Original Article

Demographic Features and Neuropsychological Correlates in a Cohort of 200 Patients with Vascular Cognitive Decline Due to Cerebral Small Vessel Disease

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ABSTRACT

Introduction: Vascular dementia is the second most common form of dementia and is potentially reversible. Small vessel disease (SVD) closely mimics degenerative dementia in view of its sub-acute onset and progressive course. Therefore, unlike large vessel disease, Hachinski Ischemic scale score may not always reflect vascular cognitive decline resulting in diagnostic and therapeutic confusions. Therefore, there is a need for detailed neuropsychological assessment for various cognitive domains for early identification of vascular cognitive decline as it carries a very good long term prognosis for cognitive morbidity, unlike degenerative dementias. **Patients and Methods:** This prospective study involves thorough domain based neuropsychological assessment of patients with a radiological diagnosis of SVD involving the following parameters-digit forward and backward, category fluency, color trails, stick test, logical memory test, and bender gestalt test. Magnetic resonance imaging scans done using 3-tesla machines and SVD graded using Fazekas visual scale. **Results:** The mean Hachinskis score was less sensitive for differentiating vascular dementia from degenerative dementia. However, the domain based neuropsychological scores were highly sensitive showing statistically significant impairment in all 6 domains tested and compared with Fazekas 1-3 grades in imaging. **Discussion and Conclusion:** This study aimed at establishing an early diagnosis of vascular mild cognitive impairment using domain wise neuropsychological testing and correlating it with radiological scores. Hachinskis score is more sensitive for large vessel disease in view of acute onset and step-like progression as against steady progression in SVD. However, domain-wise testing was highly sensitive in identifying early cognitive impairment in patients with SVD, and early therapeutic interventions are highly rewarding.

Key words: *Fazekas score, neuropsychology, small vessel disease, vascular cognitive decline*

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INTRODUCTION

Vascular dementia is the most common form of dementia second only to Alzheimer's dementia (AD).[1] The prevalence of vascular dementia increases linearly with age and varies greatly from country to country, ranging from 1.2% to 4.2% of people over 65-year-old but more so in the Asian countries.[1,2] The incidence of vascular dementia is higher in the developing countries including India because of the increased prevalence of specific risk factors contributing to vascular dementia such as advanced age, hypertension, diabetes, smoking, sedentary lifestyle, hyperhomocysteinemia, hyperfibrinogenemia, and conditions causing brain hypoperfusion such as obstructive sleep apnea, congestive heart failure, cardiac arrhythmias, and orthostatic hypotension.

In India, the prevalence of vascular dementia is about 31.9/1000 population.[2] Unlike other dementias, vascular dementia is potentially reversible, and early diagnosis and management is of profound importance.[3] Cerebral small vessel disease (SVD) is the main cause for the vascular cognitive decline and the lesions associated with cerebral SVD are present in >40% of the patients with vascular dementia. Early diagnosis and treatment of this condition can potentially improve the cognitive loss as well as prevent further deterioration.[4-6] The main pattern of cognitive decline seen in vascular cognitive impairment (VCI) due to cerebral SVD involves the decline in the information processing speed, executive dysfunction, and impairment in working memory. These manifestations probably result from ischemic interruption of parallel circuits from the prefrontal cortex to the basal ganglia and corresponding thalamocortical connections interrupting the central cholinergic pathway.[6,7] Executive function refers to those higher cognitive processes by which performance is optimized in situations requiring the simultaneous operation of several cognitive processes. Usually, the patients with VCI due to SVD have difficulty in multitasking, a common feature associated with normal aging along with apathy, disinterest, poor attention, and often irritability. Therefore, executive skills which are used to construct effective plans of action are affected most in SVD and have to be distinguished from the benign forgetfulness and executive dysfunction associated with normal aging. Executive dysfunction is mainly characterized by deficits in set shifting, verbal fluency, abstract problem solving, and attention. Decreased information processing speed might be detectable even in the initial stages of the disease. These patients also have selective impairment of the working memory and judgment owing to disruption the fronto-subcortical circuits. Patients may need to be repeated instructions to complete tasks, and they may become distracted from the same too. Due to poor attention and impaired working memory new verbal and visual learning is usually affected.[7-9] Mental and motor slowing can also be seen in patients with cerebral SVD.[10] Because of involvement of specific neuropsychological domains, neuropsychological tests are designed to assess frontal-subcortical functions which will include tailored tests such as the digit forward and backward test, trail making tests to assess attention and working memory. The category fluency test for fund of knowledge or generativity, the digit symbol substitution test to assess focused attention and performance intelligence quotient, the stick test to assess visual recall and working memory, the passage or story telling test for verbal recall and learning as well the bender gestalt test to determine organicity. Executive and activation functions are frequently assessed using timed tests with a variety of set shifting, mental flexibility, and response inhibition tasks. Memory deficits observed in SVD are distinct from those observed in other pathologies such as mild cognitive impairment and AD.

