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Correlation of MRI brain findings with executive dysfunction and vascular risk factors in elderly patients with cognitive impairment

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Abstract

Objectives: The primary objective of the present study was to investigate the relationship between gray matter changes, white matter changes and executive function among older Indian adults with vascular risk factors. *Methods:* This hospital based observational analytical study was conducted in a tertiary care health facility located in the north-western region of India for a duration of one year between October 2021 and September 2022 among patients between 60 and 90 years of age presenting to the outpatient sections of Department of Neurology with executive dysfunction. We assessed the vascular risk factors, evaluated executive function, and then the patients underwent brain MRI on a 1.5T MRI scanner. *Results:* The proportion of patients with dorsolateral atrophy was significantly higher ($p<0.001$) among patients with executive dysfunction (83.10%). Hypertension significantly contributed to predict the atrophy of temporal lobe and parietal lobe ($p<0.05$). Hyperintensity of periventricular area was found significantly higher among executive dysfunction patients (85.92%). Elevated HbA1c levels and smoking significantly contributed to predict the white matter hyperintensity of basal ganglia ($p<0.05$). The present study also found that hypertension and alcohol use significantly predicted white matter hyperintensity in the frontal area ($p<0.05$).
Conclusion: Specific white matter hyperintensity loci and grey matter volume loss were closely associated with executive dysfunction in elderly. It is understood that modifying and treating vascular risk factors can prevent progression of executive dysfunction and these findings emphasize the complex nature of the relationship between vascular risk factors, cognitive impairment, and brain structure.

Keywords: Executive function, MRI brain, white matter hyperintensity, cognitive impairment

INTRODUCTION

Executive function is a complex cognitive function that enables a person to generate thoughts, formulate plans, establish a goal, and guide behaviour, inhibiting what is irrelevant and unnecessary, and shifting cognitive sets as what and when needed. The major components of executive function are planning, initiation and monitoring of action, inhibitory control, mental flexibility, working memory, and fluency. Executive processes are mediated by networks incorporating multiple cortical regions including parietal, occipital lobes as well as prefrontal region, basal ganglia, thalamus, and cerebellum.[1,2] Executive dysfunctions can be found in neurodegenerative diseases, including frontotemporal dementia, Alzheimer's disease, vascular cognitive impairment, Parkinson disease dementia, neoplastic etiology, infectious, demyelinating disease, leukodystrophy, radiation and metabolic etiology, hydrocephalus, psychiatric conditions.

Age-related changes in the frontal lobe is associated with poorer executive function (e.g., working memory, switching/set-shifting, and inhibitory control).[3] It is recognized that ischemic brain lesions are a significant contributor to cognitive impairment and that many cases of dementia are mixed, with a cerebrovascular component.[4] White matter lesions (WML) are divided into subcortical and periventricular white matter. Subcortical white matter lesions are believed to primarily disrupt short connections, and thus impairing cognitive performance supported by the specific brain region. For example, dexterous hand and arm movements are

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generally thought to be primarily mediated by the motor cortex. Therefore, subcortical WMLs in this specific region can result in reduced performance in hand and arm dextrous movements. In contrast, periventricular white matter lesions disrupt longer connections to spatially distant cortical areas, and thus can cause cognitive performance decline in multiple domains. Ischemic white matter lesions, seen on MRI as white matter hyperintensity (WMH), have previously been associated with decreased performance on neuropsychological testing[5,6], and risk of mild cognitive impairment[7] and dementia.[8]

Gray matter volume loss can be associated with cognitive decline including executive dysfunctions. Previous studies in healthy adults suggested that executive performance is related to prefrontal volume.[9-11] However, given that executive functions and higher-order cognition in general are dependent on multiple cortical and subcortical networks, it is highly likely that the structural components underlying such functions are not limited to the prefrontal cortex but also include connections with other cortical areas.[12] It is therefore important to consider how the entire brain structurally supports executive functions. Against this background , the primary objective of the present study was to investigate the correlation of MRI brain findings with executive dysfunction (ED) and vascular risk factors in elderly patients with cognitive impairment.

