Cognitive Profile of Large-Vessel Vascular Dementia—An Observational Study from a Tertiary Care Center in Kolkata

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Abstract

Introduction   Vascular dementia is the second leading cause of dementia worldwide. Its heterogenous presentation along with potential for reversibility at earlier stages makes it unique among all dementias.

Objectives   We aimed to study the cognitive dysfunction in large-vessel vascular dementia. Second, we tried to study the cognitive dysfunction in large-vessel vascular dementia as per the arterial territory involvement. Additionally, we also tried to study the contribution of hemispheric involvement to the dementia severity as evidenced by clinical dementia rating (CDR) scale.

Materials and Methods   We recruited 28 patients of large-vessel vascular dementia and categorized them on the basis of the arterial territories and hemisphere involved. The groups were later studied for the type of cognitive and behavioral dysfunctions as well as the dementia severity.

Results   Among 28 patients of large-vessel vascular dementia, attention (100%), executive function (100%), and behavior (100%) were more impaired in anterior cerebral artery territory infarcts ($p < 0.05$). Language (53.8%) and memory (53.8%) were more impaired in middle cerebral artery territory infarcts, while visuoperceptual (33.3%) domains were more impaired in posterior cerebral artery territory infarcts ($p > 0.05$). The mean CDR was lower in patients of right-sided lesions (1.292) than in those with left-sided (1.750) or bilateral lesions (2.000).

Keywords
► age
► behavioral
► vascular dementia

Conclusion   Different arterial territory lesions have different patterns of cognitive impairment in large-vessel vascular dementia. The dementia severity is less in right-sided lesions when compared with left-sided or bilateral lesions.

Introduction

Vascular dementia is the second most common cause of dementia worldwide, surpassed only by Alzheimer's disease. Its heterogeneous pathology and clinical presentation contribute to a unique identity among its counterparts, thus, need for different diagnostic criteria and approaches. The disease affects a large proportion of the elderly population.[1,2] Notably, despite its heterogeneous nature, it remains a foremost preventable cause of cognitive impairment if diagnosed early.

Vascular cognitive impairment, a relatively newer term, is used[3] to denote cognitive impairments that occur due to a cerebrovascular cause, ranging from mild cognitive impairment stage to vascular dementia. Predominantly, it comprises cerebral small-vessel disease, large-vessel disease, or a combination of both.[2,4–6] Cognitive dysfunction after a stroke occurs in approximately two-thirds of the patients, which may be followed by complete or incomplete recovery.[3] The pattern and severity of cognitive dysfunction often depend on the location of the lesions within the brain. Different clinical manifestations in the large-vessel disease depend on the arterial territory involved; consequently, multiple domains may be involved due to arterial territory lesions in different cortical and subcortical locations.[3,7–9] For instance, memory impairment is more often lesion specific, that is, involvement of the medial temporal lobes affects the episodic memory, whereas lesions in the cortices affect different aspects of long-term memory.[10–12] Those with frontal lobe infarcts tend to have more of retrieval defect than those with middle cerebral artery (MCA) territory involvement emphasizing on the role of the prefrontal cortex in memory. Likewise, visual memory impairment is seen in lesions of the right medial temporal lobe,[13] and attention requires a multilobar orchestration between the dorsolateral and ventromedial prefrontal cortices, and the posterior parietal cortex.[14]

Furthermore, the type of cognitive and behavioral domain affected and the hemisphere involved also affect the severity of dementia, and thus, the patient's functional ability and status.[15,16] Therefore, delineating the role of vascular involvement is crucial not only for the clinical diagnosis and prognosis but also for the functional rehabilitation and care of such patients. In this regard, we conducted this study with the primary objective to examine the cognitive dysfunction in large-vessel vascular dementia. Secondarily, we aimed to delineate cognitive dysfunction in large-vessel vascular dementia as per the arterial territory involvement in these patients. Additionally, we evaluated the contribution of hemispheric involvement with respect to the patient's functional status as evident from the clinical dementia rating (CDR).

Materials and Methods

This index paper is part of a larger study that was conducted to explore the epidemiological aspects of vascular dementia in Kolkata (eastern zone of India). Prior approval from the institutional ethics committee was obtained.

The current observational cross-sectional study was performed at the department of neurology at a tertiary care center in Kolkata, India between March 2017 and October 2018.

Study Participants

The study population comprised patients referred to our department from the institute's emergency, outpatient department, and specialty clinics. Patients aged ≥ 40 years, having probable vascular dementia (as per the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) criteria)[5] and a modified Hachinski's ischemic scale score of ≥ 4 were recruited in the study. We excluded patients who were not willing to participate, and those diagnosed with any primary neurodegenerative disorders, mixed dementia or dementia with overlapping features of both degenerative and vascular types, any space-occupying lesions, or lobar hemorrhages. Patients without a complete clinical evaluation and brain imaging were also excluded. Additionally, those with combined small- and large-vessel diseases or large-vessel disease lesions were also dropped. Informed consent from the caregivers and families of the patients was obtained to include the patients in the study.

