonemic fluency, animal fluency, WMS visual memory immediate and delayed , RAVLT total list learning, 20 minute recall, recognition scores, time to complete Trail B test, WCST categories passed, DMS 48 abstract delay (immediate and delayed), DMS 48 total delay and unique delay. The VaMCI group had higher omission errors on RAVLT and WCST errors. These were further tested by logistic regression analysis adjusting for age and sex and it was found that the persons in VaMCI group had significantly lower scores on phonemic fluency ($p=0.005$) WMS- visual category immediate ($p=0.003$), RAVLT total learning score from 5 trials ($p=0.023$) as well as 20 minute recall ($p=0.041$), DMS-48 abstract immediate ($<p=0.001$), unique ($p=0.003$) and abstract delay ($p=0.001$) and had higher number of omission ($p=0.006$) on RAVLT. This was suggestive of impairment on scales

of executive function, primarily working memory and acquisition/learning. Similar findings was noted in a quantitative review by Dixon et al [69] with executive functions maximally impaired in the group with vascular mild cognitive impairment. A recently published meta-analysis by Vasquez et al[70] compared the VaMCI against controls and MCI and found that in comparison to controls the patients with VaMCI showed impaired scores in most of the cognitive domains maximally affecting the processing speed followed by executive functions. They postulated that this was due to degradation of white matter tracks. Domains with the smallest difference between groups were visuospatial construction and working memory which could suggest that these domains rely less on white matter connections than other cognitive operations evaluated. Our study also showed similar impairment in executive functions , processing speed and learning. The study by Alladi S et al[74] which is the largest study from India currently showed that patients with cognitive impairment due to small vessel disease had low scores predominantly on tests of working memory and executive functions. However, this study had patients with vascular dementia and not those with mild cognitive impairment due to vascular etiology.

Comparison of cognitive profile of VaMCI vs MCI

List learning and recall as well as visual learning deficits were more prominent in VaMCI as compared to MCI. In comparison to the MCI group, the VaMCI cohort had significantly higher scores on delayed recall on Welscher's logical memory scale (verbal) ($p=0.045$) which persisted after adjusting for age and sex. However, the VaMCI group had significantly lower scores on WMS- visual immediate recall ($p=0.042$) , RAVLT total ($p= 0.001$) learning trial score and 20 minute recall ($p=0.026$) , visual memory subsets of DMS-48, viz. abstract immediate ($p=0.002$) and abstract delay

(p=0.014). The persons in VaMCI cohort made significantly more errors on WCST (p=0.040) while the MCI group made significantly more commission errors (p<0.0001) and WCST– Perseverative errors (p=0.036). These significant differences persisted on multivariate analysis after adjusting for age and sex. The VaMCI had impaired Trail B tests and DMS 48 total delay which was significant on bivariate analysis, however they did not achieve significance on multivariate analysis (p=0.056). On bivariate analysis, the WCST categories passed was also significantly lower for patients in the VaMCI group as compared to the MCI group.

These findings suggest that VaMCI patients had signficiant acquisition and recall deficits for word lists and figures with relatively preserved recognition on cueing thereby favouring retrieval deficits along with impairment in tests of processing speed and executive functions. Similar results were reported by the meta analysis by Vasquez et al[70] wherein they had compared the neuropsychological test profile of patients with MCI due to vascular and non vascular etiologies and found individuals with VaMCI had significantly greater deficits in processing speed and executive functioning at moderate magnitudes of effect size compared to those with MCI. In contrast, patients with MCI were shown to have a more substantial deficit in delayed memory compared to those with VaMCI. There also appeared to be significant group differences in mean effect sizes for the domains of language, working memory, immediate memory, and visuospatial construction. All of these effect sizes, with the exception of immediate memory, displayed poorer performance for VaMCI, in reference to the MCI group. The setback in the meta analysis was that many of the included studies used different criteria for inclusion of patients with VaMCI.

