SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

THIRUVANANTHAPURAM, KERALA

CORRELATION BETWEEN PULSATILITY INDEX (PI) IN TRANSCRANIAL DOPPLER (TCD) AND COGNITIVE PROFILE OF PATIENTS WITH ALZHEIMER'S DEMENTIA AND VASCULAR DEMENTIA

Thesis submitted in partial fulfilment of the rules and regulations for DM Degree Examination of

Sree Chitra Tirunal Institute for Medical Sciences and Technology

By

Dr. Saraf Udit Umesh

DM Neurology Resident

Month and Year of Submission: July 2019

Department of Neurology

Sree Chitra Tirunal Institute for Medical Sciences and Technology

Thiruvananthapuram

2016-2019

DECLARATION

I, Dr. Saraf Udit Umesh , hereby declare that this project was undertaken by me under the supervision of the faculty, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Thiruvananthapuram
Date: 30-7-2019

Dr.Saraf Udit Umesh

Forwarded :

The candidate, Dr Saraf Udit Umesh, has completed the project under my guidance.

Thiruvananthapuram
Date: 30-7-2019

Dr.Sajith S.,
Additional Professor,
Department of Neurology,
SCTIMST.

Forwarded:

The candidate, Dr.Saraf Udit Umesh, has carried out the minimum required project.

Thiruvananthapuram
Date: 30-7-2019

Dr. Sanjeev V. Thomas,
Professor Senior Grade and Head,
Department of Neurology
SCTIMST.

ACKNOWLEDGEMENT

I take this opportunity to express my sincere gratitude to Dr. Sajith S., Additional Professor of Neurology, SCTIMST, my guide for the study, for his expert guidance, constant review, kind help and keen interest at each and every step of the study .

I am thankful to Dr. Ramshekhar N. Menon, Additional Professor, Department of Neurology for his guidance, encouragement and valuable suggestions during the period of the study.

I am extremely thankful to Mrs.Sushama, psychologist for her valuable input and assistance to the study.

Last but not the least, I extend my gratitude to all my patients, and their caregivers who willingly participated in this study.

Dr. Saraf Udit Umesh
Senior Resident
Department of Neurology
SCTIMST, Trivandrum, Kerala

INDEX

INTRODUCTION

Introduction

The World Health Organization (WHO) predicts that by 2025, about 3/4th of the estimated 1.2 billion people aged >60 years will reside in developing countries[1]. 4.6 million new cases of dementia are added every year, and the highest rate of growth is expected in South Asian countries including India. Education attainment is known to protect against dementia. Diet and lifestyle can also influence risk of dementia, and studies suggest that disorders affecting the vascular system, such as hypertension, diabetes mellitus and obesity, increase the risk for dementia, including Alzheimer's disease (AD).

There is increasing evidence linking cerebral hypoperfusion and neurodegeneration, specifically in Alzheimer's disease (AD) and vascular dementia (VaD)[2]. In the Rotterdam study[3], cerebral hypoperfusion was demonstrated to be a risk or an aggravating factor in dementia. Hypoperfusion because of microangiopathy, macroangiopathy or cardiac dysfunction can promote or accelerate neurodegeneration, blood-brain barrier disruption and neuroinflammation.[4] Diagnostic tools that can provide real-time functional assessment of the cerebrovascular tree can have a significant impact on our understanding of the vascular contribution to neurodegeneration at different stages of cognitive decline.

Ultrasound can evaluate the cerebrovascular tree for pathological structure and functional changes contributing to cerebral hypoperfusion. Studies have shown an association between leukoaraiosis and transcranial doppler (TCD) pulsatility index (PI) in several kinds of patients.[5] Despite increasing evidence supporting the utility of these methods in detection of microvascular pathology, cerebral hypoperfusion,

neurovascular unit dysfunction and disease progression, non-availability for routine use and incomplete standardisation limit their use in daily routine.

Studies have evaluated the utility of Middle cerebral artery-Pulsatility index (MCA PI) to differentiate between AD and VaD and have found conflicting results.[6] PI has been correlated with severity of cognitive decline in few studies. Studies have also evaluated correlation of PI with decline in cognition. However, correlation of PI with detailed cognitive profile has not been evaluated.

In this background, we planned our study to assess whether MCA PI can be used to differentiate between patients with AD and VaD. Also, we propose that increase in PI correlates with severity of cognitive deficit in patients with dementia.

REVIEW OF LITERATURE

1. Burden of dementia

The prevalence of dementia rapidly increases from ~ 2-3% among those aged 70–75 years to 20–25% among those aged >85 years[7]. Dementia rates are growing at alarming rate in all regions of the world and are related to population aging. Neurologic conditions, including dementia, were estimated by the Global Burden of Disease 2010 Study as the third leading cause of years lived with disability at global level.[8] Dementia modifies survival and increases the risk of death. In a study among Shanghai residents[9], mortality risk ratios for AD and VaD, particularly in those over 75 years of age, were found to be similar to the mortality risk ratio for cancer.

2. Alzheimer's dementia

Late-onset AD is the most common subtype of age-related dementia, even in developing countries; 60% of all cases of dementia fulfilled the US National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria.[1]

The amyloid hypothesis has been the most dominant in regards to pathophysiologic process of AD. It states the sequential cleavage of APP leading to formation of Aβ aggregates is responsible for neuronal injury and cognitive decline in AD.

Cognitive profile of patients with AD

Cognitive symptoms of AD commonly includes deficits in short-term memory, executive and visuospatial dysfunction, and praxis. Several rarer variants of AD with relative preservation of memory have been recognized.

Stages of AD

Early in the disease course, recent episodic memories are most affected, while memories from the distant past are usually spared. As the disease progresses, all aspects of episodic memory become affected. In contrast to episodic memory, working memory and semantic memory are preserved until later in the disease course.

Language disturbance, especially word-finding difficulties, is a common early symptom in AD. Subtle decline in visuospatial skills occurs in the mild dementia stages. Executive dysfunction begins in the predementia stages and, similar to all other cognitive domains, worsens over the disease course.

Atypical AD variants

Frontal variant of AD is characterized by substantial behavioral or personality changes that are out of proportion to the observed short-term memory loss.

Posterior cortical atrophy presents with visuospatial dysfunction often in the form of partial or full Balint syndrome (simultanagnosia, ocular apraxia, and ocular ataxia), partial or full Gerstmann syndrome (acalculia, agraphia, right/left disorientation, and finger agnosia), apperceptive visual agnosia, and environmental disorientation.

Patients with AD may also present with early progressive language involvement, most often in the form of logopenic aphasia with pronounced anomic deficits and impaired repetition but preserved grammar and syntax.

Findings suggestive of AD pathology include mesial temporal atrophy. Functional brain imaging using single-photon emission computed tomography (SPECT) and PET technologies can be used to identify AD-specific patterns such as temporoparietal hypoperfusion/hypometabolism in patients with AD. More recently, arterial spin-labeling MRI sequences have been shown to capture perfusion abnormalities.

3. Vascular cognitive impairment and Vascular dementia

Vascular dementia (VaD) is recognised as the second most prevalent type of dementia.[1]

In poststroke vascular cognitive impairment, the cognitive impairment is the immediate and direct consequence of a symptomatic stroke. In nonstroke-related vascular cognitive impairment, the cognitive impairment is the consequence of clinically hard to detect cerebrovascular disease, which may be evident only on neuroimaging with CT or MRI.

The term vascular cognitive impairment is intended to encompass all forms of cognitive impairment, not only dementia, and to include all cases where vascular disease contributes to impairment, including in cases where it is not the sole

contributor. Vascular cognitive impairment is a frequent contributor to mixed dementia, accompanied by other neuropathologies such as Alzheimer pathology.

Diagnostic criteria for Vascular cognitive impairment include clinical or neuroimaging evidence of presence of stroke or small vessel ischemic changes. Neuroimaging is not routinely available in developing countries, which influences the accuracy of VaD detection and the confirmation of cases of mixed dementia.

Cognitive profile of patients with Vascular dementia

Lacunar infarcts have been related to cerebral small vessel disease (SVD), pathologically characterized by lipohyalinosis in end arteries deep in the brain, and both lacunar infarcts and SVD are associated with cognitive impairment and dementia. Studies have documented cognitive impairment in the acute phase as well as in long-term follow-up. Cognitive impairment in patients with lacunar infarcts may be just as frequent and important as motor and sensory sequelae, but may be overlooked.

There can be great variety in the spatial distribution and severity of cerebrovascular disease, which determines the neuropsychological profile. Therefore, there is no uniform pattern of neuropsychological impairment in patients with vascular cognitive impairment. A systematic review by Edwards et al. documented that all major cognitive domains were affected in lacunar infarcts. No typical clinical presentation exists for vascular cognitive impairment. Patients with large-territory strokes may have a stepwise decline and focal signs (eg, hemiparesis), while those with cerebral small vessel disease may present with an insidious onset of cognitive slowing with

gait disturbance and parkinsonism. Vascular cognitive impairment is associated with relatively greater impairments in executive function and processing speed than in episodic memory for a given level of overall disability. It is important to recognize that some degree of memory impairment is very common in vascular cognitive impairment as well. Diagnosis of Vascular cognitive impairment should not be made based on neuropsychological profile alone.

4. Risk factors for dementia

Increasing age is the most consistent risk factor for dementia worldwide. Various genetic and environmental factors, including early-life brain development, body growth, socioeconomic conditions, environmental enrichment, head injury, and cognitive reserve, likely contribute to dementia risk. Illiteracy or low educational achievement has been shown to be a risk factor for dementia. Vascular factors, such as hypertension, dyslipidaemia, hyperinsulinaemia and type 2 diabetes, obesity, subclinical atherosclerosis, and arrhythmias, are associated with greater risk of cognitive impairment and dementia, including AD. Factors that decrease vascular function, such as tobacco use, might further influence cognition in old age. Current smoking, hypertension, AF, IHD, carotid stenosis and elevated Homocysteine levels were found more frequent in patients with Post stroke dementia in study by Khedr et al.[10] Control of hypertension and diabetes may help in preventing dementia.[11]

5. Association between Alzheimer's dementia and Vascular dementia

Chronic hypoperfusion is not only a result of brain tissue loss, but it actively promotes, initiates or accelerates neurodegeneration through multiple mechanisms, including induction of oxidative stress, synaptic dysfunction, tau hyperphosphorylation, amyloid beta (Aβ) accumulation and aggregation, neuronal loss, white matter hyperintensities(WMH), and neuroinflammation. Vascular aging with consequent chronic hypoperfusion may contribute to blood-brain barrier disruption which, according to emerging in vivo imaging evidence, occurs relatively early in life in selected areas, such as hippocampus, thus making individuals prone to memory disturbances.

Consensus criteria recommend that the diagnosis of nonstroke vascular cognitive impairment should be based on a pattern of diffuse, severe cerebrovascular disease. In most cases, nonstroke vascular cognitive impairment is caused by subcortical ischemic cerebral small vessel disease, also called Binswanger disease. Understanding the relationship between the location, extent, and severity of the cerebral small vessel disease and the resulting clinical syndromes is still incomplete. Silent brain infarcts and white matter hyperintensities on MRI predict risk for dementia in population-based studies, and silent brain infarcts are associated with presence of dementia in autopsy-based studies, while the relationship of cerebral microbleeds to cognition is less clear.

Roher et al.[12] documented the presence of major leptomeningeal arterial stenosis in a group of neuropathologically diagnosed AD whose magnitude was correlated with the

densities of AD neuropathology lesions and with the degree of atherosclerotic vascular disease of the circle of Willis[13]. Reduction of resting cerebral blood flow and disturbance of cerebrovascular auto-regulation were observed in the cortex and hippocampus of mice over-expressing amyloid precursor protein (APP)[14]. As hypothesized by Iadecola, Aβ amyloid could be able to compromise the ability of endothelial cells to produce vasodilatory factors, impairing cerebral auto-regulatory mechanisms to maintain an adequate flow during hypotension and to relatively increase CBF during brain activity[15].

Recent observations have shown that sporadic AD is associated with a failure of soluble amyloid-β (Aβ) clearance and that soluble Aβ can exit the brain through vascular and perivascular clearance pathways.

Data from 5715 cases from the National Alzheimer's Coordinating Center database[16] assessed the correlation between the prevalence of CVD and vascular pathology in a variety of neurodegenerative diseases with dementia severity. The study identified a significantly higher prevalence of vascular pathology and CVD in Alzheimer's disease than any other neurodegenerative diseases causative of dementias, such as α-synucleinopathy, fronto-temporal lobar dementias (FTLD), and prion disease. Vascular pathology coexisting with AD pathology is thought to act as additional "hits" to the brain thereby lowering the threshold for cognitive impairment in persons with AD pathology.

Increased neuritic plaque burden and a higher Braak stages was associated with increased grades of atherosclerosis in both subjects with AD and vascular dementia[13].

In an autopsy study, the circle of Willis arteries of AD patients exhibited numerous and severe stenosis, which correlated with AD pathology [60]. More recently developed imaging techniques have been used to visualize arterial structures and atherosclerotic plaque burden. A study using positon emission tomography showed an increase in amyloid deposition in patients having both carotid artery occlusions and dementia[17]. In contrast, examining 200 brains in the Baltimore Longitudinal Study of Aging[18] showed no correlation between atherosclerosis and AD pathology.

In one study, microscopic infarcts were present in 43% of patients with AD, 62% of patients with vascular dementia, compared to 24% of subjects of normal cognitive ability. In the Religious Orders Study[19], microscopic infarcts further add to the likelihood of dementia and cognitive impairment in persons with AD pathology and macroscopic infarcts. The effect of infarcts and AD pathologies was independent and there was no interaction between AD and infarct pathology.

White matter lesions were significantly related to progression of amyloid deposition in sporadic AD patients[20]. In addition, WM volume has also been inversely related to AD pathology[21] and reduced cerebral autoregulation[22]. In another study, overall T2 signal prolongation was related to AD pathology and gross infarcts [23]. These studies highlight the importance of the relationship between vascular factors, the white matter and neurodegenerative pathologies and how they may be interrelated in the pathogenesis of AD dementia. The underlying pathology causing WMH maybe causally related to AD pathology itself [22]. Current findings from the literature suggest that WMH and other white matter changes are complex abnormalities that are

important markers of cerebrovascular burden, but may also be related to neurodegenerative pathologies and have independent relationships with cognition.

Data from the Memory and Aging Project (MAP) and Religious Order Study (ROS)[19] found that about half the subjects whom were clinically-diagnosed with probable AD had mixed pathologies, the most common being AD and infarct pathology.

Due to the overlap of pathologies there may not be a single causative pathology for mixed dementia, and even the initiating pathology becomes unclear. Neuropathological examination of brains from participants of the Medical Research Council Cognitive Function and Ageing Study (MRC-CCFAS)[24] report 78% with vascular pathology and 70% with AD pathology in this cohort.

Overall, there is a striking overlap between AD and vascular pathologies contributing to probable AD and dementia in these community cohorts. Mixed vascular pathology with AD pathology is the most prevalent ahead of dementia with Lewy bodies, and hippocampal sclerosis[16, 24]. Due to the high prevalence of the vascular pathologies in mixed dementia, prevention and treatment of the vascular component is important to reduce risk of dementia.

Interactions between cerebrovascular and Alzheimer pathology seem to be in their combined effects on brain cellular and network function, and not because one disease directly causes the other; however, this observation does not exclude a role for variance in (non-diseased) vascular clearance of Aβ in the pathogenesis of AD.

Diabetes mellitus doubles the risk of AD corresponding with an increase in microinfarcts and without a corresponding increase in plaques and tangles[25]. Higher

total cholesterol, LDL concentrations and a history of diabetes is associated with faster cognitive decline in AD[26]. Additionally, in studies on AD patients the presence of atherosclerosis was related to an increased frequency of neuritic plaques and neurofibrillary tangles[27]. Furthermore, treatment of vascular risk factors in patients with AD is associated with slower cognitive decline.

Studies have shown hypertension is a consistent CVD risk factor for developing stroke and dementia[28]. However, most clinical–pathological studies suggest that vascular risk factors are related to infarcts rather than AD pathology.

Autopsy studies consistently show that vascular pathology, mostly consisting of manifestations of cerebral small vessel disease such as small infarcts, independently predicts the risk of dementia even when accounting for Alzheimer and Lewy body pathology. The burden of cerebrovascular and Alzheimer pathology are considered independent of one another and that effects on the odds of dementia are additive, not multiplicative.

Transcranial Doppler in patients with Dementia

While neuroimaging remains the most useful diagnostic test to link the presence and severity of cerebrovascular disease with the presence of vascular cognitive impairment, it does not have perfect sensitivity for all clinically relevant cerebrovascular lesions. It is unable to detect microinfarcts, which are infarcts as small as 0.2 mm in diameter that are visible at autopsy in approximately 1/4th of all

deceased elderly but in up to half of all deceased elderly patients with dementia. These infarcts fall below the limit of spatial resolution of clinical MRI.