The patient's relevant history was collected by oral questionnaire method from the patient or their caregiver, or by performing bedside clinical assessment using the modified Hachinski's ischemic scale score.

Cognitive Assessment

A detailed history was taken for every participant, followed by a thorough general survey and systemic evaluation, especially for the nervous system. The CDR was used to quantify the severity of symptoms of dementia. We also used Addenbrooke's cognitive assessment translated to the Bengali language (and back-translated to English by independent professional translators to ensure content validity). The memory function was tested using word list memory task in Kolkata cognitive battery (KCB)[17] for verbal memory and other standard tests, while tests from the Frontal Assessment Battery and KCB were used to evaluate executive function. The results were interpreted after considering the normative data for memory and executive function.

Brain Imaging

Patients were labeled as large-vessel vascular dementia using the NINDS-AIREN criteria[5] based on their magnetic resonance (MR) imaging (3 Tesla), which also included coronal T1-weighted three-dimensional magnetization-prepared rapid acquisition with gradient echo(, axial fluid-attenuated inversion recovery, and axial spin-echo T2-weighted sequences, and an MR angiogram.

Study Sample

A sample of 157 patients was recruited after applying the inclusion/exclusion criteria, of which, 28 subjects had large-vessel disease.

Statistical Analysis

For the statistical analysis, all data were compiled in a Microsoft Excel spreadsheet and analyzed using SPSS (version 24.0; IBM Inc., Chicago, Illinois, United States) and GraphPad Prism version 5.0. We used descriptive statistics for analyzing the baseline demographics. Data were summarized as mean and standard deviation for numerical variables, and frequency and percentages for categorical variables.

Results

Twenty-eight (36.8%) of our patients had large-vessel disease (based on the NINDS-AIREN criteria). With a mean age of 56.6 ± 5.2 years, 9 (32.1%) patients were female and 19 (67.9%) patients were male. The mean mini-mental state examination (MMSE) of these patients was 18.54 ± 1.59. Regarding the risk factors for stroke, hypertension was the most prevalent in the overall group, followed by smoking, diabetes, and hyperlipidemia.

Distribution Patterns in the Small-Vessel Disease and Large-Vessel Disease Patients

In the large-vessel disease group, 23 patients (82.1%) belonged to the 51 to 60 years age group, while 5 (17.9%) patients were in the 61 to 70 years age group. The mean age of patients was 56.6 ± 5.2 years, of which 9 (32.1%) patients were female and 19 (67.9%) were male. The mean MMSE of these patients was 18.54 ± 1.59, and the mean CDR was 1.60 ± 0.76—1 patient (3.6%) had a CDR score of 0.5, 14 (50.0%) patients had a score of 1, 9 (32.1%) patients had a score of 2, and 4 (14.3%) patients had a score of 3.

►**Table 1** shows the domain involvement as per the arterial territory affection in patients of large-vessel disease—7 (25.0%) patients had impaired attention, 8 (28.6%) had language dysfunction, 10 (35.7%) had memory impairment, 9 (32.1%) had calculation dysfunction, 10 (35.7%) had visuospatial dysfunction, 6 (21.4%) had a visuoperceptual dysfunction, 8 (28.6%) suffered apraxia, 4 (14.3%) developed agnosia along with naming difficulty, 8 (28.6%) had

Table 1 Distribution of large-vessel disease in relation to arterial territory

Arterial territory	Number of patients	Number of males	Number of females
Anterior cerebral artery territory	6	5	1
Middle cerebral artery territory	13	7	6
Posterior cerebral artery territory	9	7	2

executive dysfunction, 10 (35.7%) developed depression, and 15 (53.7%) had behavioral dysfunction.

A majority of the patients ($n = 13$) had lesions in the MCA territory, followed by posterior cerebral artery (PCA) territory ($n = 9$). ►**Table 2** presents the distribution of large-vessel disease cases as per the respective arterial territory.

Regarding hemisphere involvement, the mean CDR was lower in patients with right-sided lesions (1.292) than in those with left-sided (1.750) or bilateral lesions (2.000). A summary of the severity of cognitive impairment and its relation to the hemisphere involved is presented in ►**Table 3**. ►**Table 4** depicts the distribution of CDR scores concerning hemispheric involvement in the large-vessel disease group.

Furthermore, the mean MMSE was higher in patients with right-sided lesions (19.083) than in those with left-sided (17.917) or bilateral lesions (18.750). ►**Table 5** presents the distribution of MMSE scores with respect to hemispheric involvement in the large-vessel disease group.