MRI Characteristics of patients with VaMCI as compared to MCI

The MRI characteristics of cerebral atrophy, periventricular and deep white matter hyperintensities and cerebral microbleeds were compared between patients in the VaMCI and MCI groups. The MCI had significantly more of cerebral atrophy as compared to VaMCI (p=0.003). Also the VaMCI cohort had significantly higher periventricular ($p \leq 0.001$) and deep (p=0.003) white matter hyperintensities. These findings were in line with previous MRI studies in mild cognitive impairment by Meyer et al [69] which found that VaMCI subjects showed more lacunar infarctions of white matter and more leukoaraiosis than in patients with MCI due to non vascular etiology.

In our study, the presence of cerebral microbleeds were significantly higher in the VaMCI as compared to the MCI group (p=0.004). Though there have been no studies directly comparing the presence of microbleeds in patients with VaMCI and MCI, previous studies have implicated a role for microbleeds in cognitive dysfunction especially frontal lobe functions.[62,72]

Correlation of neuropsychological test results with MRI changes

Neuropsychological tests which had significant differences between the VaMCI and MCI groups were tested further for significant association with the grade of white matter hyperintensities and presence of cerebral microbleeds within the VaMCI cohort. It was found that there were significant differences in the RAVLT learning (p=0.012) and WMS delayed recall (p=0.014) between grade 1 (mild) compared to grade 2 and 3 (moderate to severe) deep white matter hyperintensities. However no significant differences were found in our study with the grade of periventricular white matter hyperintensities or cerebral microbleeds and the selected neuropsychological test variables. However, a study by Sachdev et al[73] found that there were significant

correlation between a composite score of neuropsychological tests (including Trails A and B , Symbol digit modalities test and visual reproduction tests I and II) after correction for age, with total brain hyperintensity scores, DWMH scores, subcortical gray matter hyperintensity scores and cortical atrophy. These results were not replicated in our study probably because we had used separate neuropsychological test variables for the correlation. Also, the AGES-Reykjavik Study[72] had found that people with multiple (≥2) cerebral microbleeds had markedly slower processing speed, poorer executive function and an increased odds ratio of vascular dementia. The results were strongest for having multiple CMBs located in the deep hemispheric or infratentorial areas. However in our study though we found significant number of patients had microbleeds compared to MCI, we could not find a correlation with neuropsychological tests within the VaMCI cohort. This could have been due to small sample size.

Limitations of the study

- Limited cohort study. We did not include all patients with stroke who did not have subjective memory complaints as we wanted to have a homogenous group that resembled MCI due to non vascular etiology and who experienced their subjective decline after stroke.
- This was an observational study without repeat neuropsychological testing in VCI
- The patients in the VaMCI cohort require serial or follow up neuropsychological evaluation to look for any progression or improvement of symptoms as the currents tests were done at a median of three months after a minor stroke.
- Biomarkers for neurodegenerative dementias were not done in patients in the VaMCI group and hence an overlap or mixed etiology for the cognitive impairment cannot be completely ruled out.

Conclusions

Vascular mild cognitive impairment is a genuine entity following minor stroke which portends significant dysfunction mainly in the executive functions, delayed recall and learning in comparison to cognitively normal healthy controls.

In comparison to mild cognitive impairment due to non vascular etiology, there were deficits of working memory, verbal list acquisition, delayed list recall in addition to visual memory with relatively minor impairment on tests for processing speed and executive functioning after adjusting for age and sex, while memory functions were more affected in the latter group.

Comparison of MRI characteristics between the vascular mild cognitive impairment showed significantly higher periventricular and deep white matter hyperintensities in persons with VaMCI. Also, the presence of cerebral microbleeds was significantly higher in the VaMCI group.Correlation of neuropsychological test results with MRI changes showed significant differences in the RAVLT learning and WMS delayed recall between mild and moderate to severe deep white matter hyperintensities. However no significant differences were found in our study with the grade of periventricular white matter hyperintensities or cerebral microbleeds and the selected neuropsychological test variables

These findings require further confirmation in a large prospective cohorts. All patients with minor stroke should undergo comprehensive screening for cognitive impairment to identify those at risk of further deterioration and to optimize prevention strategies and intensive risk-factor modification.