Unlike structural imaging, there is no optimal investigative modality to understand the hemodynamic changes coexisting with cSVD. Recently, transcranial ultrasound is increasingly being used to evaluate the hemodynamic changes of the cerebral vessels including microcirculatory disturbances.[6] Transcranial Doppler ultrasonography (TCD) is a promising investigative tool which is non-invasive, inexpensive, and mobile without having hazard of radiation exposure. It can indirectly evaluate the functional status of small vessels with a good inter-observer reliability.[29] It provides physiologic data such as mean velocity, peak systolic velocity, and end diastolic velocity from intracranial vessels. Among the various TCD parameters, the Gosling's Pulsatility Index (PI) described by Gosling and King[30, 31] was found to be the most useful parameter for evaluation of downstream resistance in cerebral vascular bed. It reflects the microvascular resistance and compliance of the small vessels.[32, 33] Cerebral small vessel disease can potentially increase downstream resistance in the cerebral circulation resulting from lipohyalinosis and micro-atherosclerosis. This can be reliably evaluated with TCD.[5]

Previous studies have indicated that TCD derived PI can be a useful tool in detection of small vessel disease (white matter hyper intensities- WMHI) with sensitivity of 70-89% and specificity of 73-86%[5]. It has a high negative predictive value for diagnosing small vessel disease.[9] In study by Xiong et al[34], the PI correlated with the volume of white matter changes.

Examination of CBF velocity, measured by transcranial Doppler, in participants of the Rotterdam Study showed subjects with a higher CBF velocity were less likely to have dementia[35]. In keeping with this, another study showed cerebrovascular reactivity was significantly reduced in subjects with AD[36]. These studies suggest that cerebral hemodynamics may be an important factor in the pathologic process of AD. Whether the relationship between amyloid deposition and CBF is direct or whether CBF decline is a byproduct of a different AD pathophysiologic process needs further study.

The majority of studies reported similar Mean Blood flow velocity (MBFV) in AD and VaD groups[37-39]. Study by Ries et al.[40] reported that the multi-infarct dementia group displayed lower MBFV and diastolic flow velocities compared to both control and AD groups. Caamaño et al.[41] reported that individuals with AD and multi-infarct dementia displayed reduced systolic and diastolic (as well as mean) flow velocities compared to healthy controls.

PI was the most commonly employed measure of vessel resistance and was found to be increased in AD [39, 42-45] and VaD or multi-infarct dementia patients[45-47], as compared to healthy controls. Some studies have shown that subjects with VaD have higher pulsatility indices, as compared to controls and AD patients[37, 38, 41, 48]. In other reports[45-47], PI was not significantly different between dementia subtypes.

TCD PI and severity of cognitive deficit

TCD studies have shown positive correlation between hemodynamic impairment and degree of cognitive deficit suggesting that microvascular damage may contribute to the cognitive changes in the early stage of dementia[36].

In study by Altmann et al.[49], TCD PI values were significantly associated with MMSE, TMT A, and TMT B performances in patients with a lacunar infarct. This study suggested TCD as a possible adjunct tool for early diagnosis of cognitive impairment after stroke.

Risk factors and pulsatility index

Patients with diabetes are more likely to develop dementia than those without diabetes. Diabetes is an independent risk factor for lacunar infarction, and has been found to be independently associated with a high PI.[50] Age, current smoking and mean arterial BP have also been shown to be correlated with PI.[51]

TCD and US technology as tools to study vascular contributions to dementia are being considered only recently. The technological aspect of US devices has not changed in recent years, but there is a constant development of new analytical tools enabling a better understanding of microvascular effects on blood flow in standardly insonated large arteries. There is a need for a greater application of these tools across

the spectrum of neurodegenerative disorders. These tools have greater significance in resource poor countries for early detection and institution of preventive measures.

AIM AND OBJECTIVES

Aims and Objectives

1. To determine whether PI in TCD correlates with cognitive profile of patients with dementia.
2. To determine whether increase in PI can differentiate between Alzheimer and Vascular dementia

MATERIALS AND METHODS

Materials and Methods

Patients above 18 years of age attending Neurology, Stroke and Cognitive Neurology services at SCTIMST, with a diagnosis of dementia were included in the study, and their eligibility was assessed as per inclusion and exclusion criteria. All the patients were recruited after written informed consent from patient/care giver. Study was done after obtaining approval from the Institutional Ethics Committee.

Sample size:

Sample size determination was done and the number required for this study using a correlation coefficient 0.5 with a significance level of 0.05 and a power of 90% was 38 patients. Hence a sample size of a total of 50 patients was decided.

Inclusion criteria:

Patients attending Neurology, Stroke or Cognitive Neurology services, SCTIMST with diagnosis of Alzheimer's dementia (as per NINCDS-ARDRA criteria) or Vascular dementia (as per VASCOG criteria)

Exclusion criteria:

1. Patients with modified Rankin score (mRS) >3.

2. Patients with evidence for large vessel atherosclerosis (>50% stenosis of the extra or intracranial vessels with any of the imaging modalities)

3. Patients with large artery territory infarcts or major ICH at any point of time.

Methodology:

Patients attending Neurology, Stroke or Cognitive Neurology services at SCTIMST were taken up in the study after applying the selection criteria. Information regarding clinical, demographic & risk factors was collected.

All the patients underwent TCD evaluation (Nicolet® Sonara® digital TCD system) using 2 Hz probe for every patient. TCD was done on both sides through the temporal window on the MCA. The depth and angle of insonation giving the highest mean flow velocity was selected. For each artery, the mean, systolic, and diastolic velocities was measured, and the Gosling pulsatility index (PI) was calculated automatically as (systolic velocity - diastolic velocity)/mean velocity. Then a mean MCA PI was calculated by averaging bilateral MCA PI. If the subject only had good temporal window on one side, then unilateral MCA PI was considered as mean MCA PI. An average over at least 10 heart beats was applied in order to have a representative value of the TCD measures.

Neuropsychology assessment was performed in detail by a trained Neuropsychologist of the Institute using a formatted questionnaire. Detailed cognitive examination included MMSE, Addenbrooke cognitive examination-Malayalam, Wisconsin card sorting test, Trail making test A and B, RAVLT and patients also underwent evaluation by HADS questionnaire for anxiety and depression.

Statistical methods:

The data was entered on to a spreadsheet and was analysed with SPSS version 25 software(SPSS Inc,Illinois,Chicago). Numerical variables were summarized as means and standard deviations. Univariate analysis was undertaken to examine relationship of various factors. A p value less than 0.05 was considered statistically

significant. Crude odds ratio with 95% confidence interval have been reported. Chi square test/ Fisher's exact test was applied to evaluate statistical significance. Multivariate analysis/ logistic regression was used to evaluate the independent and joint effect of the variable of interest on the outcome

Ethical considerations

This registry has the approval of the Institutional Ethics Committee and written informed consent was obtained from the patient or caregiver.

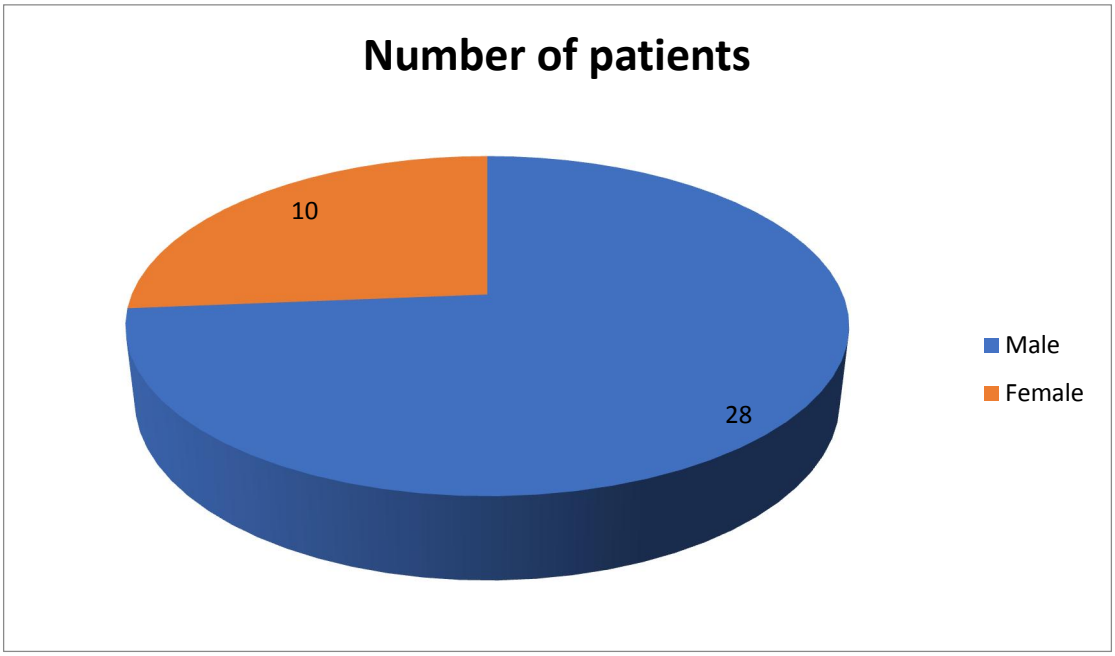
RESULTS

RESULTS:

43 patients fulfilled the inclusion and exclusion criteria. 4 patients were excluded due to poor temporal window bilaterally and 1 patient had Atrial fibrillation with variable conduction, which made averaging of MCA PI values impossible. Finally, 38 patients (28 males, 10 females) were evaluated and their data was analysed.

25 patients had Alzheimer's disease and 13 patients had Vascular dementia. Of the 25 patients with AD, 1 patient had Posterior cortical atrophy variant.

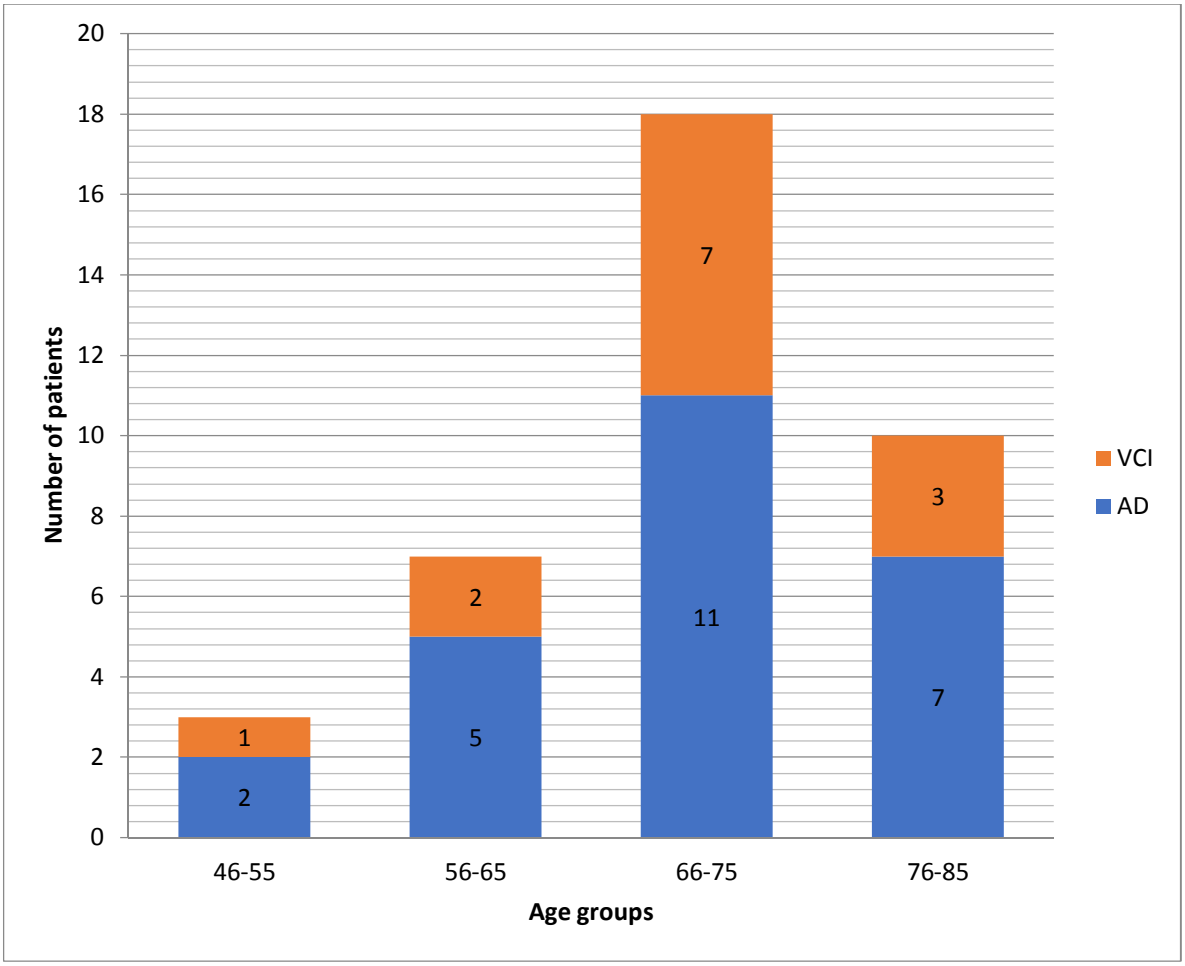
Figure 1: Gender distribution of patients



28 patients (73.7%) were males.

24 (64.1%) had hypertension, 21 (55.3%) had diabetes mellitus.

Figure 2: Age distribution of patients

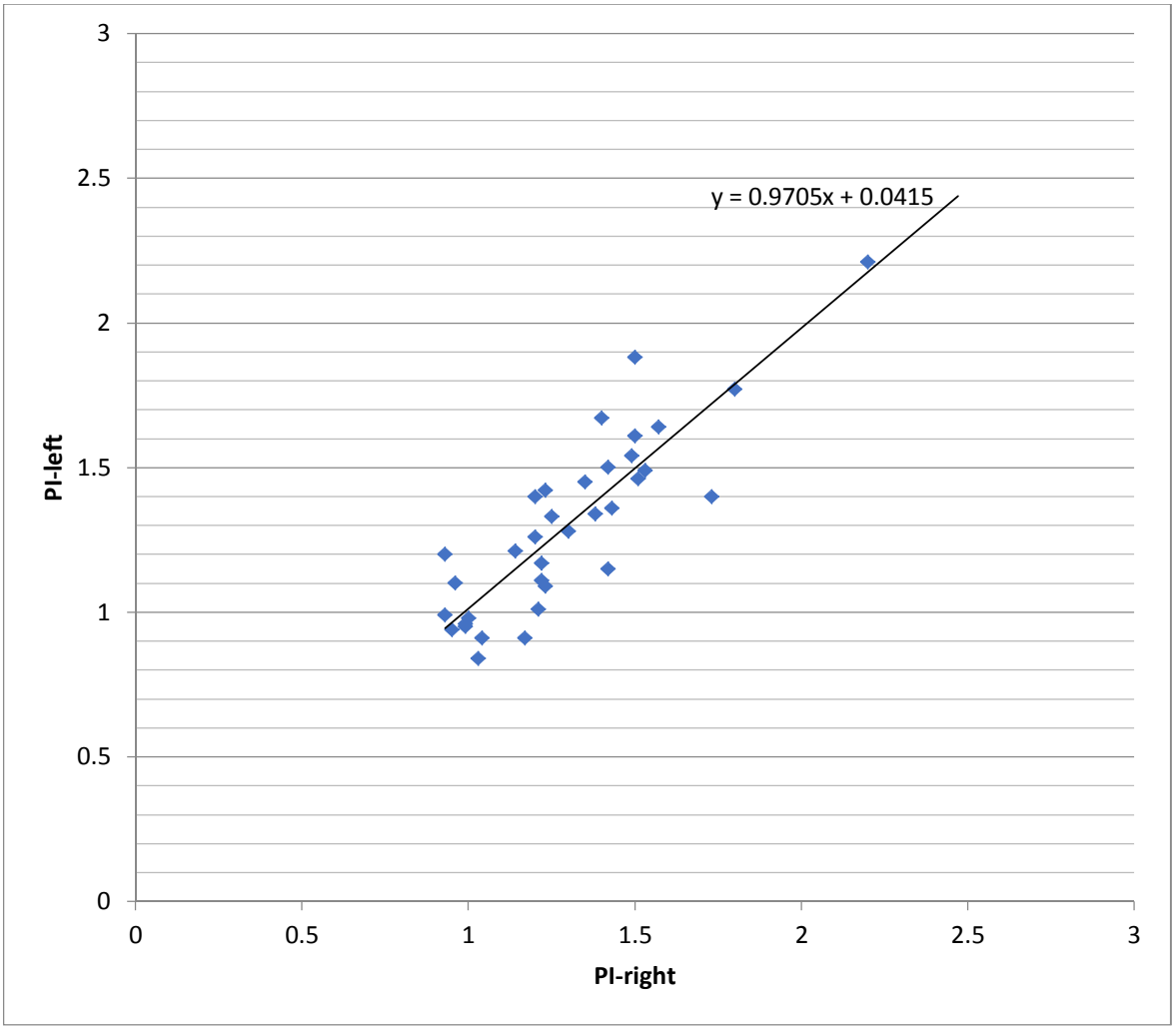


Mean age of patients was 69.63 years (SD=8.57).