METHODS

This hospital based observational analytical study was conducted in a tertiary care health facility located in the north-western region of India for a duration of one year between October 2021 and September 2022. the institution has specialty clinics for patients with cognitive impairment which is functioning once a week. The study was approved by the Institute Human Ethics Committee (IHEC). All patients between 60 and 90 years of age presenting to the outpatient sections of Department of Neurology with executive dysfunction (irrespective of type of neurodegenerative disorders) with positive risk factors including diabetes mellitus, hypertension, smoking, alcohol, hyperlipidaemia, chronic kidney injury were included in study. In cases of cognitive impairments of patients with affection of multiple domains, we had included patients who had predominant executive dysfunction which was main contributory to functional dependence. However, we excluded patients less than 60 years of age, those presenting with acute illness (within 12 weeks) including stroke, metabolic encephalopathy, acute meningoencephalitis, septic encephalopathy, altered sensorium, patients with psychiatric disorders, patients with intracranial space occupying lesions and/or planned for operative intervention (Figure 1).

Patients providing written informed consent underwent detailed general physical examination including vital signs, neurological, and psychiatric examination, battery of laboratory tests (including total cholesterol, low-density lipoprotein (LDL) cholesterol, blood glucose, haemoglobin A1c, blood urea nitrogen (BUN), serum creatinine), and MRI Brain. We used a predesigned, semi-structured, pretested questionnaire to capture the cerebrovascular risk factors.

We employed several cognitive tests to evaluate executive function in the elderly population. These tests specifically assessed different aspects of executive function, including mental flexibility, response inhibition, fluency, sequencing ability, working memory. Trail-B Test (measures mental flexibility and cognitive switching ability), Go-No-Go Test (to evaluate an individual's ability to inhibit automatic responses), Lexical Fluency Test (measure of verbal fluency and involves generating words within specific semantic or phonemic categories), Test of Sequencing or the Motor Series Luria Test (evaluates an individual's ability to sequence and organize motor movements in a prescribed order), and Backward Digit Span (measure of working memory capacity and manipulation).[13]

All participants underwent brain MRI on a 1.5T MRI scanner. Sequences included diffusion-weighted, T1-weighted, T2-weighted imaging, and fluid-attenuated inversion recovery (FLAIR) with 3D image of T1 sequences (using GE SIGNA MRI Scanners). The FLAIR sequences were obtained using TR, 9000 ms; TE, 104 ms; TI, 2500 ms; slice thickness, 5.0 mm; and gap, 0.0 mm. We have used GCA-scale for Global Cortical Atrophy, MTA-scale for Medial Temporal lobe Atrophy, Koedam score for parietal lobe atrophy. We defined white matter hyperintensity as the presence of hyperintensity in the white matter area. Periventricular hyperintensity and deep white matter hyperintensity lesions were outlined. Also, regional deep white matter hyperintensity within bilateral areas of the cornu, frontale, pars parietalis, cornu occipitale, and pars temporalis/lobar; and within bilateral areas of the frontal, parietal, occipital and temporal lobes were assessed. White matter hyperintensity was assessed by Fazekas scale.