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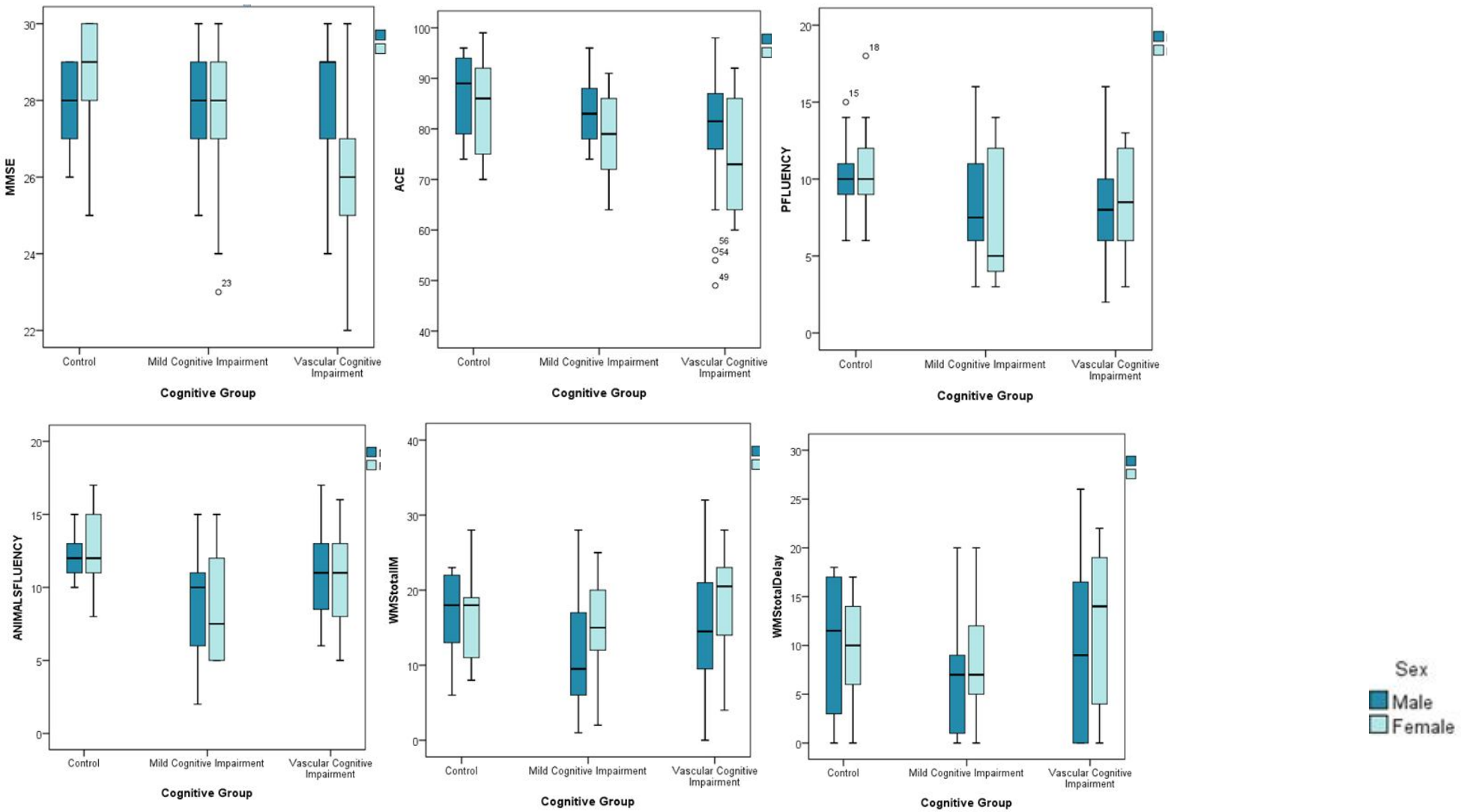