Maximum patients were in 66-75 years age group.

Mean age at onset was 65.03 years (SD=8.08).

Figure 3: Correlation of right and left MCA PI



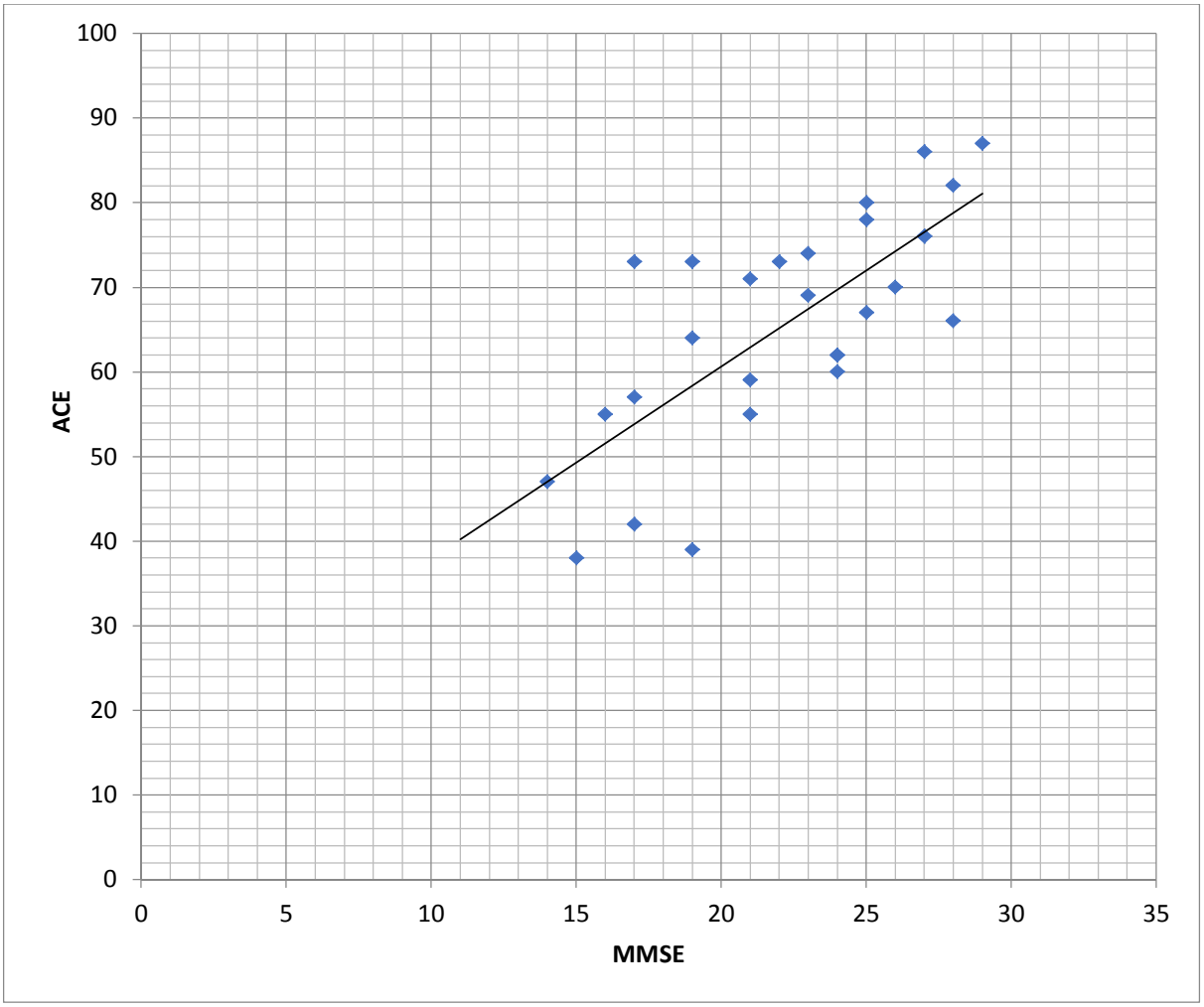
Mean PI was 1.33 (SD=0.34).

Mean PI right was 1.33 (SD=0.34) and PI left was 1.31(SD=0.31)

Left and right MCA PI showed significant correlation (Pearson's correlation co-efficient=0.865, $p<0.001$)

Mean MCA PI for females was 1.43 (SD=0.4) and for males was 1.3 (SD=0.31), p=0.291.

Figure 4: Correlation of ACE and MMSE scores



Mean ACE was 64.93 (SD=13.81). Mean MMSE was 21.49 (SD=4.63)

MMSE and ACE scores showed significant correlation (Pearson correlation co-efficient=0.738, $p<0.001$).

Mean PI did not show significant correlation with MMSE ($r=0.091$, $p=0.602$).

Table 1: Comparison between AD and VaD groups

	AD (n=25)	VaD (n=13)	P value
Age, Mean (SD)	69.56 (8.87)	69.77 (8.32)	0.944
Age at onset, Mean (SD)	64.36 (7.97)	66.31 (8.46)	0.489
Duration of illness, Mean (SD)	5.2 (4.31)	4.1 (2.78)	0.417
Males, n(%)	16 (64%)	12 (92.3%)	0.118
Hypertension, n(%)	12(48%)	12 (92.3%)	0.012
Diabetes mellitus, n(%)	12 (48%)	9 (69.2%)	0.307
CAD, n(%)	5 (20%)	3(23.1%)	1.0
Right MCA PI, Mean (SD)	1.277 (0.296)	1.437 (0.397)	0.18
Left MCA PI, Mean (SD)	1.31 (0.33)	1.30 (0.26)	0.91
Mean MCA PI, Mean (SD)	1.30 (0.30)	1.40 (0.39)	0.37
MMSE, Mean (SD)	21.54 (4.6)	21.36 (4.8)	0.92
ACE, Mean (SD)	65.47 (12.58)	63.9 (16.58)	0.78
White matter ischemic changes, Mean (SD)	0.81 (0.75)	2.50 (0.674)	<0.001

Hypertension was significantly more common in patients with VaD, as compared to AD. Mean MCA PI was similar between the 2 groups. Patients with VaD had significantly higher white matter ischemic changes, than patients with AD.

Table 2: Comparison between hypertensive and non-hypertensive patients

	Hypertensive (n=24)	Non-hypertensive(n=14)	P value
Age at onset of dementia, Mean (SD)	67.63 (7.2)	60.57 (7.8)	0.008
Age, Mean (SD)	72.58 (7.49)	64.57 (8.14)	0.004
Diabetes mellitus, n(%)	17	4	0.018
Mean PI, Mean (SD)	1.46 (0.34)	1.12 (0.19)	0.002
MMSE, Mean (SD)	22 (4.1)	20.71 (5.37)	0.429
ACE, Mean (SD)	65.79 (13.2)	63.3 (15.36)	0.653
White matter ischemic changes, Mean (SD)	1.82 (1.006)	0.64(0.81)	0.002

Hypertensive patients were older at onset of dementia, and were more likely to have associated diabetes mellitus. Mean MCA PI was significantly higher in hypertensive patients. Hypertensive patients also had higher Fazeka changes. MMSE and ACE scores did not differ significantly between groups.

Table 3: Comparison between diabetic and non-diabetic patients

	Diabetic(n=21)	Non-diabetic(n=17)	P value
Age at onset, Mean (SD)	67.43 (6.2)	62.06 (9.26)	0.040
Age, Mean (SD)	72.90 (5.5)	65.59 (10.02)	0.007
Mean MCA PI, Mean (SD)	1.5 (0.34)	1.13 (0.19)	<0.001
MMSE, Mean (SD)	21.3 (4.5)	21.73 (4.9)	0.789
ACE, Mean (SD)	63.89 (15.5)	66.42 (11.47)	0.635
White matter ischemic changes, Mean (SD)	1.82 (0.95)	1.00(1.1)	0.028

Diabetic patients were older at onset of dementia, and at evaluation. Mean MCA PI was significantly higher in diabetic patients. Diabetic patients had significantly more Fazeka changes. MMSE and ACE scores did not differ significantly between groups.

Table 4: Detailed cognitive profile of patients with AD and VaD

Cognitive domain tested	AD (n=25)	VaD (n=13)	P value
Attention, Mean (SD)	2.79 (2.0)	2.36 (1.43)	0.428
Lexical fluency, Mean (SD)	6.7 (2.96)	4.67 (3.39)	0.113
Category fluency, Mean (SD)	7.05 (3.49)	7.56 (3.64)	0.724
Retrograde memory, Mean (SD)	2.95 (1.4)	2.89 (1.27)	0.912
Verbal immediate memory, Mean (SD)	6.29 (6.18)	13.71 (7.95)	0.029
Verbal delayed memory, Mean (SD)	0.82 (1.70)	2.86 (3.34)	0.059
Visual immediate memory, Mean (SD)	7.39 (5.77)	14.67 (12.45)	0.061
Visual delayed memory, Mean (SD)	0.50 (1.43)	1.17 (2.86)	0.453
Forward digit span, Mean (SD)	4.17 (2.07)	4.13 (1.96)	0.962
Backard digit span, Mean (SD)	2.56 (1.72)	2.50 (1.77)	0.941
HADS- anxiety, Mean (SD)	4.64 (3.3)	7.0 (5.68)	0.220
HADS-depression, Mean (SD)	6.29 (5.34)	9.56 (6.1)	0.188

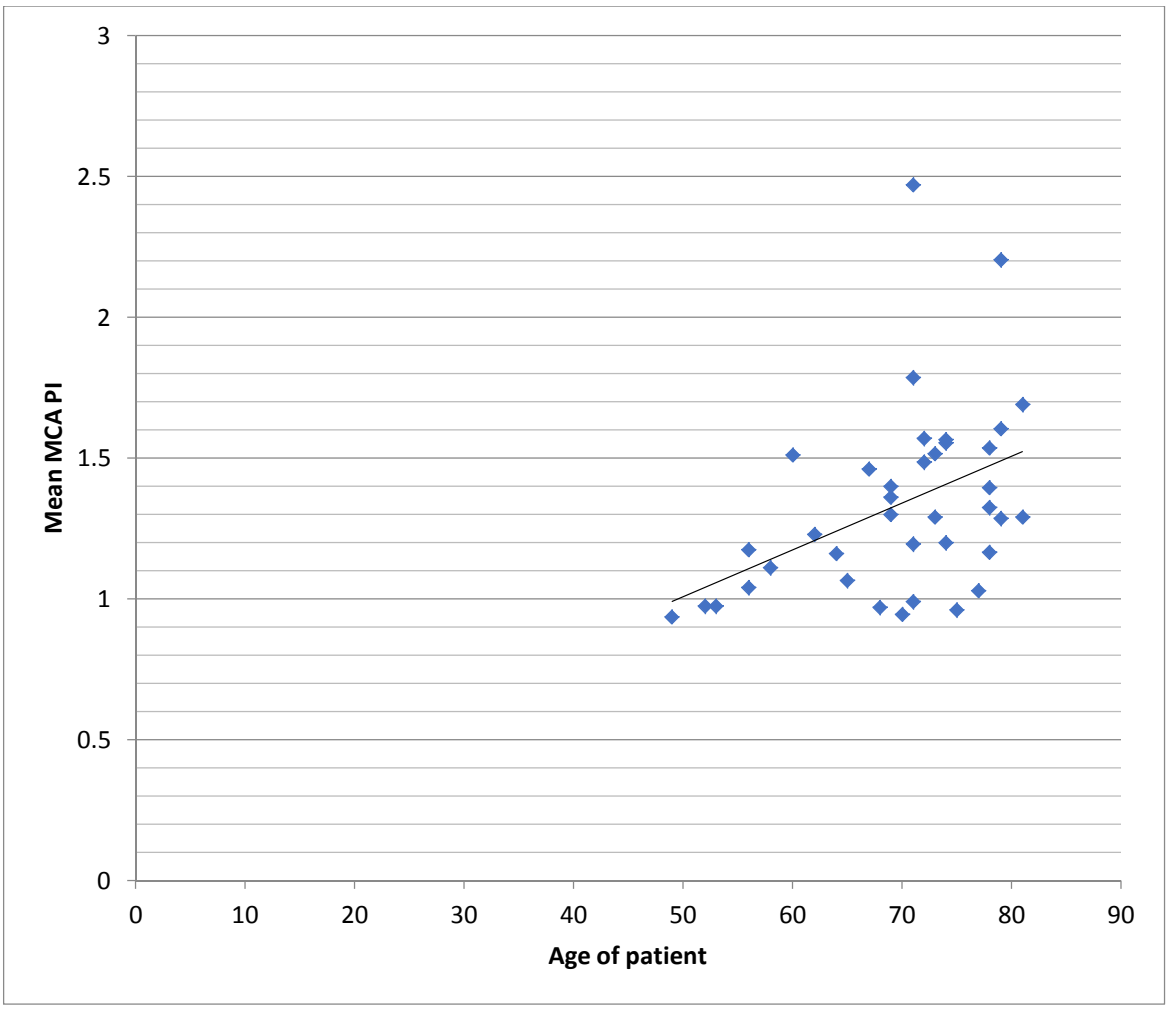
Patients with AD has significantly lower scores on verbal immediate memory, and also noted to have lower scores on verbal delayed and visual immediate memory, although it was not significant. HADS- anxiety and HADS-depression scores were higher in patient with VaD, but was non-significant.

Table 5: Correlation of mean MCA PI with cognitive profile

Cognitive parameter tested for correlation with mean MCA PI	**Pearson's correlation**	**P value**
MMSE	0.091	0.602
Attention	0.050	0.776
ACE	-0.176	0.361
Lexical fluency	0.026	0.893
Categorical fluency	-0.020	0.916
Retrograde memory	0.151	0.436
WMS-verbal immediate	0.150	0.518
WMS-verbal delayed	-0.033	0.877
WMS-visual immediate	0.106	0.620
WMS-visual delayed	-0.096	0.654
HADS-depression	0.495	0.016
HADS-anxiety	0.238	0.274

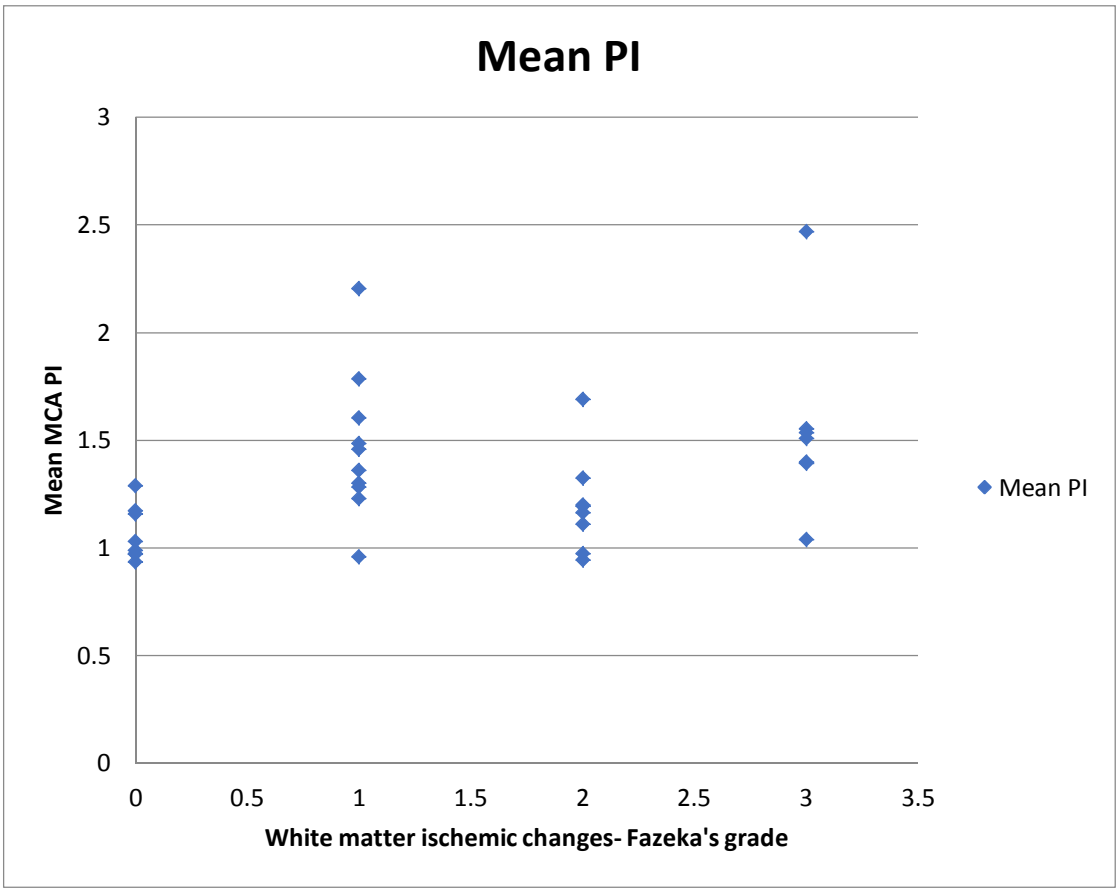
Mean PI showed significant correlation with depression as per HADS-depression score (r=0.495, p=0.016). This significance was mostly for patients with VCI (r=0.762, p=0.017) than with AD (r=0.151, p=0.607). Although insignificant, MMSE tended towards a positive correlation, while ACE as found to have a negative correlation.