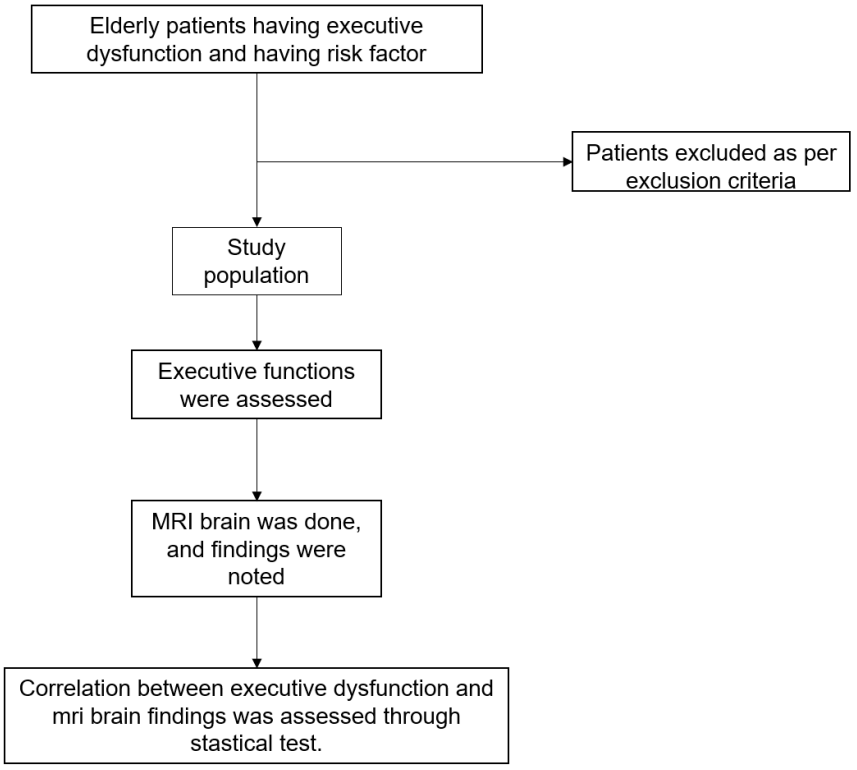

Figure 1. Workflow of the study

Images of MRI Brain were assessed by one Senior Neurologist (Senior Professor) from Neurology Department and one Radiologist (Senior Professor from Radiology Department). They are unaware of patients' clinical condition. (Blinding was done). Above findings were compared with normal age and gender-based control images by radiologist (senior professor from radiology department).

The data obtained was manually entered into Microsoft Excel and analyzed using Software for Statistics and Data Science (Stata) v16. Descriptive analysis was presented using numbers and percentages for categorical variables; mean and standard deviation or median and interquartile range for continuous variables. Chi square test of significance (two-sided) or independent "t" tests (two-sided) was applied to test for association. Statistical significance was considered at $p<0.05$. Multivariate analysis by binary logistic regression was done to predict MRI Brain findings in patients with executive dysfunction.

RESULTS

The mean (SD) age of the male and female participants was 67.32 years (5.9) and 66.27 years (9.25). We included a total of 50 males and 21 females – the number of male patients with executive dysfunction was significantly higher ($p<0.001$) than the female patients with executive dysfunction (Table 1). However, the difference between mean ages of male and female patients was not statistically significant ($p>0.05$). Regarding the independent variables considered in the present study, the proportion of patients with hypertension was 61.97%, positive smoking history was 60.56%, history of alcohol intake was 46.47%, elevated HbA1c levels was 25.35%, dyslipidaemia was 33.80%, elevated creatinine level was 5.63% and elevated urea level was 25.35%.

MRI brain findings in patients with executive dysfunction: The results of the present study found that the proportion of patients with dorsolateral atrophy was significantly higher ($p<0.001$) among patients with executive dysfunction (83.10%) (Table 2). However, the proportion of patients without atrophy of the medial lobe (60.56%), orbitofrontal (88.73%), parietal lobe (69.01%), occipital lobe (87.32%), pons (91.55%) and cerebellar lobe (78.87%) had significantly higher ED in comparison with patients having atrophy.

Table 1: Demographic profile and Proportion of patients, present with risk factor

	Present (n)	Present (%)
Male	50	70.42
Female	21	29.58
Hypertension	44	61.97
Smoking	43	60.56
Alcohol	33	46.47
Elevated HbA1c	18	25.35
Dyslipidemia	24	33.80
Elevated creatinine	4	5.63
Elevated urea	18	25.35

The results also found that the difference in proportion of patients with executive dysfunction with or without atrophy of temporal lobe and atrophy of midbrain was not statistically significant (p>0.05).

Multivariate analysis: A logistic regression analysis was done to predict brain lesion (based on MRI brain findings) among 71 executive dysfunction patients; the predictors considered in the present study were hypertension, smoking history, alcohol, elevated HbA1c level, dyslipidaemia, elevated creatinine level and elevated urea level (Table 3).

The Wald criterion demonstrated that the hypertension, smoking history, alcohol, elevated HbA1c level, dyslipidaemia, elevated creatinine levels and elevated urea levels made a nonsignificant contribution to predict dorsolateral atrophy, medial frontal lobe atrophy, occipital and cerebellar atrophy (p>0.05).

We found that smoking had a significant negative contribution (protective factor) towards predicting the atrophy of orbitofrontal lobe (p<0.05). However, hypertension, alcohol use, elevated HbA1c levels, dyslipidaemia, elevated creatinine levels and elevated urea levels made a nonsignificant contribution to predict the atrophy of orbitofrontal lobe (p>0.05).

The results showed that hypertension significantly contributed to predict the atrophy of temporal lobe and parietal lobe (p<0.05). However, alcohol use, smoking, elevated HbA1c levels, dyslipidaemia, elevated creatinine levels and elevated urea levels made a nonsignificant contribution to predict the atrophy of temporal and parietal lobe (p>0.05).

White matter hyperintensity in patients with executive dysfunction: The number of patients with hyperintensity of periventricular area was significantly higher among executive dysfunction patients (85.92%) (Table 4). However, the number of patients without hyperintensity of temporal (91.55%), parietal (90.14%) and occipital (94.37%) areas was significantly higher among executive dysfunction patients (p<0.05). We did not find any difference in the white matter hyperintensity of basal ganglia and frontal areas (p>0.05).