Figure 4a :Box plot showing the distribution of neuropsychological test variables in the three cognitive groups namely cognitively normal healthy controls , mild cognitive impairment due to non vascular etiology and vascular mild cognitive impairment. MMSE –Mini mental status examination,ACE- Addenbrooke's Cognitive Examination,P fluency-Phonemic fluency,WMS total IMM-WMS logical memory(immediate),WMS total delay-WMS logical memory delayed

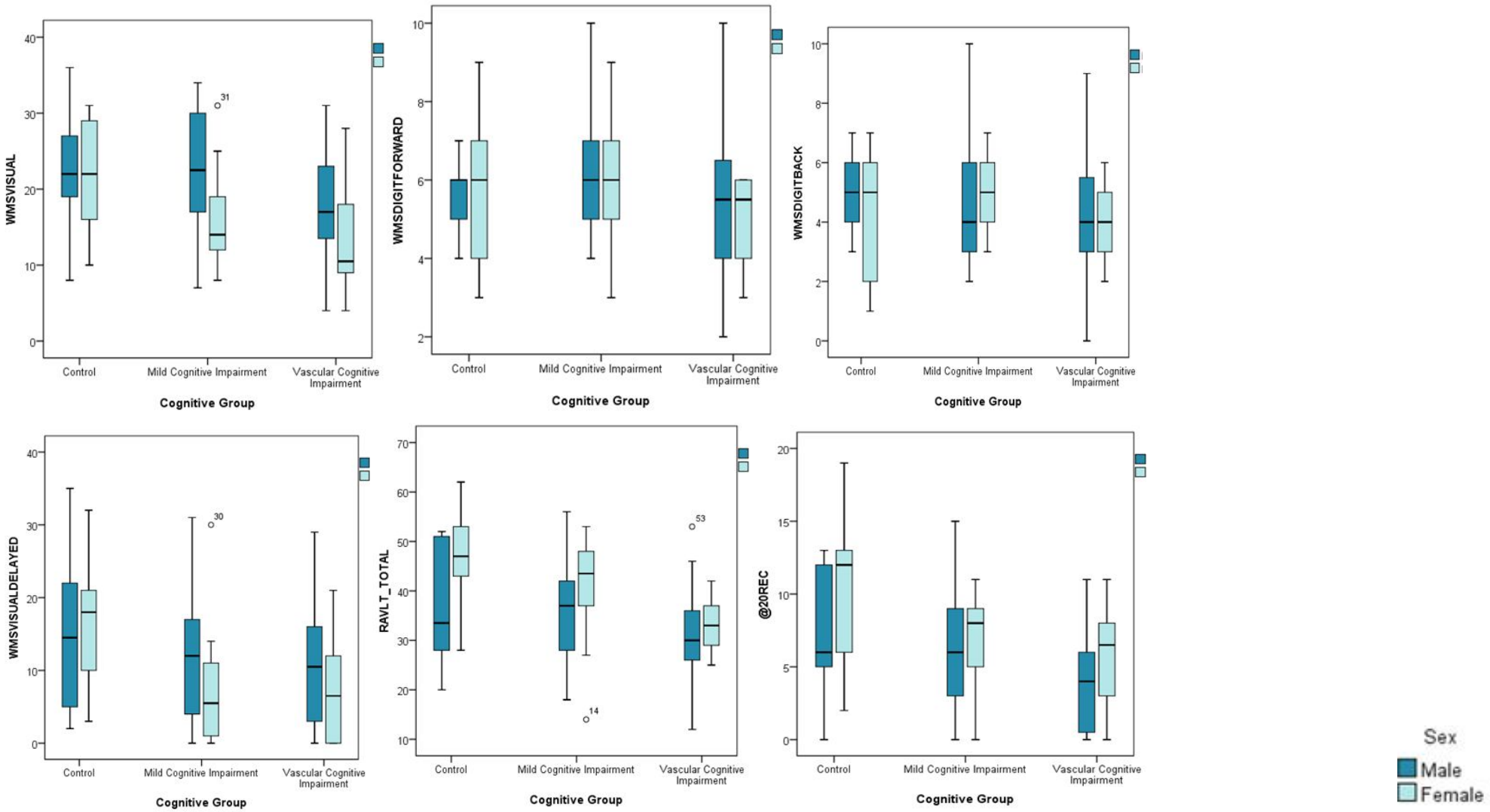

Figure 4b :Box plot showing the distribution of neuropsychological test variables in the three cognitive groups namely cognitively normal healthy controls , mild cognitive impairment due to non vascular etiology and vascular mild cognitive impairment. WMS visual-WMS visual memory immediate recall,WMS digit forward-Forward digit span,WMS digit back-Backward digit span,WMS visual delayed-WMS visual delayed memory,RAVLT total- RAVLT Immediate recall score of 5 trials,@20rec-RAVLT recall at 20minutes