Working memory performance requires an ability to hold, manipulate, and quickly access information that is dependent on mental flexibility and speed. The mediation effect of executive functions on verbal and visual memory performance of SVD patients is already described. Distinctive patterns can be observed in relation to memory impairment. Ability to store information is mainly dependent on the limbic and hippocampal structures, while retrieval and short-term memory capacities are more related with the integrity of frontal-subcortical structures and temporoparietal regions, respectively. In SVD patients deficit is characterized by difficulty in recalling information that improves in the presence of cues.[8,9] Comparing patients with initial dementia, Kertesz, and Clydesdale found that patients with periventricular hyperintensities performed worse on comprehension and attention tasks compared to those with no hyperintensities, who showed worse performances on memory and conceptualization tasks. Specific tests are thus required to be designed to look for impairment in the executive function rather than any other domain.[7,11]

Even though the involvement of the subcortical white matter is mostly due to the arteriolosclerosis of the deep penetrating arteries supplying the white matter very few studies have been carried out in the Asian population which is the hub for noncommunicable diseases such as diabetes, hypertension, and dyslipidemia which are potential risk factors for development of cerebral SVD. This study was done to examine the prevalence of risk factors, demographic profiles, and cognitive deficits attributable to vascular cognitive decline due to cerebral SVD and to elucidate their relationship with

the lesion load seen on imaging in an Indian tertiary health care setting.

PATIENTS AND METHODS

The study was designed as a prospective one spanning over 3½ years duration. Patients were recruited from the neurology outpatient department and geriatric clinic and services from a Tertiary Institute in South India. Ethical clearance was obtained from the Institutional Ethics Committee, and informed consent was obtained from the patient wherever possible or from a responsible bystander as required when the patient was not in a position to consent. Inclusion criteria included right-handed adults with radiological evidence of cerebral SVD in the form of periventricular white matter hyperintensities, lacunes, and microbleeds in isolation or in combination. Patients with subcortical infarction >1.5 cm diameter (not qualifying as a lacune), cortical infarction of any size, any cardiac source of embolism, other secondary dementias, a large-vessel cerebrovascular disease with carotid or vertebral artery stenosis >50% and patients with psychiatric or neurological illness involving intracranial structures were excluded from the study. As the patients have impaired executive functioning, working memory impairment and slowed information processing time, specific neuropsychological tests to evaluate the same was identified and utilized. Neuropsychological tests applied are as follows:

1. Digit forward and backward — Digit repetition forwards and backward is tested by predesigned numbers which are arranged in the ascending order of complexity. Numbers of digits correctly recalled are noted. Digit backward also assesses the attention and working memory component as well.
2. Category fluency — Test patients asked to generate as many names of animals as possible in 1 min which helps in assessment of the verbal fluency.
3. Color trails — Color trails A and B for focused attention, set shifting, and working memory. Color trails 1 focuses on number sequence and color trails 2 consists of sequencing and shifting colors.
4. Stick test — For spatial orientation and memory. (Immediate and delayed recall). Tested by asking the patient to represent the same set of designs presented to them earlier using 5 small sticks. This helps to assess attention and visual memory.
5. Logical memory test or story memory test (immediate and delayed recall) during which patients are asked to recall the story, presented to them earlier for assessment of verbal memory.
6. Bender Gestalt test is used to detect deficits in planning, perception and response inhibition by set pattern of testing.