Multivariate analysis: The Wald criterion demonstrated that elevated HbA1c levels and smoking significantly contributed to predict the white matter hyperintensity of basal ganglia (p<0.05). However, hypertension, alcohol, dyslipidemia, elevated creatinine levels and elevated urea levels made a nonsignificant contribution to predict the white matter hyperintensity of basal ganglia (p>0.05) (Table 5). The present study also found that hypertension and alcohol use significantly predicted white matter hyperintensity in the frontal area (p<0.05).

Table 2: MRI brain finding in patients with executive dysfunction

MRI brain finding	Yes		No		p value
	N	%	N	%	
Atrophy of dorsolateral	59	83.10	12	16.90	<0.001
Atrophy of medial lobe	28	39.44	43	60.56	0.019
Atrophy of orbitofrontal	8	11.27	63	88.73	<0.001
Atrophy of temporal lobe	41	57.75	30	42.25	0.093
Atrophy of parietal lobe	22	30.99	49	69.01	<0.001
Atrophy of occipital lobe	9	12.68	62	87.32	<0.001
Atrophy of midbrain	29	40.85	42	57.15	0.063
Atrophy of pons	6	8.45	65	91.55	<0.001
Atrophy of cerebellar	15	21.13	56	78.87	<0.001

Table 3: Association between MRI brain findings (atrophy) and risk factors

Variable	Atrophy											
	Dorsolateral		Medial lobe		Orbitofrontal		Temporal lobe		Parietal lobe		Occipital lobe		Cerebellar	
	Sig.	Exp(B)	Sig.	Exp(B)	Sig.	Exp(B)	Sig.	Exp(B)	Sig.	Exp(B)	Sig.	Exp(B)	Sig.	Exp(B)
Hypertension	0.269	2.195	0.200	2.128	0.455	2.706	0.045	3.153	0.002	0.128	0.418	0.522	0.321	0.533
HbA1c	0.530	0.609	0.983	0.986	0.705	1.534	0.152	2.657	0.301	0.460	0.821	0.810	0.348	1.933
Hyperlipidemia	0.664	0.716	0.225	0.460	0.338	2.914	0.574	0.706	0.714	1.286	0.330	0.403	0.560	0.663
Creatinine	0.357	0.281	0.999	0.000	0.999	0.000	0.298	0.263	0.999	0.000	0.999	0.000	0.772	1.456
Urea	0.541	1.837	0.705	1.281	0.998	0.000	0.954	1.039	0.136	2.969	0.326	2.317	0.985	0.986
Smoking/tobacco	0.948	1.048	0.264	0.524	0.017	0.055	0.754	1.198	0.366	0.531	0.509	0.575	0.753	0.816
Alcohol	0.172	3.118	0.115	2.521	0.620	1.698	0.378	1.681	0.356	1.825	0.904	1.103	0.857	1.125
Constant	0.276	2.490	0.359	0.522	0.136	0.134	0.266	0.459	0.572	1.542	0.245	0.331	0.223	0.392

However, none of the predictors considered in the study significantly predicted white matter hyperintensity in periventricular, temporal, parietal and occipital areas ($p>0.05$).

DISCUSSION

The present study aimed to investigate the relationship between gray matter volume, white matter changes, and executive function among older Indian adults with vascular risk factors. The results revealed interesting findings regarding the association between specific brain regions' atrophy and executive dysfunction in this population. The results indicated that the proportion of patients with dorsolateral atrophy was significantly higher among patients with executive dysfunction. The dorsolateral prefrontal cortex (DLPFC) is known to be involved in various executive functions, such as working memory, cognitive flexibility, and inhibitory control.[14-17] Damage or atrophy in this region can lead to impairments in these cognitive processes, which are characteristic of executive dysfunction. Interestingly, the results showed that patients without atrophy in certain brain regions, such as the medial frontal lobe, orbitofrontal cortex, partial lobe, occipital lobe, pons, and cerebellar lobe, had a higher proportion of executive dysfunction compared to patients with atrophy in those regions. These findings suggest that executive dysfunction may not be solely attributed to atrophy in these specific brain regions among older adults with vascular risk factors.

It is important to consider the potential underlying mechanisms that may contribute to these findings. Vascular risk factors, such as hypertension, diabetes, and atherosclerosis, can lead to cerebral small vessel disease (SVD) and contribute to white matter changes.[18] White matter hyperintensities (WMH) commonly associated with SVD have been linked to executive dysfunction.[19] Therefore, the observed executive dysfunction in patients without atrophy in certain brain regions could be related to white matter changes rather than gray matter atrophy alone.