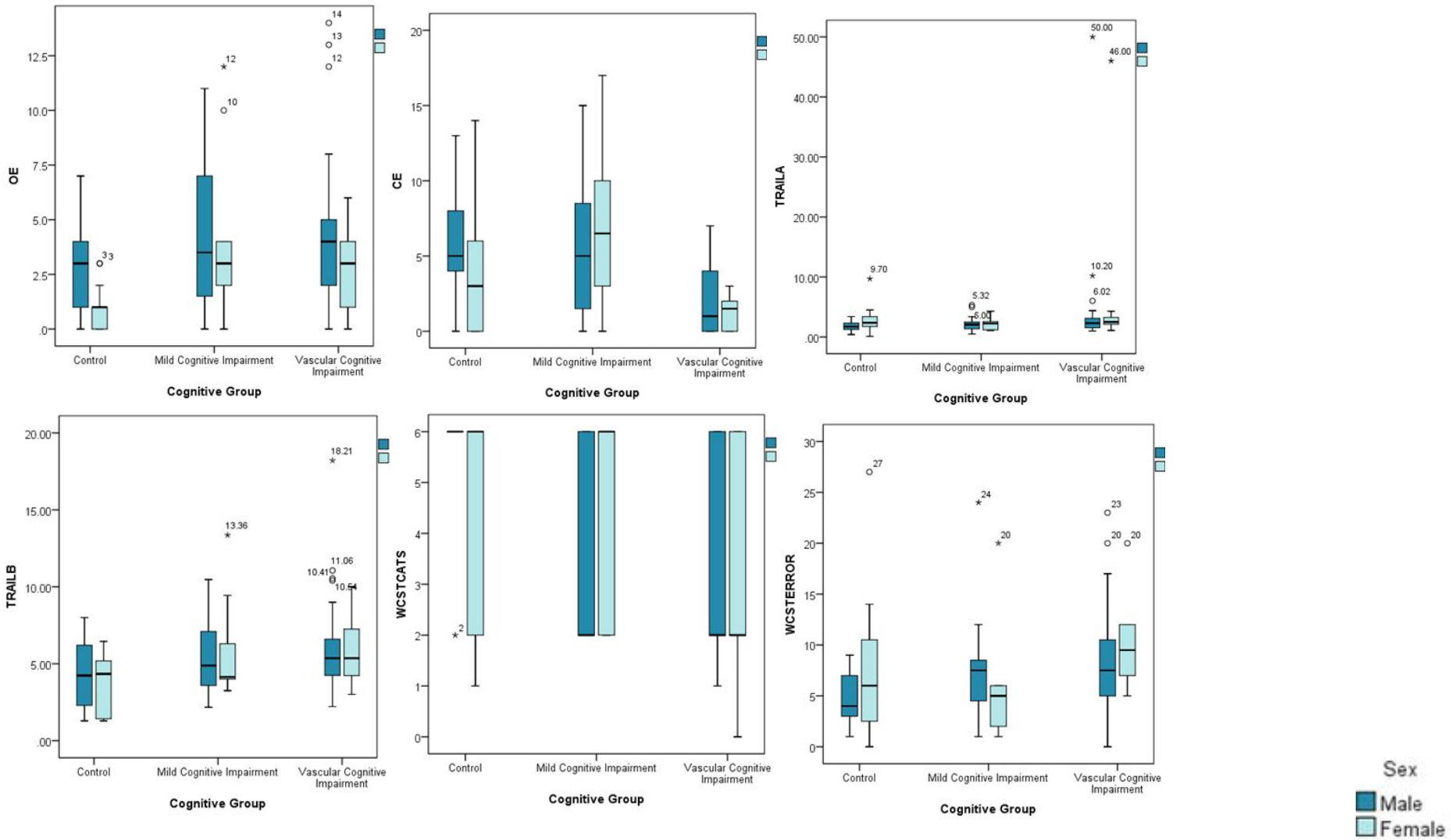

Figure 4c :Box plot showing the distribution of neuropsychological test variables in the three cognitive groups namely cognitively normal healthy controls , mild cognitive impairment due to non vascular etiology and vascular mild cognitive impairment. OE-Omission errors on RAVLT recognition, CE-Comission errors on RAVLT recognition,Trail A and Trail B-Time taken in minutes for trails A and B respectively,WCST CATS-Categories passed on Wisconsin card sorting test,WCST error-Errors made on WCST