Figure 6: Correlation of Mean MCA PI with age



Mean MCA PI significantly correlated with age of the patient (Pearson correlation co-efficient=0.422, p=0.008)

Figure 7: Correlation of mean MCA PI with White matter ischemic changes



Mean MCA PI showed significant correlation with White matter ischemic changes- Fazeka's grade (Pearson's correlation co-efficient=0.355, p=0.043)

Table 6: Logistic regression assessing predictors for mean MCA PI >1.3

Variables	P value	Adjusted OR	95% CI for adjusted OR	
Age	.685	1.028	.899	1.175
Male	.382	.390	.047	3.225
Hypertension	.104	7.620	.658	88.198
Diabetes mellitus	.011	12.464	1.763	88.128

Mean MCA PI was 1.33, and MCA PI value of 1.3 was taken as cut-off to perform binary regression.

On binary logistic regression analysis, diabetes mellitus was found to be significant predictor for mean MCA PI >1.3 (OR=12.464, p=0.011). Although age correlated significantly with mean MCA PI, it lost significance on regression analysis.

Table 7: Logistic regression assessing predictor for MMSE ≤ 22

Variables	P value	Adjusted OR	95% CI for adjusted OR	
Age	.205	.932	.837	1.039
Male	.847	1.209	.176	8.320
Hypertension	.859	.840	.122	5.784
Diabetes mellitus	.056	10.186	.940	110.434
Mean MCA PI	.125	.035	.000	2.544

Mean MMSE was 21.49, and was converted to binary variable with 22 as cut-off. No significant predictor for worse cognition (MMSE ≤ 22) was found. Patients with low MMSE had higher odds of being diabetic.

Table 8: Logistic regression assessing predictor for ACE $\leq$ 70

Variables	P value	Adjusted OR	95% CI for adjusted OR	
Age	.425	.955	.854	1.069
Male	.907	.888	.121	6.538
Hypertension	.971	1.041	.120	9.058
Diabetes mellitus	.837	1.239	.161	9.543
Mean MCA PI	.751	1.643	.077	35.275

Mean ACE was 64.93. ACE cut-off score of 75/76 was found optimal to detect dementia in a Japanese population[52]. For detecting dementia in Parkinson's disease patients, ACE cut-off of 70.5 showed greatest accuracy.[53] We took cut off of 70 to separate patients with mild and moderate dementia

No significant predictor for worse cognition (ACE $\leq$ 70) was found.

Table 9: Logistic regression assessing predictor for Vascular dementia

Variables	P value	Adjusted OR	95% CI for adjusted OR	
Age	.138	.910	.804	1.031
Hypertension	.016	29.185	1.880	453.155
Diabetes mellitus	.423	2.295	.300	17.535
Mean MCA PI	.717	.609	.042	8.919

Hypertension was found to be a significant predictor for Vascular dementia, after adjusting for age, diabetes mellitus and mean MCA PI.

DISCUSSION

Discussion

38 patients with dementia (25 AD, 13 VaD) were recruited for the study. Patients with significant major vessel stenosis or large strategic infarct were excluded. Mean age was 69.63 years, which was similar to other studies evaluating patients with dementia.[39, 40, 45]

Risk factors for dementia

64.1% patients had hypertension and 55.4% had diabetes mellitus in our study. Patients with VaD were more likely to be hypertensive and had more white matter ischemic changes. Lacunar stroke and white matter hyperintensities are associated with a hypertensive arteriopathy, which was earlier considered primarily responsible for Vascular dementia.

We found that hypertensive patients were older at disease onset and were more likely to have associated diabetes mellitus. Diabetic patients were also older at disease onset. Age, hypertension and diabetes have been independently identified as risk factors for dementia. Long standing hypertension predisposes to subcortical white matter disease, and can cause cognitive impairment.[54]

Mean MCA PI significantly correlated with age of the patient. Mean MCA PI was significantly higher in hypertensive and diabetic patients. Hypertensive and diabetic patients also had higher Fazeka grade.

Cognitive evaluation of patients

After detailed cognitive testing, few parameters could be assessed uniformly in all patients, including ACE and MMSE. Detailed analysis of cognitive domains

evaluated in ACE and MMSE was done. MMSE is usually considered a screening test and cannot detect mild cognitive impairment or single domain impairment.[55]For evaluating patients with Vascular cognitive impairment, ACE has been shown to have better sensitivity and specificity.[56]

In our study, MMSE and ACE scores showed significant correlation. Correlation between MMSE and ACE scores has been reported earlier. [57]

Patients with AD and VaD did not differ in their MMSE and ACE scores. Patients with AD had significantly lower scores on verbal immediate memory, and also noted to have lower scores on verbal delayed and visual immediate memory, although it was not significant. In an earlier review, no significant difference between neuropsychological profile has been found in patients with AD and VaD, except for worse executive functioning, verbal fluency and motor performance in VaD[58]. In another study, memory has been found to be more severely impaired in early stages of AD, with the difference getting diluted as disease progresses.[59]

Differentiating Alzheimer's disease from Vascular dementia based on Pulsatility index

Both AD and VaD had similar mean MCA PI values in our study, and it did not help in differentiating between them. Similar conclusion has been reached in other studies[45-47], however few studies have reported higher PI in patients with VaD [37, 38]. The response to vasodilatory stimuli, such as CO2 or acetazolamide, has been used to evaluate and quantify cerebral vasoreactivity. Initial study assessed cerebral vasoreactivity in patients with dementia, and had found reduced vasodilatory reserve in patients with VaD as compared to AD[60]. This finding also was challenged in recent

study, which found that vasoreactivity cannot be used to differentiate between dementia subtypes[47].

Correlation of Pulsatility index with cognitive parameters

Mean MCA PI did not show significant correlation with MMSE scores or ACE scores. Studies have reported varying results on such correlation[61]. Although insignificant, ACE tended to have a negative correlation with mean MCA PI. In study by Silvestrini et al[36], cognitive decline was associated with increase in MCA PI. Impaired VR has been found to be associated with worse evolution of cognitive function in AD patients.[62, 63] In a cohort of patients with asymptomatic carotid stenosis, vasoreactivity was shown to be strong predictor of cognitive decline[64]. TCD evaluation for vasoreactivity was not done in our study.

Mean MCA PI showed significant correlation with depression as per HADS-depression score (r=0.495, p=0.016). This significance was mostly for patients with VaD (r=0.762, p=0.017) than with AD (r=0.151, p=0.607). The term "Vascular depression" has been suggested for late life depression with white matter lesions[65, 66]. Patients with Vascular depression are prone for dementia, if risk factors are not adequately controlled. Brain tissue pulsatility, as measured by tissue pulsatility imaging, has been found to be significantly higher in depressed patients as compared to controls.[67]

Pulsatility index and correlation with clinical/radiological parameters

Mean MCA PI showed significant correlation with White matter ischemic changes, as per Fazeka's grading (Pearson's correlation co-efficient=0.355, p=0.043). Previous

studies have indicated that TCD derived PI can be a useful tool in detection of small vessel disease (white matter hyperintensities- WMHI) with sensitivity of 70-89% and specificity of 73-86%[5]. It has a high negative predictive value for diagnosing small vessel disease.[68] In study by Mok et al, MCA PI correlated significantly with WMC volume, independent of age, sex, and vascular risk factors. However, MCA PI was found to have low specificity for this association.[69] In study by Xiong et al, the PI correlated with the volume of white matter changes.[34] Previous studies have reported that age[70, 71], diabetes[72], hypertension[73] and vascular dementia[46] were associated with increase in PI.

On univariate analysis, age, hypertension and diabetes.was associated with higher mean MCA PI. Diabetes mellitus was found to be the sole significant predictor for mean MCA PI >1.3 (OR=12.464, p=0.011) after adjusting for age, gender and hypertension.

Strengths of the study:

1. This is one of the first study to assess the association between Pulsatility index and detailed cognitive profile. Even though previous studies have studied association between MMSE and PI, executive functions are poorly covered in MMSE and may not detect early executive dysunction.
2. Since we have ruled out significant proximal vessel disease with vessel imaging, confounding effect of co-existing large vessel disease on the TCD parameters could be avoided.

Limitations of the study

1. The major limitation of the study was the small sample size.
2. This was a cross-sectional study and follow-up changes in PI and cognitive performance was not assessed, which could give a better insight into relation between PI and severity of cognitive deficit.
3. Controls were not used for comparison

CONCLUSIONS

Conclusions

1. There was no difference in MCA-Pulsatility Index between patients with AD and VaD, however MCA-PI correlated with the presence of hypertension and diabetes mellitus (irrespective of the clinical type of dementia), probably reflecting their etiopathological role in microcirculatory disturbances.
2. We did not find any correlation between elevated mean MCA PI and MMSE, ACE and cognitive subtests.
3. Elevated mean MCA PI was significantly associated with higher scores of depression, as per HADS-depression scoring.
4. There was significant correlation between mean MCA PI and presence of white matter ischemic changes (Leukoaraiosis) indicating presence of microcirculatory disturbances along with white matter disease.

REFERENCES

References

1. Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K, et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. The Lancet Neurology. 2008;7(9):812-26.

2. Fleisher AS, Podraza KM, Bangen KJ, Taylor C, Sherzai A, Sidhar K, et al. Cerebral perfusion and oxygenation differences in Alzheimer's disease risk. Neurobiology of aging. 2009;30(11):1737-48.

3. Ruitenberg A, den Heijer T, Bakker SL, van Swieten JC, Koudstaal PJ, Hofman A, et al. Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam Study. Annals of neurology. 2005;57(6):789-94.

4. Breteler MM, van Swieten JC, Bots ML, Grobbee DE, Claus JJ, van den Hout JH, et al. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. Neurology. 1994;44(7):1246-52.

5. Kidwell CS, el-Saden S, Livshits Z, Martin NA, Glenn TC, Saver JL. Transcranial Doppler pulsatility indices as a measure of diffuse small-vessel disease. Journal of neuroimaging : official journal of the American Society of Neuroimaging. 2001;11(3):229-35.

6. Malojcic B, Giannakopoulos P, Sorond FA, Azevedo E, Diomedi M, Oblak JP, et al. Ultrasound and dynamic functional imaging in vascular cognitive impairment and Alzheimer's disease. BMC medicine. 2017;15(1):27.

7. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al. Global prevalence of dementia: a Delphi consensus study. Lancet. 2005;366(9503):2112-7.

8. Horton R. GBD 2010: understanding disease, injury, and risk. Lancet. 2012;380(9859):2053-4.

9. Katzman R, Hill LR, Yu ES, Wang ZY, Booth A, Salmon DP, et al. The malignancy of dementia. Predictors of mortality in clinically diagnosed dementia in a population survey of Shanghai, China. Archives of neurology. 1994;51(12):1220-5.

10. Khedr EM, Hamed SA, El-Shereef HK, Shawky OA, Mohamed KA, Awad EM, et al. Cognitive impairment after cerebrovascular stroke: Relationship to vascular risk factors. Neuropsychiatric disease and treatment. 2009;5:103-16.

11. Rawlings AM, Sharrett AR, Schneider AL, Coresh J, Albert M, Couper D, et al. Diabetes in midlife and cognitive change over 20 years: a cohort study. Annals of internal medicine. 2014;161(11):785-93.

12. Roher AE, Tyas SL, Maarouf CL, Daugs ID, Kokjohn TA, Emmerling MR, et al. Intracranial atherosclerosis as a contributing factor to Alzheimer's disease dementia. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2011;7(4):436-44.

13. Beach TG, Wilson JR, Sue LI, Newell A, Poston M, Cisneros R, et al. Circle of Willis atherosclerosis: association with Alzheimer's disease, neuritic plaques and neurofibrillary tangles. Acta neuropathologica. 2007;113(1):13-21.

14. Iadecola C, Gorelick PB. Converging pathogenic mechanisms in vascular and neurodegenerative dementia. Stroke. 2003;34(2):335-7.

15. Iadecola C, Park L, Capone C. Threats to the mind: aging, amyloid, and hypertension. Stroke. 2009;40(3 Suppl):S40-4.

16. Toledo JB, Arnold SE, Raible K, Brettschneider J, Xie SX, Grossman M, et al. Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative

disease cases in the National Alzheimer's Coordinating Centre. Brain : a journal of neurology. 2013;136(Pt 9):2697-706.

17. Huang KL, Lin KJ, Ho MY, Chang YJ, Chang CH, Wey SP, et al. Amyloid deposition after cerebral hypoperfusion: evidenced on [(18)F]AV-45 positron emission tomography. Journal of the neurological sciences. 2012;319(1-2):124-9.

18. Dolan D, Troncoso J, Resnick SM, Crain BJ, Zonderman AB, O'Brien RJ. Age, Alzheimer's disease and dementia in the Baltimore Longitudinal Study of Ageing. Brain : a journal of neurology. 2010;133(Pt 8):2225-31.

19. Arvanitakis Z, Leurgans SE, Barnes LL, Bennett DA, Schneider JA. Microinfarct pathology, dementia, and cognitive systems. Stroke. 2011;42(3):722-7.

20. Grimmer T, Faust M, Auer F, Alexopoulos P, Forstl H, Henriksen G, et al. White matter hyperintensities predict amyloid increase in Alzheimer's disease. Neurobiology of aging. 2012;33(12):2766-73.

21. Kotrotsou A, Schneider JA, Bennett DA, Leurgans SE, Dawe RJ, Boyle PA, et al. Neuropathologic correlates of regional brain volumes in a community cohort of older adults. Neurobiology of aging. 2015;36(10):2798-805.

22. Brickman AM. Contemplating Alzheimer's disease and the contribution of white matter hyperintensities. Current neurology and neuroscience reports. 2013;13(12):415.

23. Dawe RJ, Bennett DA, Schneider JA, Leurgans SE, Kotrotsou A, Boyle PA, et al. Ex vivo T2 relaxation: associations with age-related neuropathology and cognition. Neurobiology of aging. 2014;35(7):1549-61.

24. Neuropathology Group. Medical Research Council Cognitive F, Aging S. Pathological correlates of late-onset dementia in a multicentre, community-based

population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Lancet. 2001;357(9251):169-75.

25. Kalaria RN. Neurodegenerative disease: Diabetes, microvascular pathology and Alzheimer disease. Nature reviews Neurology. 2009;5(6):305-6.

26. Helzner EP, Luchsinger JA, Scarmeas N, Cosentino S, Brickman AM, Glymour MM, et al. Contribution of vascular risk factors to the progression in Alzheimer disease. Archives of neurology. 2009;66(3):343-8.

27. Honig LS, Kukull W, Mayeux R. Atherosclerosis and AD: analysis of data from the US National Alzheimer's Coordinating Center. Neurology. 2005;64(3):494-500.

28. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiology of aging. 2000;21(1):49-55.

29. Tomek A, Urbanova B, Hort J. Utility of transcranial ultrasound in predicting Alzheimer's disease risk. Journal of Alzheimer's disease : JAD. 2014;42 Suppl 4:S365-74.

30. Gosling RG, King DH. Arterial assessment by Doppler-shift ultrasound. Proceedings of the Royal Society of Medicine. 1974;67(6 Pt 1):447-9.

31. Michel E, Zernikow B. Gosling's Doppler pulsatility index revisited. Ultrasound in medicine & biology. 1998;24(4):597-9.