Discussion

Most of our patients had an abrupt onset and a stuttering course as has been reported in previous studies.[12] The presence of executive and attention dysfunctions in the anterior cerebral artery (ACA) territory infarcts can be attributed to the role of the dorsolateral prefrontal cortex

Table 2 Domain involvement and patient distribution as per arterial territory in large-vessel disease

Domain involved	ACA territory	MCA territory	PCA territory	*p*-Value
Attention	6 (100%)	1 (7.69%)	0 (0%)	0.000 for ACA vs. MCA, PCA
Language	1 (16.7%)	7 (53.8%)	0 (0%)	0.362
Memory	1 (16.7%)	7 (53.8%)	2 (22.22%)	0.510
Calculation	4 (66.64%)	4 (30.6%)	1 (11.11%)	0.256
Visuospatial	0 (0%)	6 (45.9%)	4 (44.44%)	0.452
Visuoperceptual	0 (0%)	2 (15.3%)	4 (44.44%)	0.299
Praxis	2 (33.3%)	6 (45.9%)	0 (0%)	0.544
Naming, gnosis, and semantics	0 (0%)	2 (15.3%)	2 (22.22%)	0.478
Executive	6 (100%)	1 (7.69%)	1 (11.11%)	0.000 for ACA vs. MCA, PCA
Behavior	6 (100%)	6 (45.9%)	3 (33.33%)	0.050 for ACA vs. MCA, PCA

Abbreviations: ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.

Table 3 Comparison of severity of cognitive impairment and its relation to hemispheric involvement in large-vessel disease

		N	Mean	Std. deviation	Std. error mean	Sig.
Left						
CDR	Yes	12	1.750	0.8660	0.2500	0.341
	No	16	1.469	0.6700	0.1675	
Right						
CDR	Yes	12	1.292	0.5418	0.1564	0.056
	No	16	1.813	0.8342	0.2085	
Bilateral						
CDR	Yes	4	2.000	0.8165	0.4082	0.335
	No	24	1.521	0.7442	0.1519	

Abbreviation: CDR, clinical dementia rating; Sig., intergroup significance; Std., standard.

Table 4 Distribution of CDR score in relation to the arterial territory involvement in large-vessel disease

	N	Mean	Std. deviation	Std. error	95% confidence interval for mean		Minimum	Maximum	Sig.
ACA	6	1.500	0.8367	0.3416	0.622	2.378	1.0	3.0	
MCA	13	1.692	0.7511	0.2083	1.238	2.146	1.0	3.0	$p = 0.811$
PCA	9	1.500	0.7906	0.2635	0.892	2.108	0.5	3.0	
Total	28	1.589	0.7583	0.1433	1.295	1.883	0.5	3.0	

Abbreviation: ACA, anterior cerebral artery; CDR, clinical dementia rating; MCA, middle cerebral artery; PCA, posterior cerebral artery; Sig., intergroup significance; Std., standard.

Table 5 Distribution of MMSE score in relation to hemispheric involvement in large-vessel disease

		N	Mean	Std. deviation	Std. error mean	Sig.
Bilateral						
MMSE	Yes	4	18.750	1.7078	0.8539	0.778
	No	24	18.500	1.6151	0.3297	
Left						
MMSE	Yes	12	17.917	1.5643	0.4516	0.075
	No	16	19.000	1.5055	0.3764	
Right						
MMSE	Yes	12	19.083	1.5050	0.4345	0.118
	No	16	18.125	1.5864	0.3966	

Abbreviations: MMSE, mini-mental state examination; Sig., intergroup significance; Std., standard.

and its connections in the executive function as well as attention, whereas the calculation defect in these patients could be secondary to executive dysfunction or lack of attention. Further, behavioral dysfunction in patients with ACA territory infarcts could be due to the involvement of the frontal cortex, especially the dorsolateral prefrontal, the orbitofrontal, and the medial prefrontal cortex, which are responsible for behavior. Lesions in these areas have been linked to behavioral dysfunction and abnormal behavior in some previous studies.[11,18] Therefore, the presence of significant association of impaired attention, executive dysfunction, and behavioral dysfunction with the ACA territory lesions in our group further corroborates the role of these areas in attention, behavior, and executive function.