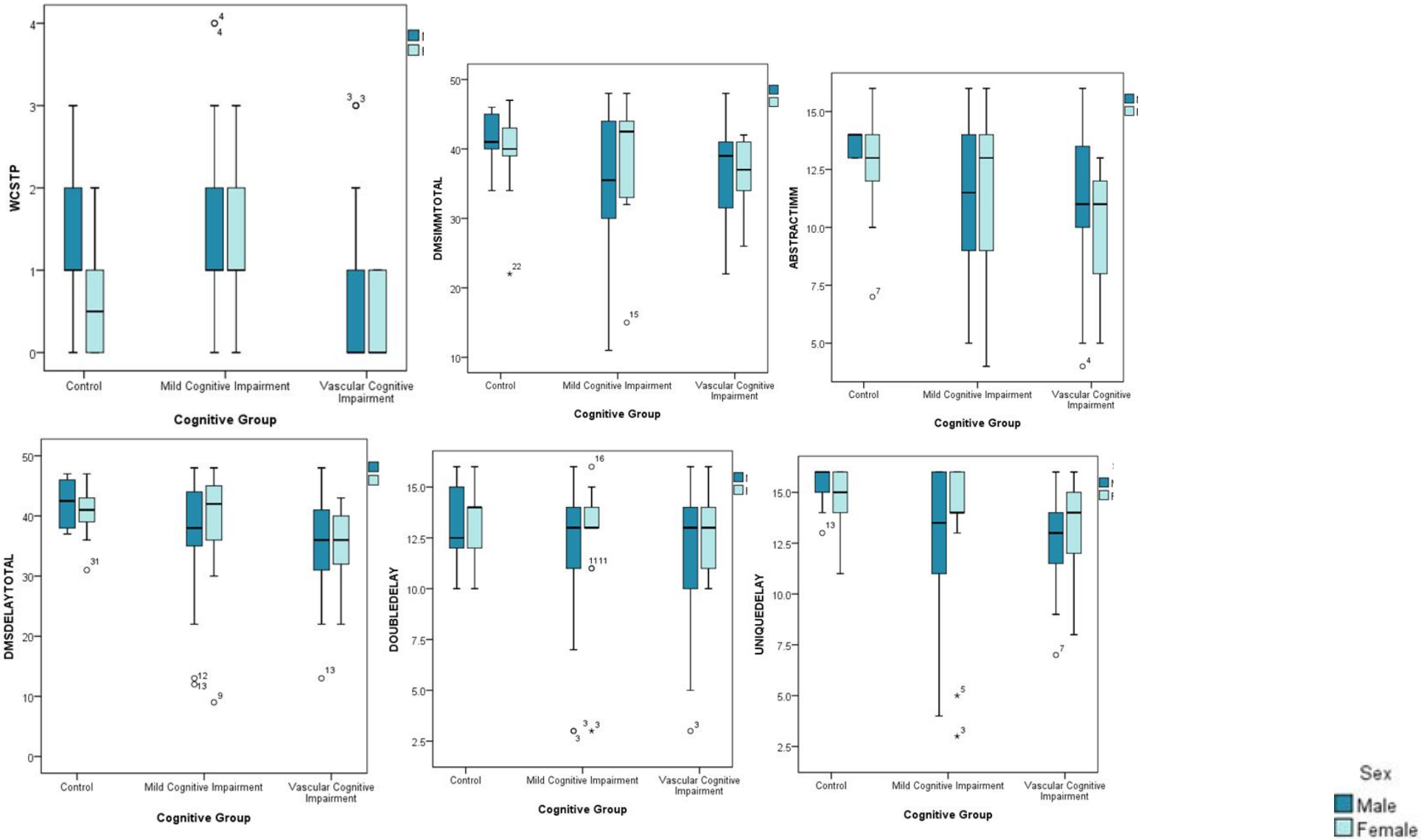

Figure 4d :Box plot showing the distribution of neuropsychological test variables in the three cognitive groups namely cognitively normal healthy controls , mild cognitive impairment due to non vascular etiology and vascular mild cognitive impairment. WCST-P-Perseverative errors on Wisconsin card sorting test, DMS imm total-Immediate recall on DMS-48,Abstract imm-Abstract recognition immediate on DMS-48,DMS delay total-Total delayed score on DMS 48,Double Delay-delayed recognition of paired items on DMS48,Unique delay-Delayed recall of unique items on DMS48

Appendix I

PROFORMA- FOR VaMCI PATIENTS

A Comparison Of Cognitive Profiles And Structural Correlates In Vascular And Non Vascular Mild Cognitive Impairment

Date of Evaluation:

1. Patient's details and history:

Name: _____ Hospital no: _____

Age: _____ Gender:_____

1.Male 2.Female

Address : _____

Level of Education: Total number of years of formal education: _____

1. 0 2.1-4 yrs 3. 5-8yrs 4. 9-12 yrs 5. >12 years

1.8 Marital status: _____ 1.Married 2.Single

2. Risk factors (1=yes, 2=No)

Hypertension---------- Duration in years ----------