32. Wagshul ME, Eide PK, Madsen JR. The pulsating brain: A review of experimental and clinical studies of intracranial pulsatility. Fluids and barriers of the CNS. 2011;8(1):5.

33. Baumgartner RW. Transcranial insonation. Frontiers of neurology and neuroscience. 2006;21:105-16.

34. Xiong YY, Mok V, Wong A, Leung T, Chen XY, Chu WC, et al. Evaluation of age-related white matter changes using transcranial Doppler ultrasonography. Journal of neuroimaging : official journal of the American Society of Neuroimaging. 2013;23(1):53-7.

35. Bakker SL, de Leeuw FE, den Heijer T, Koudstaal PJ, Hofman A, Breteler MM. Cerebral haemodynamics in the elderly: the rotterdam study. Neuroepidemiology. 2004;23(4):178-84.

36. Silvestrini M, Pasqualetti P, Baruffaldi R, Bartolini M, Handouk Y, Matteis M, et al. Cerebrovascular reactivity and cognitive decline in patients with Alzheimer disease. Stroke. 2006;37(4):1010-5.

37. Sattel H, Forstl H, Biedert S. Senile dementia of Alzheimer type and multi-infarct dementia investigated by transcranial Doppler sonography. Dementia. 1996;7(1):41-6.

38. Biedert S, Forstl H, Hewer W. The value of transcranial Doppler sonography in the differential diagnosis of Alzheimer disease vs multi-infarct dementia. Molecular and chemical neuropathology. 1993;19(1-2):15-23.

39. Stefani A, Sancesario G, Pierantozzi M, Leone G, Galati S, Hainsworth AH, et al. CSF biomarkers, impairment of cerebral hemodynamics and degree of cognitive decline in Alzheimer's and mixed dementia. Journal of the neurological sciences. 2009;283(1-2):109-15.

40. Ries F, Horn R, Hillekamp J, Honisch C, Konig M, Solymosi L. Differentiation of multi-infarct and Alzheimer dementia by intracranial hemodynamic parameters. Stroke. 1993;24(2):228-35.

41. Caamano J, Gomez MJ, Cacabelos R. Transcranial Doppler ultrasonography in senile dementia: neuropsychological correlations. Methods and findings in experimental and clinical pharmacology. 1993;15(3):193-9.

42. Roher AE, Garami Z, Alexandrov AV, Kokjohn TA, Esh CL, Kalback WM, et al. Interaction of cardiovascular disease and neurodegeneration: transcranial Doppler ultrasonography and Alzheimer's disease. Neurological research. 2006;28(6):672-8.

43. Roher AE, Garami Z, Tyas SL, Maarouf CL, Kokjohn TA, Belohlavek M, et al. Transcranial doppler ultrasound blood flow velocity and pulsatility index as systemic indicators for Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2011;7(4):445-55.

44. Kong XD, Zhang Y, Liu L, Sun N, Zhang MY, Zhang JN. Endothelial progenitor cells with Alzheimer's disease. Chinese medical journal. 2011;124(6):901-6.

45. Provinciali L, Minciotti P, Ceravolo G, Angeleri F, Sanguinetti CM. Transcranial Doppler sonography as a diagnostic tool in vascular dementia. European neurology. 1990;30(2):98-103.

46. Foerstl H, Biedert S, Hewer W. Multiinfarct and Alzheimer-type dementia investigated by transcranial Doppler sonography. Biological psychiatry. 1989;26(6):590-4.

47. Vicenzini E, Ricciardi MC, Altieri M, Puccinelli F, Bonaffini N, Di Piero V, et al. Cerebrovascular reactivity in degenerative and vascular dementia: a transcranial Doppler study. European neurology. 2007;58(2):84-9.

48. Biedert S, Forstl H, Hewer W. Multiinfarct dementia vs Alzheimer's disease: sonographic criteria. Angiology. 1995;46(2):129-35.

49. Altmann M, Thommessen B, Ronning OM, Benth JS, Reichenbach AS, Fure B. Middle Cerebral Artery Pulsatility Index is Associated with Cognitive Impairment in Lacunar Stroke. Journal of neuroimaging : official journal of the American Society of Neuroimaging. 2016;26(4):431-5.

50. Sanahuja J, Alonso N, Diez J, Ortega E, Rubinat E, Traveset A, et al. Increased Burden of Cerebral Small Vessel Disease in Patients With Type 2 Diabetes and Retinopathy. Diabetes care. 2016;39(9):1614-20.

51. Xu TY, Staessen JA, Wei FF, Xu J, Li FH, Fan WX, et al. Blood flow pattern in the middle cerebral artery in relation to indices of arterial stiffness in the systemic circulation. American journal of hypertension. 2012;25(3):319-24.

52. Takenoshita S, Terada S, Yoshida H, Yamaguchi M, Yabe M, Imai N, et al. Validation of Addenbrooke's cognitive examination III for detecting mild cognitive impairment and dementia in Japan. BMC geriatrics. 2019;19(1):123.

53. Lucza T, Ascherman Z, Kovacs M, Makkos A, Harmat M, Juhasz A, et al. Comparing Sensitivity and Specificity of Addenbrooke's Cognitive Examination-I, III and Mini-Addenbrooke's Cognitive Examination in Parkinson's Disease. Behavioural neurology. 2018;2018:5932028.

54. Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, et al. 15-year longitudinal study of blood pressure and dementia. Lancet. 1996;347(9009):1141-5.

55. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research. 1975;12(3):189-98.

56. Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. MoCA, ACE-R, and MMSE versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery after TIA and stroke. Stroke. 2012;43(2):464-9.

57. Matias-Guiu JA, Pytel V, Cortes-Martinez A, Valles-Salgado M, Rognoni T, Moreno-Ramos T, et al. Conversion between Addenbrooke's Cognitive Examination III and Mini-Mental State Examination. International psychogeriatrics. 2018;30(8):1227-33.

58. Almkvist O. Neuropsychological deficits in vascular dementia in relation to Alzheimer's disease: reviewing evidence for functional similarity or divergence. Dementia. 1994;5(3-4):203-9.

59. Bowler JV, Eliasziw M, Steenhuis R, Munoz DG, Fry R, Merskey H, et al. Comparative evolution of Alzheimer disease, vascular dementia, and mixed dementia. Archives of neurology. 1997;54(6):697-703.

60. Matteis M, Silvestrini M, Troisi E, Bragoni M, Vernieri F, Caltagirone C. Cerebral hemodynamic patterns during stimuli tasks in multi-infarct and Alzheimer types of dementia. Acta neurologica Scandinavica. 1998;97(6):374-80.

61. Lim JS, Lee JY, Kwon HM, Lee YS. The correlation between cerebral arterial pulsatility and cognitive dysfunction in Alzheimer's disease patients. Journal of the neurological sciences. 2017;373:285-8.

62. Zavoreo I, Demarin V. Breath holding index and arterial stiffness as markers of vascular aging. Current aging science. 2010;3(1):67-70.

63. Zavoreo I, Kes VB, Morovic S, Seric V, Demarin V. Breath holding index in detection of early cognitive decline. Journal of the neurological sciences. 2010;299(1-2):116-9.

64. Balestrini S, Perozzi C, Altamura C, Vernieri F, Luzzi S, Bartolini M, et al. Severe carotid stenosis and impaired cerebral hemodynamics can influence cognitive deterioration. Neurology. 2013;80(23):2145-50.

65. Puglisi V, Bramanti A, Lanza G, Cantone M, Vinciguerra L, Pennisi M, et al. Impaired Cerebral Haemodynamics in Vascular Depression: Insights From Transcranial Doppler Ultrasonography. Frontiers in psychiatry. 2018;9:316.

66. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. Molecular psychiatry. 2013;18(9):963-74.

67. Desmidt T, Brizard B, Dujardin PA, Ternifi R, Remenieras JP, Patat F, et al. Brain Tissue Pulsatility is Increased in Midlife Depression: a Comparative Study Using Ultrasound Tissue Pulsatility Imaging. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2017;42(13):2575-82.

68. Mok V, Ding D, Fu J, Xiong Y, Chu WW, Wang D, et al. Transcranial Doppler ultrasound for screening cerebral small vessel disease: a community study. Stroke. 2012;43(10):2791-3.

69. Mok VC, Ma RC, Chu WW. Transcranial Doppler ultrasonography for detection of cerebral white matter changes in a high-risk population. Hong Kong medical journal = Xianggang yi xue za zhi. 2017;23 Suppl 2(3):16-8.

70. Titianova EB, Velcheva IV, Mateev PS. Effects of aging and hematocrit on cerebral blood flow velocity in patients with unilateral cerebral infarctions: a Doppler ultrasound evaluation. Angiology. 1993;44(2):100-6.

71. Ackerstaff RG, Keunen RW, van Pelt W, Montauban van Swijndregt AD, Stijnen T. Influence of biological factors on changes in mean cerebral blood flow velocity in normal ageing: a transcranial Doppler study. Neurological research. 1990;12(3):187-91.

72. Lee KY, Sohn YH, Baik JS, Kim GW, Kim JS. Arterial pulsatility as an index of cerebral microangiopathy in diabetes. Stroke. 2000;31(5):1111-5.

73. Cho SJ, Sohn YH, Kim GW, Kim JS. Blood flow velocity changes in the middle cerebral artery as an index of the chronicity of hypertension. Journal of the neurological sciences. 1997;150(1):77-80.

APPENDIX

a.ABBREVIATIONS:

ACE: Addenbrooke cognitive examination-Malayalam

AD: Alzheimer's disease

AF: Atrial fibrillation

CBF: Cerebral blood flow

HADS: Hospital anxiety and depression scale

IHD: Ischemic heart disease

MCA: Middle cerebral artery

MMSE: Mini mental state examination

RAVLT: Rey Auditory verbal learning test

PI: Pulsatility index

TCD: Trail making test

VaD: Vascular dementia

VaMCI: Vascular mild cognitive impairment

VCI: Vascular cognitive impairment

WMS: Wechsler Memory scale

b. Proforma

1. Personal Data:

1.1. Patient ID----------

1.2. Age ---------- years

1.4 Sex ---------- 1.Male 2.female

1.5. If outpatient or inpatient ----------

1.6. Educational status----------

1.7 Age at onset of symptoms---------

2. Risk factors:(1=Yes, 2=No)

2.1. Hypertension---------- Duration in years

2.2. Diabetes mellitus--------Duration in years

2.3 Current smoking---------Pack years----------

2.3a. Ex-Smoker----------Stopped ----------years back

2.3b.Tobacco chewing ----------

2.3c. Alcoholism----------

2.4. Coronary artery disease-------- Duration in years ----------Detected now ------

2.5. Peripheral vascular disease--------

2.6. Hyperlipidemia----------Duration in years----------Detected now----------

2.7. History of prior stroke --------Date of ictus----------

2.8. History of prior TIA----------Date of ictus----------

2.9. Patients on treatment ----------

2.9a. If yes, Type of treatment ----------

2.10. Family history of stroke/CAD (first degree relatives) ---------- (Male<55yrs and Female <65 years of age

2.11 Family history of dementia (first degree relatives)----------

3. Symptoms:

3.1 Memory disturbances 1. Present 2. Absent If present, duration - - - - - -

3.2 Executive dysfunction 1. Present 2. Absent If present, duration - - - - - -

3.3 Visuospatial dysfunction 1. Present 2. Absent If present, duration - - - - - -

3.4 Behavioural disturbances 1. Present 2. Absent If present, duration - - - - - -

3.5 Impaired attention 1. Present 2. Absent If present, duration - - - - - -

3.6 Language problems 1. Present 2. Absent If present, duration - - - - - -

3.7 Depression 1. Present 2. Absent If present, duration - - - - - -

3.8 Disinhibition 1. Present 2. Absent If present, duration - - - - - -

3.9 Insight 1. Present 2. Absent If present, duration - - - - - -

4. Neuropsychology assessment :

4.1 Test for executive function and attention

4.1.1 Colour object matching test----------

4.1.2 Category Fluency

4.1.3. Verbal fluency

4.1.4. Trail Making Test (TMT)

DiceBead Test

4.2. Visuospatial

4.2.1. Modified Taylor Complex Figure Test (MTCF)

Stick FigureTest (for illiterates)Copy

4.2.2 Line Bisection

4.3 Language

4.3.1. Picture Naming Test (PN)-finalizing stimuli

4.3.2 Franchay'sAphasia Test (FAST)

4.4 Memory

4.4.1. Verbal Memory(Kolkatta Screening Battery)- Recall

4.4.2 Modified Taylor ComplexFigure Test (MTCF) [Recall]

Stick FigureTest (for illiterates) Recall

4.4.3 Verbal Memory(KolkattaScreening Battery)- Recognition

4.4.4 Modified Taylor Complex Figure Test (MTCF) [Recognition]

Stick FigureTest (for illiterates) Recognition

4.5 Cognitive Screening

4.5.1. Montreal Cognitive Assessment (MoCA)

4.5.2 Addenbrooke's Cognitive Examination-III(ACE-III)

4.5.3 Hindi Mental State Examination (HMSE)

4.6 Behavioral Screening

4.6.1 NeuroPsychiatric Inventory–brief (NPI-Brief)

4.6.2 IQCODE

4.6.3. Inventory of Activities of Daily Living(IADL)

4.6.4 Quality of Life Scale [SF-36 (RAND)]

4.6.5 Geriatric Depression Scale-30

5. Investigations:

5.1. Serum cholesterol----------

5.2. LDL--------

5.3. HDL----------

5.4. Serum triglycerides----------

5.5. Hb A1C----------

6. Imaging

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

6.2MRI scan ----------1. DWI negative 2.DWI positive single lesion 3.DWI-Multiple lesions 4.Not done

6.2a Fazeka changes----------1. Present 2. Absent If present, specify----------

6.2b Microbleeds----------1. Present 2. Absent If present, specify

6.2c Old infarcts--------1. Present 2. Absent If present, specify

6.3 Transcranial doppler

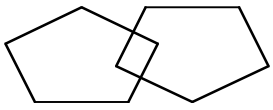
6.3a Mean blood flow velocity 1. Right MCA--------- 2. Left MCA--------

6.3b Pulsatility index 1. Right MCA--------- 2. Left MCA----------

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Addenbrooke's Cognitive Examination - Malayalam

NAME: _____	HOSP. NO.: _____
D.O.B.: _____	TESTING DATE(S): _____
AGE: _____	EDUCATION (YEARS): _____
Handedness: _____	Tested in (Language): _____
Gender:	Urban / Rural:

ORIENTATION

Ask the subject the following questions and score a point for each correct answer. Record all errors. Total Score for Orientation (0 - 10) [ ] **O**

1 a) **What is the** ഇത് / ഇന്നു

year _____
ഏതു വർഷമാണ്

season _____
ഏതു കാലമാണ് (സീസൺ)

month _____
ഏതു മാസമാണ്

*** date** _____
തീയതി എത്രയാണ്

day _____
ആഴ്ചയിലെ ഏതു ദിവസമാണ്

b) **Where are we** ഇത് ഏതാണ് / എത്രാമത്തെ

**** country** _____
രാജ്യം

state _____
സംസ്ഥാനം

city _____
നഗരം

***** hospital (or street/road)** _____
ആശുപത്രി (റോഡ്)

***** floor (or house name/no.)** _____
നില (വീട്ട് പേര്/നമ്പർ)

**Allow an error of ± 2.*

*** Give the example of **SriLanka** if the subject gives the name of the state when asked the country*

**** The items in the brackets are to be used if the subject is being tested in his/her house*

ATTENTION/CONCENTRATION

2 *Tell the subject* **I will name three objects and you have to remember and repeat them after I finish**. *Taking one second for each, say aloud* : lemon, key, ball.
Say them only once and ask the patient to repeat all three. Give one point for each correct answer at first attempt only. If score <3 repeat all three items until the patient learns all 3. Maximum trials allowed = 5.

ഞാൻ നിങ്ങളോട് മൂന്ന് സാധനങ്ങളുടെ പേര് പറയും.
പറഞ്ഞ് നിർത്തുമ്പോൾ അത് ഓർത്ത് വച്ച് ഏറ്റുപറയുക.
നാരങ്ങ, താക്കോൽ, പന്ത്. Score (0 - 3) [ ]

Number of trials administered = _____

3 *Ask the patient to* **subtract 7 from 100.**
നൂറിൽ നിന്ന് ഏഴ് കുറയ്ക്കുക

Step 1 *Give one point only for the right answer (93).*
Step 2 *If the subject's answer is wrong then tell the correct answer.*
Step 3 *Ask the subject to* **now subtract 7 from** *the correct answer* **(93).**
അതിൽ നിന്ന് വീണ്ടും ഏഴ് കുറയ്ക്കുക (93).