The lack of a statistically significant difference in the proportion of patients with executive dysfunction, with or without atrophy of the temporal lobe and midbrain, is an interesting finding. Previous studies have reported the involvement of the temporal lobe in executive functions, particularly in tasks requiring episodic memory and semantic processing.[20] However, the absence of a significant association in this study

Table 4: White matter hyperintensity in patients with ED

MRI brain finding	Yes		No		Test of significance
	N	%	N	%	
Basal ganglia area	40	56.34	31	43.66	0.179
Periventricular area	61	85.92	10	14.08	<0.001
Frontal area	21	29.58	50	70.42	0.585
Temporal area	6	8.45	65	91.55	<0.001
Parietal area	7	9.86	64	90.14	<0.001
Occipital area	4	5.63	67	94.37	<0.001

suggests that other factors, such as white matter changes or the influence of vascular risk factors, may contribute more prominently to executive dysfunction in this population.

The present study employed logistic regression analysis to predict brain lesion based on MRI brain findings among 71 executive dysfunction patients. The results indicated that hypertension, smoking history, alcohol use, elevated HbA1c level, dyslipidemia, elevated creatinine level, and elevated urea level did not significantly contribute to predicting dorsolateral atrophy, medial lobe atrophy, occipital lobe atrophy, and cerebellar atrophy. These findings suggest that these factors may not play a significant role in the development of atrophy in these specific brain regions among executive dysfunction patients in the present study. However, it is important to note that these results do not imply the absence of any relationship between these predictors and brain atrophy. Other factors, such as the sample size, heterogeneity of the patient population, and the specific characteristics of the vascular risk factors, may have influenced the lack of significant associations in this study.

Smoking history was found to have a significant negative contribution (a protective factor) in predicting the atrophy of the orbitofrontal lobe. This finding suggests that smoking may have a potential protective effect against orbitofrontal lobe atrophy among executive dysfunction patients. However, it is crucial to interpret this finding with caution due to the well-established detrimental effects of smoking on overall health, including the increased risk of various diseases, including cardiovascular and cerebrovascular conditions.

Hypertension was found to have a significant contribution in predicting the atrophy of the temporal lobe and parietal lobe. This finding aligns with previous research that has consistently linked hypertension to structural brain changes, including atrophy in specific brain regions.[21-24] Hypertension can lead to vascular damage, such as arteriosclerosis and impaired cerebral blood flow, which can contribute to brain atrophy.[25] The association between hypertension and atrophy in the temporal and parietal lobes may have implications for the cognitive functions associated with these brain regions, including memory and attention.

The results showed that the number of patients with hyperintensity in the periventricular area was significantly higher among executive dysfunction patients. Periventricular hyperintensity is commonly associated with white matter changes and cerebral SVD.[26] These hyperintensities often result from chronic ischemia and damage to small vessels in the brain, which can lead to cognitive impairment.[27] The higher prevalence of periventricular hyperintensity among executive dysfunction patients suggests that white matter changes in this region may contribute to the development of executive dysfunction. In contrast, the number of patients without hyperintensity in the temporal and parietal areas was significantly higher among executive dysfunction patients. The temporal and parietal lobes are involved in various cognitive functions, including memory, attention, and language processing.[28] White matter hyperintensities in these areas have been associated with cognitive impairment and an increased risk of dementia.[29] The lower prevalence of hyperintensities in the temporal and parietal areas among executive dysfunction patients may indicate a different underlying etiology or pathophysiological mechanism contributing to their cognitive impairment. Literature evidence highlights that WMHs displayed by MRI such as of the periventricular and parietal white matter regions have been shown to be a risk factor for the conversion from mild cognitive impairment (MCI) to AD.[30] The comorbidities associated with white matter hyperintensities include hypertension, dyslipidemia, tobacco use, ischemic heart disease, previous stroke, atrial fibrillation,

Table 5: Association between MRI brain findings (white matter hyperintensity) and risk factors