Diabetes milletus---------- Duration in years ----------

Current smoking---------- pack years ----------

Ex smoker……Stopped ----------years back

Drug addiction ----------

Alcoholism----------

Coronary artery disease-------- Duration in years ----------

Hyperlipidaemia---------- Duration in years----------

Atrial fibrillation---------- Duration in years----------

History of prior stroke ----------

NIHSS at discharge _____

mRS at discharge _____

3.Cognitive Symptoms:

Duration of symptoms: Age at onset:

4.Family History of Dementia: 4.1 No of family members affected:

5.Clinical Examination:

6.1 NIHSS

6.2 mRS

7.Neuropsychological evaluation:

7.1 Domain

7.2 MMSE

7.3 ACE

7.4 P-FLUENCY

7.5 ANIMALS FLUENCY

7.6 WMS-LM I

7.7 WMS-D1

7.8 WMS-LM II

7.9 WMS-D2

7.10 WMS-VISUAL

7.11 WMS-DIGIT FORWARD

7.12 WMS-DIGIT BACK

7.13 WMS-VISUAL DELAYED

7.14 RAVLT Total

7.15 20'REC

7.16 RECOG

7.17 OE

7.18 CE

7.19 TRAIL A

7.20 ERROR A

7.21 TRAIL B

7.22 ERROR B

7.23 WCST CATS

7.24 WCST ERROR

7.25 WCST P

7.26 HADS-A

7.27 HADS-D

9.Imaging

CT scan ---------- 1.Normal.2. New infarct 3. Old infarct 4.Small vessel Ischaemic changes 5.Not done