Magnetic resonance imaging scans were done at National Institute of Mental Health and Neurosciences in 3 tesla (Phillips magnetic resonance [MR] scanne-Achieva, Philips Health Care, Best, The Netherlands) and 1.5 tesla (Magnetom Vision-Plus, Superconducting System - Siemens AG, Erlangen, Germany) MR scanners. Patients with features of cerebral SVD in MRI as described before were identified and recruited after a detailed history and thorough clinical examination. Fazekas visual scale for assessment of the severity of deep white matter hyperintensities (WMH) was applied as follows: 0 - No or a single punctate WMH lesion, 1 - Multiple punctate lesions, 2 - Beginning confluence of lesions, 3 - Large confluent lesions, and correlated with the neuropsychological assessment scores[12] [Figure 1].

Details of modified mini-mental status examination (MMSE) for the Indian population known as the Hindi mental status examination (HMSE) was utilized and the modified Hachinski Ischemic Scale (HIS) score was also recorded.[13] Correlation of imaging and neuropsychological data with clinical features and co-morbidities was done using standard statistical tools.
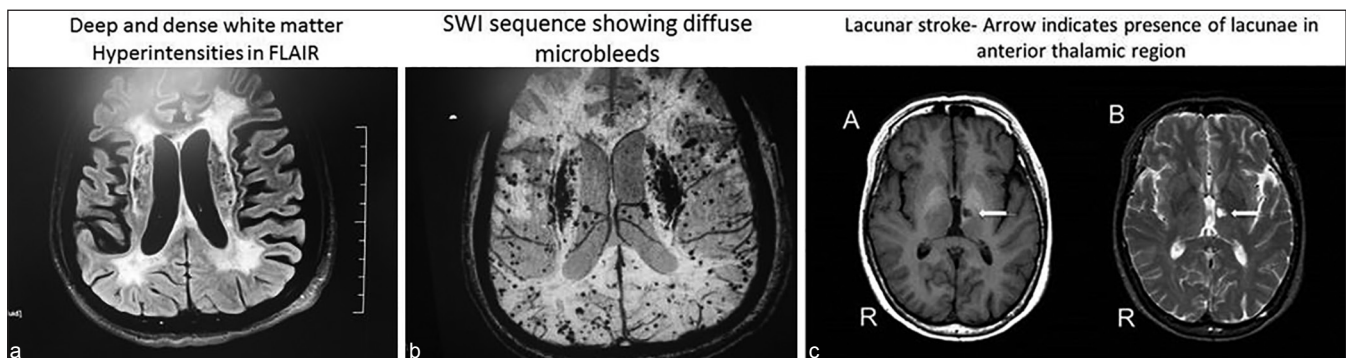

Figure 1: Various lesions seen in magnetic resonance imaging in cerebral small vessel disease. (a) Deep and dense white matter hyperintensities in fluid-attenuated inversion recovery. (b) SWI sequence showing diffuse microbleeds. (c) Lacunar stroke: White arrows indicate presence of lacune in anterior thalamic region in axial MR images in the following sequences - A.FLAIR(Fluid Attenuation Inversion Recovery) sequence of MRI. B. T2 weighted sequence. R indicates Right side of the patient