Repeat steps 1 to 3 for a total of 5 subtractions (93, 86, 79, 72, 65).
Score the total number of correct subtractions Score (0 - 5) [ ]

Spell 'WORLD' backwards: This test is not scored for m-ACE.
Score the number of letters in the correct order, e.g., dlorw = 3.
'പരിശോധന' എന്ന വാക്കിന്റെ അക്ഷരങ്ങൾ, എതിർക്രമത്തിൽ (പിറകിൽ നിന്ന് മുന്നോട്ട്) പറയുക. 'ആന' എന്ന് ഞാൻ പറഞ്ഞാൽ നിങ്ങൾ ' നആ ' എന്ന് പറയണം.

MEMORY

4 *Ask the subject to* **recall the names of the 3 objects learnt earlier** *in question 2. Score a point for each correct recall.*
നേരത്തെ പറഞ്ഞ മൂന്ന് സാധനങ്ങളുടെ പേര് ഓർമ്മിച്ച് പറയുക Score (0 - 3) [ ]

5 *Anterograde Memory* : *Tell the subject* **I will read a name followed by an address and ask you to repeat it when I have finished.** *Now read aloud the following name and address which has a total of seven elements in it. Score one point for each element recalled correctly. Regardless of the score after the first trial, repeat the instruction and the task twice in exactly the same way. Record scores for each of the three trials. Record errors.*

ഞാൻ പറയുന്ന പേരും, വിലാസവും കേട്ടിട്ട് ഓർത്തു പറയുക.

		Elements	Trial 1	Trial 2	Trial 3	Delayed
Velayuthan Thambi	വേലായുധൻ തമ്പി	2				
42 Kovil Road	42 കോവിൽ റോഡ്	3				
Chengammanad	ചെങ്ങമനാട്	1				
Elanji	ഇലഞ്ഞി	1				
	Total	/7	/7	/7	/7	/7

Trial 1-3: Score (0 - 21) ☐

Delayed: Score (0 - 7) ☐ **M**

6 *Retrograde Memory: Score one point for each correct answer to the following questions and record errors.*

Tell me the name of	മുഴുവൻ പേര് പറയുക	Score (0 - 4) ☐
the capital of India	ഇന്ത്യയുടെ തലസ്ഥാനം	_____
the Indian currency	ഭാരതത്തിന്റെ നാണയം	_____
the Chief Minister of Kerala	കേരളത്തിന്റെ മുഖ്യമന്ത്രി	_____
the town where Taj Mahal is	താജ്മഹൽ എവിടെ സ്ഥിതി ചെയ്യുന്നു	_____

VERBAL FLUENCY

7 *Letter: Ask the patient to* **tell me all the words you can think of, but not people or places, beginning with the letter P**. *Time the subject for 1 minute and record all answers in the space provided below. Error types: perseverations and intrusions.*

'പ' കൊണ്ടു തുടങ്ങുന്ന കുറച്ചു വാക്കുകൾ പറയുക,
സ്ഥലത്തിന്റെയോ, ആളിന്റെയോ പേര് ആകരുത്.

8 *Category: In the same way ask the patient to generate and* **now tell the names of as many animals as you can beginning with any letter of the alphabet**. *Time the subject for 1 minute & record all responses in the space provided below. Errors: perseverations and intrusions.*

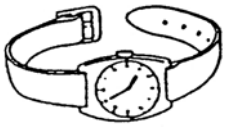
അറിയാവുന്ന മൃഗങ്ങളുടെ എല്ലാം പേരു പറയുക. അവ ഏത് അക്ഷരം കൊണ്ടും തുടങ്ങാം

P പ	Animals മൃഗങ്ങൾ	Scoring Raw Score P	Raw Score Animals	Scaled Score
		>12	>15	7
		11 to 12	13 to 15	6
		8 to 10	10 to 12	5
		5 to 7	7 to 9	4
		3 to 4	4 to 6	3
		2	2 to 3	2
		<2	<2	1
Raw Score =				
Scaled Score = /7		/7		Total Scaled Score (0 - 14) ☐ **V**

LANGUAGE

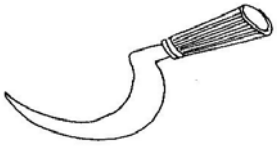
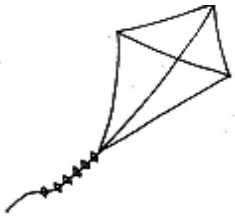
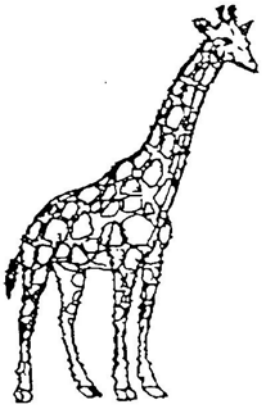
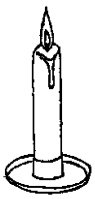
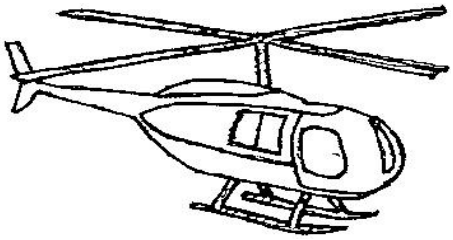
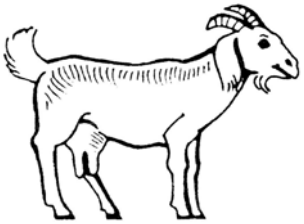
9 *Observe the subject's spontaneous speech and record the following*
Fluency (phrases > 5 words)
Paraphasic errors (phonemic or semantic)
Word finding difficulties

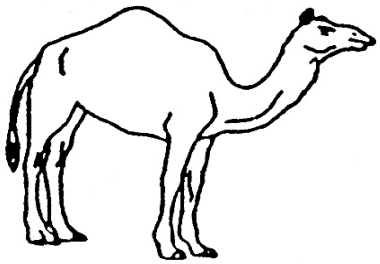
10 *Naming: Show the subject the following two line-drawings and ask him/her to* **name each of the these**. *Record responses and errors. Give one point for each correct response.*
ഓരോന്നിന്റെയും പേരു പറയുക.




Score (0 - 2) **L**

Naming: Show the subject the following ten line-drawings and ask him/her to **name each of these**. *Record responses and errors. Give one point for each correct response. If response is different from expected then ask them if it resembles anything else.*
ഓരോന്നിന്റെയും പേരു പറയുക.



Score (0 - 10) **L**

11 *Comprehension (one -stage): Request the subject to* **obey the following simple commands.**

Score (0 - 2) **L**

താഴെ പറയുന്ന നിർദ്ദേശങ്ങൾ അനുസരിക്കുക.

point to the door വാതിൽ ചൂണ്ടി കാണിക്കുക
point to the ceiling തട്ട് ചൂണ്ടി കാണിക്കുക

12 *Show the subject the instruction in the box below and ask him/her to* **read this aloud and obey it.**

താഴെ എഴുതിയിരിക്കുന്നത് വായിക്കുക എന്നിട്ട്, അത് അനുസരിക്കുക

Score one point if performed correct. Score (0 - 1) ☐ **L**

CLOSE YOUR EYES

കണ്ണുകൾ അടയ്ക്കുക

13 *Comprehension (3-stages): Give the subject a piece of paper and tell him to* **take this paper in your right / left hand. Fold the paper in half. Then put it on the floor.**

ഈ കടലാസ് വലതു / ഇടതു കയ്യിൽ എടുക്കുക നേർ പകുതി മടക്കുക എന്നിട്ട് അത് തറയിൽ വയ്ക്കുക.

Score one point for each correctly performed step Score (0 - 3) ☐ **L**

14 *Comprehension (complex grammar): Request the subject to* **obey the following commands.**

ഈ നിർദ്ദേശങ്ങൾ പാലിക്കുക Score (0 - 2) ☐ **L**

point to the ceiling then the door	തട്ടിലേയ്ക്കു ചൂണ്ടിയ ശേഷം വാതിലിലേയ്ക്കു ചൂണ്ടുക
point to the door after touching the bed/desk	മേശയോ, കിടക്കയോ തൊട്ടിട്ട് കതകിലേയ്ക്കു ചൂണ്ടുക.

Score one point only if entire command is performed correctly .

15 *Repetition (single words): Ask the subject to* **repeat each of these words after me**.

Score one point for each correct repetition. Allow only one repetition Score (0 - 3) ☐ **L**

ഞാൻ പറഞ്ഞു കഴിയുമ്പോൾ നിങ്ങൾ അത് ആവർത്തിക്കുക

Brown	വ്രണം
Conversation	കാലവർഷം
Articulate	അറകുറം

16 *Repetition (phrases): Ask the subject to* **repeat each of these phrases after me**.

ഞാൻ പറയുന്ന വാചകങ്ങൾ നിങ്ങൾ ആവർത്തിക്കുക.

Score one point for each correct repetition. Allow only one repetition.

No ifs, ands or buts Score (0 - 1) ☐ **L**

അവർ ഇവിടെ വന്നിരുന്നുവെങ്കിൽ എനിക്ക് അവരെ കാണാമായിരുന്നു

The orchestra played and the audience applauded Score (0 - 1) ☐ **L**

ഒഴിവുകഴിവുകളൊന്നും പറയരുത്.

17 *Reading (regular): Ask the subject to* **read each of these words aloud** *and show him/her the following five words.* Score (0 - 1) **L**

താഴെ പറയുന്നവ ഉറക്കെ വായിക്കുക.

SHED	ശബ്ദം
WIPE	വെപ്പ്
BOARD	ബോധം
FLAME	ഫ്രെയിം
BRIDGE	ഭൃത്യൻ

18 *Reading (irregular): Ask the subject to* ***read each of these words aloud*** *and show him/her the following five words.* Score (0 - 1) **L**

താഴെ പറയുന്ന വാക്കുകൾ ഉറക്കെ വായിക്കുക.

SEW	സഞ്ചി
PINT	സുന്ദരി
SOOT	ഫലിതം
DOUGH	ഉത്കണ്ഠ
HEIGHT	ബ്രഹ്മാണ്ഡം

19 *Writing: Ask the patient to* **make up a sentence and write it down in the space below**. *If stuck, suggest a topic e.g. weather, journey. Score one point if the sentence has a correct subject and verb and is meaningful.*

ഒരു വാചകം താഴെ എഴുതുക. Score (0 - 1) **L**

_____

_____

20 *Now to check delayed recall ask the subject* **Tell me the name and address that I had told you and you had practiced at the beginning of the test**. *Record points, scores and errors as for question 6 in the space provided in question 5 on page 2.*

നേരത്തെ, ഞാൻ പറഞ്ഞു തന്ന പേരും, വിലാസവും നിങ്ങൾക്ക്
ഓർത്ത് പറയുക.

VISUOSPATIAL ABILITIES

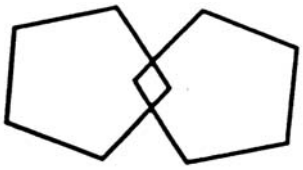
21 *Overlapping pentagons and Wire Cube: Show the subject the two figures in the next page and* ask him/her to **copy these figures in the space provided.** Score as follows

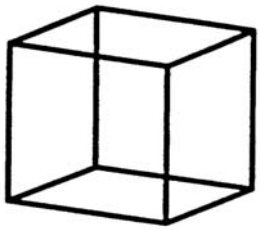
For the Overlapping pentagons, score one point if both figures have 5 sides and overlap.

For the Cube, score one point if the figure is correct.

താഴെ കാണിച്ചിട്ടുള്ള ചിത്രം ഒന്നു വരച്ചു കാണിക്കാമോ?

Score (0 - 1)





Score (0 - 1)

22 *Clock* **:** *Ask the patient to* **draw a clock-face with all the numbers and the hands at 5:10**

Score 1 point each for- correct circle, numbering of the clock-face & position of the hands

ഒരു ഘടികാരത്തിൽ /ക്ലോക്കിൽ എല്ല അക്കങ്ങളും വരച്ച്, അതിൽ 5:10 എന്ന സമയം വരച്ച് കാണിയ്ക്കുക.

Score (0 - 3)

23 ***CHECK*** *: Have you recorded the delayed recall for name and address in Q 5 on page 2?*

OVERALL SCORES : **MMSE** (0 - 30)

(Enter the sum of the scores in the boxes on each side of the vertical line) +

ACE (0 - 100)

VLOM Ratio

V	+	Sum of **L**	→	
O	+	**M**		→

If < 2.2 FTD	If > 3.2 AD

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013)

SCT/IEC/1158/DECEMBER-2017 01.01.2018

Dr. Saraf Udit Umesh
Senior Resident
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Saraf Udit Umesh,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "CORRELATION BETWEEN PULSATILITY INDEX IN TRANSCRANIAL DOPPLER (TCD) AND SEVERITY OF COGNITIVE IMPAIRMENT IN PATIENTS WITH ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA (IEC/1158)" on 16th December, 2017.

The following documents were reviewed:

Original submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 18/11/2017 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *Patient Information Sheet and Consent Form in English and Malayalam*
7. *CV of Principal Investigator and Co-Principal Investigators*

Revised submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 28/12/2017 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *Patient Information Sheet and Consent Form in English and Malayalam*
7. *CV of Principal Investigator and Co-Principal Investigators*

The following members of the Ethics Committee were present at the meeting held on 16th December, 2017 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
3.	Dr. S S Giri Sankar	LL.M. Ph.D.	Male	Legal Expert	No
4.	Dr. Aneesh V Pillai	BA. LLB (Hons.), LLM, Ph. D, SET (Law)	Male	Legal Expert	No
5	Mr. Satheesh Chandran	MSW, PGDPM	Male	Lay person/ NGO/ Social Scientist	No
6.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
7.	Dr. P. Manickam	BSMS, MSc (Epid).,PhD	Male	Health Science Expert/ Social Scientist	No
8.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
9.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
10.	Dr. V. Raman Kutty	M D, M Phil, M P H	Male	Health Sciences Expert/Clinician	Yes
11.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

SmallSEOTools

PLAGIARISM SCAN REPORT

Words	987	Date	July 29,2019
Characters	6965	Exclude Url	

0%	100%	0	45
Plagiarism	Unique	Plagiarized Sentences	Unique Sentences

Content Checked For Plagiarism

The World Health Organization (WHO) predicts that by 2025, about 3/4th of the estimated 1.2 billion people aged >60 years will reside in developing countries1. 4.6 million new cases of dementia are added every year, and the highest rate of growth is expected in South Asian countries including India. Education attainment is known to protect against dementia. Diet and lifestyle can also influence risk of dementia, and studies suggest that disorders affecting the vascular system, such as hypertension, diabetes mellitus and obesity, increase the risk for dementia, including Alzheimer's disease (AD). There is increasing evidence linking cerebral hypoperfusion and neurodegeneration, specifically in Alzheimer's disease (AD) and vascular dementia (VaD)2. In the Rotterdam study3, cerebral hypoperfusion was demonstrated to be a risk or an aggravating factor in dementia. Hypoperfusion because of microangiopathy, macroangiopathy or cardiac dysfunction can promote or accelerate neurodegeneration, blood-brain barrier disruption and neuroinflammation.4 Diagnostic tools that can provide real-time functional assessment of the cerebrovascular tree can have a significant impact on our understanding of the vascular contribution to neurodegeneration at different stages of cognitive decline. Ultrasound can evaluate the cerebrovascular tree for pathological structure and functional changes contributing to cerebral hypoperfusion. Studies have shown an association between leukoaraiosis and transcranial doppler (TCD) pulsatility index (PI) in several kinds of patients.5 Despite increasing evidence supporting the utility of these methods in detection of microvascular pathology, cerebral hypoperfusion, neurovascular unit dysfunction and disease progression, non-availability for routine use and incomplete standardisation limit their use in daily routine. Studies have evaluated the utility of Middle cerebral artery-Pulsatility index (MCA PI) to differentiate between AD and VaD and have found conflicting results.6 PI has been correlated with severity of cognitive decline in few studies. Studies have also evaluated correlation of PI with decline in cognition. However, correlation of PI with detailed cognitive profile has not been evaluated. In this background, we planned our study to assess whether MCA PI can be used to differentiate between patients with AD and VaD. Also, we propose that increase in PI correlates with severity of cognitive deficit in patients with dementia. REVIEW OF LITERATURE 1. Burden of dementia The prevalence of dementia rapidly increases from ~ 2-3% among those aged 70–75 years to 20–25% among those aged >85 years7. Dementia rates are growing at alarming rate in all regions of the world and are related to population aging. Neurologic conditions, including dementia, were estimated by the Global Burden of Disease 2010 Study as the third leading cause of years lived with disability at global level.8 Dementia modifies survival and increases the risk of death. In a study among Shanghai residents9, mortality risk ratios for AD and VaD, particularly in those over 75 years of age, were found to be similar to the mortality risk ratio for cancer. 2. Alzheimer's dementia Late-onset AD is the most common subtype of age-related dementia, even in developing countries; 60% of all cases of dementia fulfilled the US National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria.1 The amyloid hypothesis has been the most dominant in regards to pathophysiologic process of AD. It states the sequential cleavage of APP leading to formation of Aβ aggregates is responsible for neuronal injury and cognitive decline in AD. Cognitive profile of patients with AD Cognitive symptoms of AD commonly includes deficits in short-term memory, executive and visuospatial dysfunction, and praxis. Several rarer variants of AD with relative preservation of memory have been recognized. Stages of AD Early in the disease course, recent episodic memories are most affected, while memories from the distant past are usually spared. As the disease progresses, all aspects of episodic memory become affected. In contrast to episodic memory, working memory and semantic memory are preserved until later in the disease course. Language disturbance, especially word-finding difficulties, is a common early symptom in AD. Subtle decline in visuospatial skills occurs in the mild dementia stages. Executive dysfunction begins in the predementia stages and, similar to all other cognitive domains, worsens over the disease course. Atypical AD variants Frontal variant of AD is characterized by substantial behavioral or personality changes that are out of proportion to the observed short-term memory loss. Posterior cortical atrophy presents with visuospatial dysfunction often in the form of partial or full Balint syndrome (simultanagnosia, ocular apraxia, and ocular ataxia), partial or full Gerstmann syndrome (acalculia, agraphia, right/left disorientation, and finger agnosia), apperceptive visual agnosia, and environmental disorientation. Patients with AD may also present with early progressive language involvement, most often in the form of logopenic aphasia with pronounced anomic deficits and impaired repetition but preserved grammar and syntax. Findings suggestive of AD pathology include mesial temporal atrophy. Functional brain imaging using single-photon emission computed tomography (SPECT) and PET technologies can be used to identify AD-specific patterns such as temporoparietal