MRI scan ---------- 1. DWI negative 2.DWI positive single lesion3.DWI – Multiple lesions 4.Not done

Describe the MRI findings (acute and old lesions) ----------

Stroke subtype----------1.large artery atherosclerosis 2.Cardioembolic.3Other Specific causes.4.Undetermined 5.lacunar

White matter hyperintensities *Fazekas et al (Total Score Minimum, 0; Maximum, 6)*

Periventricular Hyperintensities _____

Scores : 0.absence, 1.“caps” or pencil-thin lining,2.smooth “halo,” 3. irregular periventricular hyperintensities extending into the deep white matter.

Deep White Matter Hyperintense Signals _____

Scores : 0.absence, 1.punctuate foci, 2.beginning confluence of foci, 3.large confluent areas.

SWI microbleeds – Present /Absent

- Number of microbleeds , if present

PROFORMA- FOR NORMAL CONTROLS

A Comparison Of Cognitive Profiles And Structural Correlates In Vascular

And Non Vascular Mild Cognitive Impairment

Date of Evaluation:

Subject details and history:

Name: Age:

Gender:

Level of Education: Total number of years of formal education:

Marital status:

Address:

Details of any medical illnesses:

2.Details of any Medications which the subject is taking

Present Medications

3.Clinical Examination:

4.Neuropsychological evaluation:

1. Domain
2. MMSE
3. ACE
4. P-FLUENCY
5. ANIMALS FLUENCY
6. WMS-LM I
7. WMS-D1
8. WMS-LM II
9. WMS-D2
10. WMS-VISUAL
11. WMS-DIGIT FORWARD
12. WMS-DIGIT BACK
13. WMS-VISUAL DELAYED
14. RAVLT total
15. 20'REC
16. RECOG
17. OE

18. CE

19. TRAIL A

20. ERROR A

21. TRAIL B

22. ERROR B

23. WCST CATS

24. WCST ERROR

25. WCST P

26. DMS 48

27. HADS-A

28. HADS-D

MRI Brain- white matter hyperintensities_____ 1.Yes 2.No ; If yes ,Grade_____

Microbleeds -_____1.Yes 2.No ; If yes , location _____

Abbreviations

ACE	Addenbrooke's Cognitive Examination
ADL	Activities of Daily Living
CIND	Cognitive Impairment No Dementia
CMB	Cerebral micerobleeds
CNHC	Cognitively Normal Healthy Controls
CSVD	Cerebral small vessel disease
DMS 48	Delayed Matching to Sample 48
FLAIR	Fluid Attenuation And Inversion Recovery
HADS	Hospital Anxiety and Depression Scale
IADL	Scale for the Instrumental Activities of Daily Living
M-ACE	Addenbrooke’s Cognitive Examination –Malayalam
MCI	Mild Cognitive Impairment
MMSE	Mini Mental Status Examination
MRI	Magnetic Resonance Imaging
NIHSS	National Institute of Health Stroke Scale
RAVLT	Rey Auditory Verbal Learning Test
SMC	Subjective Memory Complaints
TIA	Transient Ischemic Attack
VaMCI	Vascular Mild Cognitive Impairment
VaD	Vascular Dementia
VCI	Vascular Cognitive Impairment
WCST	Wisconsin card sorting test
WMH	White Matter Hyperintensities
WMLs	White matter lesions
WMS	Wechsler’s Memory Scale
WMS	Weschler Memory Scale
WMS-LM	Wechsler’s Memory Scale-Logical Memory
WMS-VM	Wechsler’s Memory Scale-Verbal Memory