RESULTS

Of the 200 patients recruited, the mean age was 65.69 ± 8.02 years implicating that majority of the patients belonged to the geriatric age group. 39% of the patients were unemployed, 26% employed, and 35.1% were retired from service. Sixty-two percent of the patients were nonvegetarians. The mean HMSE Score is 23.27 ± 5.11 suggesting that majority of the patients were not severely impaired. It also shows that HMSE is not sensitive enough to pick up subtle changes in subcortical dementias due to a lesser number of tests to assess executive dysfunction, a hallmark of dementia due to SVD. The mean Hachinskis Ischemic score is 3.95 ± 1.91 indicating cognitive decline but not correlating with etiology. The male to female ratio is 155:45. 45.3% of the study population were smokers. All of them were males (70 patients). 11.4% of the patients are chronic alcoholics.7% of the patients had a history of hypothyroidism. More than one-third of the patients (34.5%) have a history of ischemic heart disease, and 1.5% has the coexisting chronic renal disease [Figure 2]. Eight percent of the patients had HIS score ≥7, 20% of the patients had an HIS of 4 followed by 17.9% having a score of 6 which was definitive of the cognitive decline due to the vascular cause by SVD.

Mean HMSE score is 23.27 ± 5.11 with 44.3% having HMSE score <24. The mean score for digit forward and backward tests are 6.25 and 3.77 respectively. Majority of the patients have a digit forward score of 6 (27%) and a digit backward score of 4 (43.8%). Abnormal total digit forward and digit backward score was observed in 5.5% of patients whose scores were below the 15th percentile. Mean category fluency score was 12 and 13% of these patients had a score below the 15th percentile of normal values. In color trails 1, scores <15th percentile was seen in 18.4% of the patients (55 patients) whereas scores <40th percentile seen in 52% of the patients. In color trails 2, scores <15th percentile
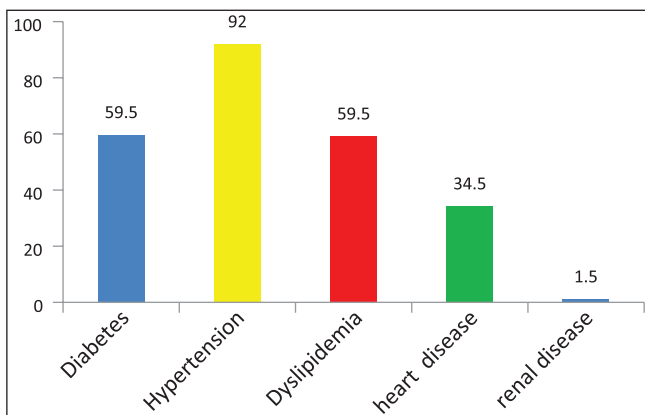
seen in 24.4% and <40th percentile seen in 62%. Ninety percent of the patients had a score <50th percentile in the normal range. The mean bender gestalt score was 109.8% and 56% of the patients had abnormal performance in the test. In passage test, immediate recalls for 25.5% of the patient population scores were below the 15th percentile. In delayed recall assessment of passage test, score <15th percentile was seen in 58.5% of patients. A significant difference ($P < 0.001$) was observed in all the six neuropsychological tests between Grade 1 versus Grade 2, Grade 2 versus Grade 3 and between Grade 1 versus Grade 3 Fazekas scoring. The relationship of HMSE score with Fazekas score is described in Table 1.

DISCUSSION

This study has tried to explore the different aspects of vascular cognitive decline due to cerebral SVD in the Indian scenario. The rapid change in lifestyle and increase in the prevalence of vascular risk factors such as diabetes, hypertension, and dyslipidemia might increase the burden of vascular cognitive decline in India in the coming future and contribute heavily to the disability-adjusted life years.

Our study identified that aging constituted an important risk factor as majority of the patients were in the geriatric age group. The various age-related changes in the vessel wall vasculature like fibrinoid necrosis and hyalinosis associated with aging tends to affect the smooth muscle walls of the arterioles along with other age and lifestyle related risk factors such as diabetes mellitus, hypertension, and dyslipidemia resulting increased SVD lesion load contributing to cognitive decline. This study is in line with the previous study by Chandra *et al.* that implicated hypertension as a major contributor followed by smoking and dyslipidemia.[12] Our study also showed a predilection for aged males than aged females for vascular cognitive decline as well as smoking as a risk factor was observed in about half of the population (45.3%). Chronic alcohol abuse which is another important contributor was observed in more than 10% of the population (11.4%). Our study thus reveals a trend towards continuous smoking and alcoholism in the elderly population co-morbidity related to other systems as well.