hypoperfusion/hypometabolism in patients with AD. More recently, arterial spin-labeling MRI sequences have been shown to capture perfusion abnormalities. 3. Vascular cognitive impairment and Vascular dementia Vascular dementia (VaD) is recognised as the second most prevalent type of dementia.1 In poststroke vascular cognitive impairment, the cognitive impairment is the immediate and direct consequence of a symptomatic stroke. In nonstroke-related vascular cognitive impairment, the cognitive impairment is the consequence of clinically hard to detect cerebrovascular disease, which may be evident only on neuroimaging with CT or MRI. The term vascular cognitive impairment is intended to encompass all forms of cognitive impairment, not only dementia, and to include all cases where vascular disease contributes to impairment, including in cases where it is not the sole contributor. Vascular cognitive impairment is a frequent contributor to mixed dementia, accompanied by other neuropathologies such as Alzheimer pathology. Diagnostic criteria for Vascular cognitive impairment include clinical or neuroimaging evidence of presence of stroke or small vessel ischemic changes. Neuroimaging is not routinely available in developing countries, which influences the accuracy of VaD detection and the confirmation of cases of mixed dementia.

Sources	Similarity

SmallSEOTools

PLAGIARISM SCAN REPORT

Words	974	Date	July 29,2019
Characters	7028	Exclude Url	

0%	100%	0	43
Plagiarism	Unique	Plagiarized Sentences	Unique Sentences

Content Checked For Plagiarism

Cognitive profile of patients with Vascular dementia Lacunar infarcts have been related to cerebral small vessel disease (SVD), pathologically characterized by lipohyalinosis in end arteries deep in the brain, and both lacunar infarcts and SVD are associated with cognitive impairment and dementia. Studies have documented cognitive impairment in the acute phase as well as in long-term follow-up. Cognitive impairment in patients with lacunar infarcts may be just as frequent and important as motor and sensory sequelae, but may be overlooked. There can be great variety in the spatial distribution and severity of cerebrovascular disease, which determines the neuropsychological profile. Therefore, there is no uniform pattern of neuropsychological impairment in patients with vascular cognitive impairment. A systematic review by Edwards et al. documented that all major cognitive domains were affected in lacunar infarcts. No typical clinical presentation exists for vascular cognitive impairment. Patients with large-territory strokes may have a stepwise decline and focal signs (eg, hemiparesis), while those with cerebral small vessel disease may present with an insidious onset of cognitive slowing with gait disturbance and parkinsonism. Vascular cognitive impairment is associated with relatively greater impairments in executive function and processing speed than in episodic memory for a given level of overall disability. It is important to recognize that some degree of memory impairment is very common in vascular cognitive impairment as well. Diagnosis of Vascular cognitive impairment should not be made based on neuropsychological profile alone. 4. Risk factors for dementia Increasing age is the most consistent risk factor for dementia worldwide. Various genetic and environmental factors, including early-life brain development, body growth, socioeconomic conditions, environmental enrichment, head injury, and cognitive reserve, likely contribute to dementia risk. Illiteracy or low educational achievement has been shown to be a risk factor for dementia. Vascular factors, such as hypertension, dyslipidaemia, hyperinsulinaemia and type 2 diabetes, obesity, subclinical atherosclerosis, and arrhythmias, are associated with greater risk of cognitive impairment and dementia, including AD. Factors that decrease vascular function, such as tobacco use, might further influence cognition in old age. Current smoking, hypertension, AF, IHD, carotid stenosis and elevated Homocysteine levels were found more frequent in patients with Post stroke dementia in study by Khedr et al.10 Control of hypertension and diabetes may help in preventing dementia.11 5. Association between Alzheimer’s dementia and Vascular dementia Chronic hypoperfusion is not only a result of brain tissue loss, but it actively promotes, initiates or accelerates neurodegeneration through multiple mechanisms, including induction of oxidative stress, synaptic dysfunction, tau hyperphosphorylation, amyloid beta (Aβ) accumulation and aggregation, neuronal loss, white matter hyperintensities(WMH), and neuroinflammation. Vascular aging with consequent chronic hypoperfusion may contribute to blood-brain barrier disruption which, according to emerging in vivo imaging evidence, occurs relatively early in life in selected areas, such as hippocampus, thus making individuals prone to memory disturbances. Consensus criteria recommend that the diagnosis of nonstroke vascular cognitive impairment should be based on a pattern of diffuse, severe cerebrovascular disease. In most cases, nonstroke vascular cognitive impairment is caused by subcortical ischemic cerebral small vessel disease, also called Binswanger disease. Understanding the relationship between the location, extent, and severity of the cerebral small vessel disease and the resulting clinical syndromes is still incomplete. Silent brain infarcts and white matter hyperintensities on MRI predict risk for dementia in population-based studies, and silent brain infarcts are associated with presence of dementia in autopsy-based studies, while the relationship of cerebral microbleeds to cognition is less clear. Roher et al.12 documented the presence of major leptomeningeal arterial stenosis in a group of neuropathologically diagnosed AD whose magnitude was correlated with the densities of AD neuropathology lesions and with the degree of atherosclerotic vascular disease of the circle of Willis13. Reduction of resting cerebral blood flow and disturbance of cerebrovascular auto-regulation were observed in the cortex and hippocampus of mice over-expressing amyloid precursor protein (APP)14. As hypothesized by Iadecola, Aβ amyloid could be able to compromise the ability of endothelial cells to produce vasodilatory factors, impairing cerebral auto-regulatory mechanisms to maintain an adequate flow during hypotension and to relatively increase CBF during brain activity15. Recent observations have shown that sporadic

AD is associated with a failure of soluble amyloid-β (Aβ) clearance and that soluble Aβ can exit the brain through vascular and perivascular clearance pathways. Data from 5715 cases from the National Alzheimer's Coordinating Center database16 assessed the correlation between the prevalence of CVD and vascular pathology in a variety of neurodegenerative diseases with dementia severity. The study identified a significantly higher prevalence of vascular pathology and CVD in Alzheimer's disease than any other neurodegenerative diseases causative of dementias, such as α-synucleinopathy, fronto-temporal lobar

dementias (FTLD), and prion disease. Vascular pathology coexisting with AD pathology is thought to act as additional “hits” to the brain thereby lowering the threshold for cognitive impairment in persons with AD pathology. Increased neuritic plaque burden and a higher Braak stages was associated with increased grades of atherosclerosis in both subjects with AD and vascular dementia13. In an autopsy study, the circle of Willis arteries of AD patients exhibited numerous and severe stenosis, which correlated with AD pathology [60]. More recently developed imaging techniques have been used to visualize arterial structures and atherosclerotic plaque burden. A study using positon emission tomography showed an increase in amyloid deposition in patients having both carotid artery occlusions and dementia17. In contrast, examining 200 brains in the Baltimore Longitudinal Study of Aging18 showed no correlation between atherosclerosis and AD pathology. In one study, microscopic infarcts were present in 43% of patients with AD, 62% of patients with vascular dementia, compared to 24% of subjects of normal cognitive ability. In the Religious Orders Study19, microscopic infarcts further add to the likelihood of dementia and cognitive impairment in persons with AD pathology and macroscopic infarcts. The effect of infarcts and AD pathologies was independent and there was no interaction between AD and infarct pathology.

Sources	Similarity

SmallSEOTools

PLAGIARISM SCAN REPORT

Words	970	Date	July 29,2019
Characters	6682	Exclude Url	

2%	98%	1	41
Plagiarism	Unique	Plagiarized Sentences	Unique Sentences

Content Checked For Plagiarism

White matter lesions were significantly related to progression of amyloid deposition in sporadic AD patients20. In addition, WM volume has also been inversely related to AD pathology21 and reduced cerebral autoregulation22. In another study, overall T2 signal prolongation was related to AD pathology and gross infarcts 23. These studies highlight the importance of the relationship between vascular factors, the white matter and neurodegenerative pathologies and how they may be interrelated in the pathogenesis of AD dementia. The underlying pathology causing WMH maybe causally related to AD pathology itself 22. Current findings from the literature suggest that WMH and other white matter changes are complex abnormalities that are important markers of cerebrovascular burden, but may also be related to neurodegenerative pathologies and have independent relationships with cognition. Data from the Memory and Aging Project (MAP) and Religious Order Study (ROS)19 found that about half the subjects whom were clinically-diagnosed with probable AD had mixed pathologies, the most common being AD and infarct pathology. Due to the overlap of pathologies there may not be a single causative pathology for mixed dementia, and even the initiating pathology becomes unclear. Neuropathological examination of brains from participants of the Medical Research Council Cognitive Function and Ageing Study (MRC-CCFAS)24 report 78% with vascular pathology and 70% with AD pathology in this cohort. Overall, there is a striking overlap between AD and vascular pathologies contributing to probable AD and dementia in these community cohorts. Mixed vascular pathology with AD pathology is the most prevalent ahead of dementia with Lewy bodies, and hippocampal sclerosis16, 24. Due to the high prevalence of the vascular pathologies in mixed dementia, prevention and treatment of the vascular component is important to reduce risk of dementia. Interactions between cerebrovascular and Alzheimer pathology seem to be in their combined effects on brain cellular and network function, and not because one disease directly causes the other; however, this observation does not exclude a role for variance in (non-diseased) vascular clearance of Aβ in the pathogenesis of AD. Diabetes mellitus doubles the risk of AD corresponding with an increase in microinfarcts and without a corresponding increase in plaques and tangles25. Higher total cholesterol, LDL concentrations and a history of diabetes is associated with faster cognitive decline in AD26. Additionally, in studies on AD patients the presence of atherosclerosis was related to an increased frequency of neuritic plaques and neurofibrillary tangles27. Furthermore, treatment of vascular risk factors in patients with AD is associated with slower cognitive decline. Studies have shown hypertension is a consistent CVD risk factor for developing stroke and dementia28. However, most clinical–pathological studies suggest that vascular risk factors are related to infarcts rather than AD pathology. Autopsy studies consistently show that vascular pathology, mostly consisting of manifestations of cerebral small vessel disease such as small infarcts, independently predicts the risk of dementia even when accounting for Alzheimer and Lewy body pathology. The burden of cerebrovascular and Alzheimer pathology are considered independent of one another and that effects on the odds of dementia are additive, not multiplicative. Transcranial Doppler in patients with Dementia While neuroimaging remains the most useful diagnostic test to link the presence and severity of cerebrovascular disease with the presence of vascular cognitive impairment, it does not have perfect sensitivity for all clinically relevant cerebrovascular lesions. It is unable to detect microinfarcts, which are infarcts as small as 0.2 mm in diameter that are visible at autopsy in approximately 1/4th of all deceased elderly but in up to half of all deceased elderly patients with dementia. These infarcts fall below the limit of spatial resolution of clinical MRI. Unlike structural imaging, there is no optimal investigative modality to understand the hemodynamic changes coexisting with cSVD. Recently, transcranial ultrasound is increasingly being used to evaluate the hemodynamic changes of the cerebral vessels including microcirculatory disturbances.6 Transcranial Doppler ultrasonography (TCD) is a promising investigative tool which is non-invasive, inexpensive, and mobile without having hazard of radiation exposure. It can indirectly evaluate the functional status of small vessels with a good inter-observer reliability.29 It provides physiologic data such as mean velocity, peak systolic velocity, and end diastolic velocity from intracranial vessels. Among the various TCD parameters, the Gosling's Pulsatility Index (PI) described by Gosling and King30, 31 was found to be the most useful parameter for evaluation of downstream resistance in cerebral vascular bed. It reflects the microvascular resistance and compliance of the small vessels.32, 33 Cerebral small vessel disease can potentially increase downstream resistance in the cerebral circulation resulting from lipohyalinosis and micro-atherosclerosis. This can be reliably evaluated with TCD.5 Previous studies have indicated that TCD derived PI can be a useful tool in detection of small vessel disease (white matter hyper intensities- WMHI) with sensitivity of 70-89% and specificity of 73-86%5. It has a high negative predictive value for diagnosing small vessel disease.9 In study by Xiong et al34, the PI correlated with the volume of white matter changes. Examination of CBF velocity, measured by transcranial Doppler, in participants of the Rotterdam Study showed subjects with a higher CBF velocity were less likely to have dementia35. In keeping with this, another study showed cerebrovascular reactivity was significantly reduced in subjects with AD36. These studies suggest that cerebral hemodynamics may be an important factor in the pathologic process of AD. Whether the relationship between amyloid deposition and CBF is direct or whether CBF decline is a byproduct of a different AD pathophysiologic process needs further study. The majority of studies reported similar Mean Blood flow velocity (MBFV) in AD and VaD groups37-39. Study by Ries et al.40 reported that the multi-infarct dementia group displayed lower MBFV and diastolic flow velocities compared to both control and AD groups. Caamaño et al.41 reported that individuals with AD and multi-infarct dementia displayed reduced systolic and diastolic (as well as mean) flow velocities compared to healthy controls.