The MCA territory infarcts largely led to memory and language dysfunction, along with visuospatial dysfunction and apraxia. Since the MCA territory predominantly involves both the anterior and posterior language areas, there is a high possibility of language disorders in these patients.[19–21] It is also known that damage to these areas can cause various types of language abnormalities.[22]

Memory is also a function of the medial temporal lobes, the left is mainly concerned with verbal memory, while the right is concerned with visual memory.[23–25] This explains the involvement of memory in the patients having infarcts in the MCA territory. Most commonly, the episodic memory was affected which did not improve on giving cues, thus proving that the memory involvement was cortical rather than subcortical. Two patients having lesions in the right medial temporal lobes had visual memory impairment. Likewise, the presence of apraxia in MCA territory strokes could be explained by the blood supply of the praxis pathway and neuroanatomical substrates.[26–29]

Visuospatial dysfunction was seen in MCA territory strokes with right-sided involvement, and all these patients showed involvement of the parietal cortex. The visuospatial function is a feature of the right parietal cortex and its connections. Further, this dysfunction also occurred in the lesions of the PCA territory which may be attributed to the involvement of the pathway comprising the occipitoparietal areas and their connections.[30,31] Similarly, occipitotemporal lesions led to disruption of the "what" pathway causing the visuoperceptual dysfunction in the form of visual object agnosia and prosopagnosia.

In our study, we found attention and executive dysfunction followed by calculation to be more impaired in ACA territory infarcts. The association was significant in domains of attention, executive dysfunction, and nearly significant in case of behavior for ACA territory lesions. Among other cognitive domains, our results could not achieve statistical significance for any domain. This may have been because of the small sample size in our study, and a lack of quantitative cognitive scoring for various domains which could have provided a better overview and comparison among the various subgroups. Nevertheless, we could still infer that attention and executive function were significantly impaired for ACA territory lesions.

We also compared the patients' functional status with respect to the hemispheric involvement using the CDR scale. Patients with lesions on the right side were compared with patients having lesions on the left side or bilateral lesions. There was a significant difference in the mean CDR between the two groups—those with lesions on the left side or bilateral lesions had a higher mean CDR than patients with right-sided lesions. This implies that vascular cognitive impairment in large-vessel disease might be more severe when presenting on the left side. Considering that the left side is the dominant hemisphere, and all our patients of large-vessel disease were right handed, we can presume that left-sided lesions are involved in a majority of cognitive functions, including executive function, verbal memory, and attention. Also, these patients had a lower MMSE when compared with the patients on the right side. Thus, our results suggest that laterality affects the severity of vascular dementia in large-vessel disease. A CDR score of 3 was present in left-sided lesions or bilateral lesions and not in patients with right-sided lesions. Our findings are supported by previous studies which have also reported asymmetry in the dementia severity and functional status

depending on the hemisphere involved or the cognitive domain affected.[15,16,32] We also compared the mean CDR scores in between the arterial territories. Although the mean CDR was higher for MCA territory infarcts, we could not find any statistically significant difference in between the groups. This could be due to the small sample size of our study. Moreover, we could not measure the infarct volume in these patients. Nevertheless, it implies that the cognitive impairment in MCA territory infarcts was more severe than ACA and PCA territory infarcts, respectively.

We did not observe any association between gender and the arterial territory involved, which implies that gender has no effect on the arterial territory in these patients. Furthermore, there was no difference in the mean MMSE between the three groups of left-sided, bilateral, and right-sided lesions. Thus, MMSE was disturbed irrespective of the arterial territory involved or the laterality of the lesion in patients with vascular cognitive impairment. Although MMSE is a reliable screening tool for dementia, it has many limitations, such as a lack of frontal assessment or the inability to administer MMSE in patients having features predominantly of frontal lobe dysfunction.[33] The above factors could have affected our findings, especially in patients having features of frontal lobe dysfunction. Many previous studies have studied the MMSE in vascular dementia patients; however, these studies did not subcategorize them based on the arterial territory or hemispheric involvement.[11,15,34,35]

Strengths

Our study is one of the few endeavors to examine all cognitive domains in vascular dementia and compare between different arterial territories and the right and left hemispheric lesions. We excluded all patients of mixed vascular and degenerative etiologies, as well as mixed large- and small-vessel diseases.

Limitations

Some potential limitations of our study are worthy of mention. Functional and diffusion tensor imaging was not available for the present study due to financial and logistic constraints. These methods could have helped objectively corroborate our clinical findings. We excluded patients with mixed dementia who had a concomitant degenerative pathology to remove possible sampling bias. The use of histopathological examination could have substantiated our results.

Conclusion

The above findings suggest that the nature of cognitive impairment varies with different arterial territory lesions in large-vessel disease and delineating the specific subtypes and their anatomical distribution can aid in predicting the clinical course and diagnosis. We also observed that executive dysfunction, calculation, attention, and behavioral

dysfunction were more prevalent in ACA territory infarcts, while memory, language, and apraxia were more frequent prevalent with MCA territory infarcts, and agnosia and visuoperceptual dysfunction were more commonly observed with PCA territory infarcts. However, this can only be substantiated by functional or diffusion tensor imaging studies. Also, hemispheric involvement is an important predictor of dementia severity. Memory dysfunction is an important contributor to the severity of dementia, and those with right-sided involvement have less severe dementia as compared with those with left-sided or bilateral lesions.

Conflict of Interest
None declared.

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