Figure 2: Percentage of associated comorbidities in cerebral small vessel disease patient population

Table 1: Relation between Fazekas score and Hindi mental status examination scores

Fazekas score	Number	Percentages	Mean HMSE scores
Grade 1	51	25%	27.46
Grade 2	93	46.5%	23.88
Grade 3	57	28.5%	18.70

More than one-third of the patients (34.5%) had a history of ischemic heart disease and 1.5% had a coexisting chronic renal disease which corroborates with the Fischer's rule of a single cerebral vessel occlusion being associated with two coronary arterial and three peripheral arterial occlusions.

The HMSE scores were normal for 55.7% of the population indicating that HMSE is not able to detect subtle neuropsychological abnormalities making the utilization of specific tests for assessment of executive and memory domains an important prerequisite while studying VCI. A study by Garrett *et al.* looking at the neuropsychological profile of vascular dementia found, higher mean MMSE score 22.2 ± 1.4.[13-15]

Attention assessed by digit forward and the backward test was impaired in more than 5% of the population who had a score below the 15th percentile among normal age and gender matched controls. Verbal fluency assessed by category fluency was abnormal in 13% of the individuals making it a better alternative than digit forward and backward test in uneducated patients with disorders of peripheral senses. Color trail 2 was important as it could pick up even subtle problems with attention and working memory-related circuitry as more than 90% of the patients had scores below the 50th percentile of normal though only scores <50th percentile seen in <40% of the patients. This is corroborative with the study by McGuinness *et al.* which demonstrates problems in the attentional network with color trails in vascular dementia.[15]

The mean bender gestalt score was abnormal in 56% of the patients which corroborated the work by Alexopoulos, *et al.*, who also found similar deficits but in a lesser number of patient population.[16] This study was also consistent with the earlier study by Graham *et al.* With more than half of the patients having deficits in delayed recall of the passage thereby indicating deficits in verbal recall and deficits in speed of verbal processing.[17]

In our study, significant difference ($P < 0.001$)was observed in all the six neuropsychological tests between Grade 1 versus Grade 2, Grade 2 versus Grade 3, and between Grade 1 versus Grade 3 Fazekas scoring was observed corroborative with Yeonwook *et al.* study which had made similar observation with regard to frontal-subcortical impairment in vascular dementia when compared to AD.[14] Schmidt *et al.* also had found that severity of cognitive dysfunction is related to white matter lesion load in imaging whereas Rockwood *et al.* has identified that patients with VCI, who do not have lesions on neuroimaging can have a particularly poor prognosis may be due to yet undetected underlying degenerative pathology.[13,17-19]

Unlike other degenerative dementias, vascular dementia is potentially treatable, and early detection is often helpful in this regard to initiate early treatment and alternative strategies for health promotion while also providing rehabilitative services to those afflicted with increased severity of the disease.

CONCLUSION

Hypertension is the most common risk factor for vascular dementia and the total white matter score in MRI is an important biomarker for the severity of VCI due to SVD. Domain wise neuropsychological testing is mandatory in all patients with radiological evidence of cerebral SVD to detect early cognitive decline and initiate disease-modifying treatment strategies. We acknowledge that our findings are similar to those in previous studies and emphasize the need to control hypertension, the need for a well-balanced diet, proper control of blood sugars, maintaining high level of cognitive function by attempting new learning like music, language, instruments and also remaining intellectually active, and routine neuropsychological assessment in the community to identify subtle changes and manage this potentially treatable cause of dementia.

Conflicts of interest
There are no conflicts of interest.

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