Sources	Similarity
(PDF) Ultrasound and dynamic functional imaging in vascular cognitive...Compare text MBFV in AD and VaD groups [42, 48, 55, 56, 58, 60, 62], with the exception of one study, where Ries et al. [63]. reported that the multi-infarct dementia group displayed. lower MBFV and diastolic flow velocities compared to. both control and AD groups. Caamaño et al. https://www.researchgate.net/publication/313507144_Ultrasound_and_dynamic_functional_imaging_in_vascular_cognitive_impairment_and_Alzheimer's_disease	3%

SmallSEOTools

PLAGIARISM SCAN REPORT

Words	788	Date	July 29,2019
Characters	5234	Exclude Url	

8%	92%	3	36
Plagiarism	Unique	Plagiarized Sentences	Unique Sentences

Content Checked For Plagiarism

PI was the most commonly employed measure of vessel resistance and was found to be increased in AD 39, 42-45 and VaD or multi-infarct dementia patients45-47, as compared to healthy controls. Some studies have shown that subjects with VaD have higher pulsatility indices, as compared to controls and AD patients37, 38, 41, 48. In other reports45-47, PI was not significantly different between dementia subtypes. TCD PI and severity of cognitive deficit TCD studies have shown positive correlation between hemodynamic impairment and degree of cognitive deficit suggesting that microvascular damage may contribute to the cognitive changes in the early stage of dementia36. In study by Altmann et al.49, TCD PI values were significantly associated with MMSE, TMT A, and TMT B performances in patients with a lacunar infarct. This study suggested TCD as a possible adjunct tool for early diagnosis of cognitive impairment after stroke. Risk factors and pulsatility index Patients with diabetes are more likely to develop dementia than those without diabetes. Diabetes is an independent risk factor for lacunar infarction, and has been found to be independently associated with a high PI.50 Age, current smoking and mean arterial BP have also been shown to be correlated with PI.51 TCD and US technology as tools to study vascular contributions to dementia are being considered only recently. The technological aspect of US devices has not changed in recent years, but there is a constant development of new analytical tools enabling a better understanding of microvascular effects on blood flow in standardly insonated large arteries. There is a need for a greater application of these tools across the spectrum of neurodegenerative disorders. These tools have greater significance in resource poor countries for early detection and institution of preventive measures. Materials and Methods Patients above 18 years of age attending Neurology, Stroke and Cognitive Neurology services at SCTIMST, with a diagnosis of dementia were included in the study, and their eligibility was assessed as per inclusion and exclusion criteria. All the patients were recruited after written informed consent from patient/care giver. Study was done after obtaining approval from the Institutional Ethics Committee. Sample size: Sample size determination was done and the number required for this study using a correlation coefficient 0.5 with a significance level of 0.05 and a power of 90% was 38 patients. Hence a sample size of a total of 50 patients was decided. Inclusion criteria: Patients attending Neurology, Stroke or Cognitive Neurology services, SCTIMST with diagnosis of Alzheimer's dementia (as per NINCDS-ARDRA criteria) or Vascular dementia (as per VASCOG criteria) Exclusion criteria: 1. Patients with modified Rankin score (mRS) >3. 2. Patients with evidence for large vessel atherosclerosis (>50% stenosis of the extra or intracranial vessels with any of the imaging modalities) 3. Patients with large artery territory infarcts or major ICH at any point of time. Methodology: Patients attending Neurology, Stroke or Cognitive Neurology services at SCTIMST were taken up in the study after applying the selection criteria. Information regarding clinical, demographic & risk factors was collected. All the patients underwent TCD evaluation (Nicolet® Sonara® digital TCD system) using 2 Hz probe for every patient. TCD was done on both sides through the temporal window on the MCA. The depth and angle of insonation giving the highest mean flow velocity was selected. For each artery, the mean, systolic, and diastolic velocities was measured, and the Gosling pulsatility index (PI) was calculated automatically as (systolic velocity - diastolic velocity)/mean velocity. Then a mean MCA PI was calculated by averaging bilateral MCA PI. If the subject only had good temporal window on one side, then unilateral MCA PI was considered as mean MCA PI. An average over at least 10 heart beats was applied in order to have a representative value of the TCD measures. Neuropsychology assessment was performed in detail by a trained Neuropsychologist of the Institute using a formatted questionnaire. Detailed cognitive examination included MMSE, Addenbrooke cognitive examination, Wisconsin card sorting test, Trail making test A and B, RAVLT and patients also underwent evaluation by HADS questionnaire for anxiety and depression. Statistical methods: The data was entered on to a spreadsheet and was analysed with SPSS version 25 software(SPSS Inc,Illinois,Chicago). Numerical variables were summarized as means and standard deviations. Univariate analysis was undertaken to examine relationship of various factors. A p value less than 0.05 was considered statistically significant. Crude odds ratio with 95% confidence interval have been reported. Chi square test/ Fisher's exact test was applied to evaluate statistical significance. Multivariate analysis/ logistic regression was used to evaluate the independent and joint effect of the variable of interest on the outcome Ethical considerations This registry has the approval of the Institutional Ethics Committee and written informed consent was obtained from the patient or caregiver.

Sources	Similarity
OSMF | Standard Deviation (19 views)3. 2. Patients with evidence for large vessel atherosclerosis (>50% stenosis of the extra or intracranial vessels with any of the imaging modalities) 3. Patients with large artery territory infarcts or major ICH at any point of time. Methodology: Patients attending Neurology, Stroke or Cognitive Neurology services at SCTIMST were taken up in the study after applying the selection criteria. Information regarding clinical, demographic & risk factors was collected. All the patients underwent TCD evaluation (Nicolet® Sonara® digital TCD system) using 2 Hz probe for every patient. TCD was done on both sides through the temporal window on the MCA. The depth and angle of insonation giving the highest mean flow velocity was selected. For each artery, the mean, systolic, and diastolic velocities was measured, and the Gosling pulsatility index (PI) was calculated automatically as (systolic velocity - diastolic velocity)/mean velocity. Then a mean MCA PI was calculated by averaging bilateral MCA PI. If the subject only had good temporal window on one side, then unilateral MCA PI was considered as mean MCA PI. An average over at least 10 heart beats was applied in order to have a representative value of the TCD measures. Neuropsychology assessment was performed in detail by a trained Neuropsychologist of the Institute using a formatted questionnaire. Detailed cognitive examination included MMSE, Addenbrooke cognitive examination, Wisconsin card sorting test, Trail making test A and B, RAVLT and patients also underwent evaluation by HADS questionnaire for anxiety and depression. Statistical methods: The data was entered on to a spreadsheet and was analysed with SPSS version 25 software(SPSS Inc,Illinois,Chicago). Numerical variables were summarized as means and standard deviations. Univariate analysis was undertaken to examine relationship of various factors. A p value less than 0.05 was considered statistically significant. Crude odds ratio with 95% confidence interval have been reported. Chi square test/ Fisher's exact test was applied to evaluate statistical significance. Multivariate analysis/ logistic regression was used to evaluate the independent and joint effect of the variable of interest on the outcome Ethical considerations This registry has the approval of the Institutional Ethics Committee and written informed consent was obtained from the patient or caregiver. ">Compare text the study was done after obtaining approval from the institutional ethics committee. the subjects of the study were as follows: group 1 (grade i osmf): 15the patient was then asked to attend the next morning after an overnight fast, to avoid any dietary influence on the serum beta carotene level. https://www.scribd.com/document/86065563/OSMF	5%
(PDF) The value of transcranial Doppler derived pulsatility index for...3. 2. Patients with evidence for large vessel atherosclerosis (>50% stenosis of the extra or intracranial vessels with any of the imaging modalities) 3. Patients with large artery territory infarcts or major ICH at any point of time. Methodology: Patients attending Neurology, Stroke or Cognitive Neurology services at SCTIMST were taken up in the study after applying the selection criteria. Information regarding clinical, demographic & risk factors was collected. All the patients underwent TCD evaluation (Nicolet® Sonara® digital TCD system) using 2 Hz probe for every patient. TCD was done on both sides through the temporal window on the MCA. The depth and angle of insonation giving the highest mean flow velocity was selected. For each artery, the mean, systolic, and diastolic velocities was measured, and the Gosling pulsatility index (PI) was calculated automatically as (systolic velocity - diastolic velocity)/mean velocity. Then a mean MCA PI was calculated by averaging bilateral MCA PI. If the subject only had good temporal window on one side, then unilateral MCA PI was	

MCA PI was calculated by averaging bilateral MCA PI. If the subject only had good temporal window on one side, then unilateral MCA PI was considered as mean MCA PI. An average over at least 10 heart beats was applied in order to have a representative value of the TCD measures. Neuropsychology assessment was performed in detail by a trained Neuropsychologist of the Institute using a formatted questionnaire. Detailed cognitive examination included MMSE, Addenbrooke cognitive examination, Wisconsin card sorting test, Trail making test A and B, RAVLT and patients also underwent evaluation by HADS questionnaire for anxiety and depression. Statistical methods: The data was entered on to a spreadsheet and was analysed with SPSS version 25 software(SPSS Inc,Illinois,Chicago). Numerical variables were summarized as means and standard deviations. Univariate analysis was undertaken to examine relationship of various factors. A p value less than 0.05 was considered statistically significant. Crude odds ratio with 95% confidence interval have been reported. Chi square test/ Fisher's exact test was applied to evaluate statistical significance. Multivariate analysis/ logistic regression was used to evaluate the independent and joint effect of the variable of interest on the outcome Ethical considerations This registry has the approval of the Institutional Ethics Committee and written informed consent was obtained from the patient or caregiver. ">Compare text the depth and angle of insonation giving the. highest mean flow velocity was selected.among all ultrasound parameters the highest auc (areas under the receiver operating characteristic curve) were documented for mca-pi (auc = 0.82, 95% ci = 0.68−0.95, p < 0.001) and mean cca diameter... https://www.researchgate.net/publication/273520185_The_value_of_transcranial_Doppler_derived_pulsatility_index_for_diagnosing_cerebral_small-vessel_disease	4%
Prevalence of impacted and transmigrated canine teeth in a Cypriote...3. 2. Patients with evidence for large vessel atherosclerosis (>50% stenosis of the extra or intracranial vessels with any of the imaging modalities) 3. Patients with large artery territory infarcts or major ICH at any point of time. Methodology: Patients attending Neurology, Stroke or Cognitive Neurology services at SCTIMST were taken up in the study after applying the selection criteria. Information regarding clinical, demographic & risk factors was collected. All the patients underwent TCD evaluation (Nicolet® Sonara® digital TCD system) using 2 Hz probe for every patient. TCD was done on both sides through the temporal window on the MCA. The depth and angle of insonation giving the highest mean flow velocity was selected. For each artery, the mean, systolic, and diastolic velocities was measured, and the Gosling pulsatility index (PI) was calculated automatically as (systolic velocity - diastolic velocity)/mean velocity. Then a mean MCA PI was calculated by averaging bilateral MCA PI. If the subject only had good temporal window on one side, then unilateral MCA PI was considered as mean MCA PI. An average over at least 10 heart beats was applied in order to have a representative value of the TCD measures. Neuropsychology assessment was performed in detail by a trained Neuropsychologist of the Institute using a formatted questionnaire. Detailed cognitive examination included MMSE, Addenbrooke cognitive examination, Wisconsin card sorting test, Trail making test A and B, RAVLT and patients also underwent evaluation by HADS questionnaire for anxiety and depression. Statistical methods: The data was entered on to a spreadsheet and was analysed with SPSS version 25 software(SPSS Inc,Illinois,Chicago). Numerical variables were summarized as means and standard deviations. Univariate analysis was undertaken to examine relationship of various factors. A p value less than 0.05 was considered statistically significant. Crude odds ratio with 95% confidence interval have been reported. Chi square test/ Fisher's exact test was applied to evaluate statistical significance. Multivariate analysis/ logistic regression was used to evaluate the independent and joint effect of the variable of interest on the outcome Ethical considerations This registry has the approval of the Institutional Ethics Committee and written informed consent was obtained from the patient or caregiver. ">Compare text a p-value less than 0.05 was considered statistically significant. impacted and transmigrated canine teeth were found in 16 (3.53%) and two (0.44%) patients in the study groupan impacted canine was considered to be transmigrated when at least part of its length had crossed the midline. https://bmcresnotes.biomedcentral.com/articles/10.1186/1756-0500-7-346	3%

SmallSEOTools

PLAGIARISM SCAN REPORT

Words	932	Date	July 29,2019
Characters	6178	Exclude Url	

0%	100%	0	48
Plagiarism	Unique	Plagiarized Sentences	Unique Sentences

Content Checked For Plagiarism

38 patients with dementia (25 AD, 13 VaD) were recruited for the study. Patients with significant major vessel stenosis or large strategic infarct were excluded. Mean age was 69.63 years, which was similar to other studies evaluating patients with dementia.39, 40, 45 64.1% patients had hypertension and 55.4% had diabetes mellitus in our study. Patients with VaD were more likely to be hypertensive and had more white matter ischemic changes. Lacunar stroke and white matter hyperintensities are associated with a hypertensive arteriopathy, which was earlier considered primarily responsible for Vascular dementia. We found that hypertensive patients were older at disease onset and were more likely to have associated diabetes mellitus. Diabetic patients were also older at disease onset. Age, hypertension and diabetes have been independently identified as risk factors for dementia. Long standing hypertension predisposes to subcortical white matter disease, and can cause cognitive impairment.54 Mean MCA PI significantly correlated with age of the patient. Mean MCA PI was significantly higher in hypertensive and diabetic patients. Hypertensive and diabetic patients also had higher Fazeka grade. After detailed cognitive testing, few parameters could be assessed uniformly in all patients, including ACE and MMSE. Detailed analysis of cognitive domains evaluated in ACE and MMSE was done. MMSE is usually considered a screening test and cannot detect mild cognitive impairment or single domain impairment.55For evaluating patients with Vascular cognitive impairment, ACE has been shown to have better sensitivity and specificity.56 In our study, MMSE and ACE scores showed significant correlation. Correlation between MMSE and ACE scores has been reported earlier. 57 Patients with AD and VaD did not differ in their MMSE and ACE scores. Patients with AD had significantly lower scores on verbal immediate memory, and also noted to have lower scores on verbal delayed and visual immediate memory, although it was not significant. In an earlier review, no significant difference between neuropsychological profile has been found in patients with AD and VaD, except for worse executive functioning, verbal fluency and motor performance in VaD58. In another study, memory has been found to be more severely impaired in early stages of AD, with the difference getting diluted as disease progresses.59 Both AD and VaD had similar mean MCA PI values in our study, and it did not help in differentiating between them. Similar conclusion has been reached in other studies45-47, however few studies have reported higher PI in patients with VaD 37, 38. The response to vasodilatory stimuli, such as CO2 or acetazolamide, has been used to evaluate and quantify cerebral vasoreactivity. Initial study assessed cerebral vasoreactivity in patients with dementia, and had found reduced vasodilatory reserve in patients with VaD as compared to AD60. This finding also was challenged in recent study, which found that vasoreactivity cannot be used to differentiate between dementia subtypes47. Mean MCA PI did not show significant correlation with MMSE scores or ACE scores. Studies have reported varying results on such correlation61. Although insignificant, ACE tended to have a negative correlation with mean MCA PI. In study by Silvestrini et al36, cognitive decline was associated with increase in MCA PI. Impaired VR has been found to be associated with worse evolution of cognitive function in AD patients.62, 63 In a cohort of patients with asymptomatic carotid stenosis, vasoreactivity was shown to be strong predictor of cognitive decline64. TCD evaluation for vasoreactivity was not done in our study. Mean MCA PI showed significant correlation with depression as per HADS-depression score (r=0.495, p=0.016). This significance was mostly for patients with VaD (r=0.762, p=0.017) than with AD (r=0.151, p=0.607). The term “Vascular depression” has been suggested for late life depression with white matter lesions65, 66. Patients with Vascular depression are prone for dementia, if risk factors are not adequately controlled. Brain tissue pulsatility, as measured by tissue pulsatility imaging, has been found to be significantly higher in depressed patients as compared to controls.67 Mean MCA PI showed significant correlation with White matter ischemic changes, as per Fazeka’s grading (Pearson’s correlation co-efficient=0.355, p=0.043). Previous studies have indicated that TCD derived PI can be a useful tool in detection of small vessel disease (white matter hyperintensities- WMHI) with sensitivity of 70-89% and specificity of 73-86%5. It has a high negative predictive value for diagnosing small vessel disease.68 In study by Mok et al, MCA PI correlated significantly with WMC volume, independent of age, sex, and vascular risk factors. However, MCA PI was found to have low specificity for this association.69 In study by Xiong et al, the PI correlated with the volume of white matter changes.34 Previous studies have reported that age70, 71, diabetes72, hypertension73 and vascular dementia46 were associated with increase in PI. On univariate analysis, age, hypertension and diabetes.was associated with higher mean MCA PI. Diabetes mellitus was found to be the sole significant predictor for mean MCA PI >1.3 (OR=12.464, p=0.011) after adjusting for age, gender and hypertension. 1. This is one of the first study to assess the association between Pulsatility index and detailed cognitive profile. Even though previous studies have studied association between MMSE and PI, executive functions are poorly covered in MMSE and may

not detect early executive dysunction. 2. Since we have ruled out significant proximal vessel disease with vessel imaging, confounding effect of co-existing large vessel disease on the TCD parameters could be avoided. 1. The major limitation of the study was the small sample size. 2. This was a cross-sectional study and follow-up changes in PI and cognitive performance was not assessed, which could give a better insight into relation between PI and severity of cognitive deficit. 3. Controls were not used for comparison

Sources	Similarity

SmallSEOTools

PLAGIARISM SCAN REPORT

Words	103	Date	July 29,2019
Characters	725	Exclude Url	

0%	100%	0	5
Plagiarism	Unique	Plagiarized Sentences	Unique Sentences

Content Checked For Plagiarism

1. There was no difference in MCA-Pulsatility Index between patients with AD and VaD, however MCA-PI correlated with the presence of hypertension and diabetes mellitus (irrespective of the clinical type of dementia), probably reflecting their etiopathological role in microcirculatory disturbances. 2. We did not find any correlation between elevated mean MCA PI and MMSE, ACE and cognitive subtests. 3. Elevated mean MCA PI was significantly associated with higher scores of depression, as per HADS-depression scoring. 4. There was significant correlation between mean MCA PI and presence of white matter ischemic changes (Leukoaraiosis) indicating presence of microcirculatory disturbances along with white matter disease.

Sources	Similarity