Variable	White matter hyperintensity											
	Basal ganglia		Periventricular area		Frontal area		Temporal area		Parietal area		Occipital area	
	Sig.	Exp(B)	Sig.	Exp(B)	Sig.	Exp(B)	Sig.	Exp(B)	Sig.	Exp(B)	Sig.	Exp(B)
Hypertension	0.102	2.917	0.705	1.349	0.045	4.720	0.829	1.689	0.490	0.155	0.792	0.224
HbA1c	0.003	15.562	0.750	1.356	0.792	0.802	0.998	1.146	0.998	0.542	0.398	0.572
Hyperlipidemia	0.095	0.268	0.984	1.017	0.504	1.675	0.693	0.462	0.930	0.809	0.489	0.389
Creatinine	0.444	2.714	0.471	0.375	0.847	0.758	0.998	0.171	1.000	2.590	1.000	2.510
Urea	0.897	1.103	0.246	0.327	0.942	1.061	0.885	1.402	0.754	0.433	0.727	0.793
Smoking/tobacco	0.041	3.808	0.668	0.714	0.076	3.968	0.431	3.333	0.865	0.720	0.835	0.720
Alcohol	0.963	1.030	0.069	7.798	0.037	4.436	0.821	1.539	0.821	0.582	0.801	0.512
Constant	0.048	0.196	0.139	4.074	0.000	0.018	0.998	0.000	0.998	0.000	0.321	0.089

chronic renal failure, hyper-homocystinuria and bariatric surgery.[31,32]

Interestingly, no significant difference was found in the white matter hyperintensities of the basal ganglia and frontal areas between executive dysfunction patients and the comparison group. The basal ganglia and frontal areas are also implicated in executive functions.[33,34] White matter changes in these regions have been associated with executive dysfunction and cognitive decline.[35] The lack of a significant difference in hyperintensities in these areas among executive dysfunction patients in the present study may be influenced by various factors, including the heterogeneity of the patient population and the specific characteristics of the vascular risk factors.

The findings of the study revealed associations between certain predictors and white matter hyperintensity in specific brain regions. The results demonstrated that elevated HbA1c levels and smoking significantly contributed to the prediction of white matter hyperintensity in the basal ganglia. Elevated HbA1c levels, which reflect long-term glucose control and are commonly used as a marker for diabetes, have been associated with microvascular damage and cerebral small vessel disease (SVD).[36-39] This vascular damage can lead to white matter changes and the development of hyperintensity in the basal ganglia. Smoking, on the other hand, is known to contribute to endothelial dysfunction, oxidative stress, and inflammation, all of which can adversely affect the integrity of cerebral blood vessels and contribute to white matter hyperintensity.[40] However, hypertension, alcohol use, dyslipidemia, elevated creatinine levels, and elevated urea levels did not significantly contribute to the prediction of white matter hyperintensity in the basal ganglia. These findings may suggest that the impact of these factors on white matter changes in this specific brain region is not as pronounced or that other factors not considered in the present study may have influenced the results. It is important to consider that the relationship between vascular risk factors and white matter changes can be complex and may vary depending on the specific brain regions and the underlying pathophysiology involved.[26]

The study also found that hypertension and alcohol use significantly predicted white matter hyperintensity in the frontal area. Hypertension, as a major risk factor for cerebrovascular disease, can lead to structural changes and compromised blood flow in the frontal regions, resulting in white

matter hyperintensity.[26] Alcohol use, particularly heavy or chronic alcohol consumption, has been associated with neurotoxic effects and damage to white matter integrity.[41-43] The significant contributions of hypertension and alcohol use to the prediction of white matter hyperintensity in the frontal area support the existing evidence linking these factors to frontal lobe dysfunction and structural changes.

In contrast, none of the predictors considered in the present study significantly predicted white matter hyperintensity in the periventricular, temporal, and posterior areas. It is important to note that white matter hyperintensity patterns can vary across different brain regions and may be influenced by multiple factors, including the severity and duration of vascular risk factors, genetic predispositions, and the interaction of various vascular and metabolic pathways.[18] The lack of significant associations in these regions may be due to the complex interplay of factors influencing white matter changes and the specific characteristics of the study population.

It is important to acknowledge certain limitations of the present study. Firstly, the cross-sectional design (patient data obtained at only one time point, that is, at the time of first hospital visit) limits our ability to establish causality or determine the temporal sequence of events. Longitudinal studies would provide a more comprehensive understanding of the relationship between brain atrophy, white matter changes, and executive dysfunction over time. Secondly, the study focused specifically on older Indian adults with vascular risk factors, which may limit the generalization of the findings to other populations or age groups. Third, we have also included patients with executive dysfunction having minimal cognitive impairment and as well as major neurocognitive disorders with mix neurodegenerative and vascular risk factors – limiting the external validity. Finally, the relatively small sample size of 71 executive dysfunction patients may have limited the statistical power to detect significant associations. Importantly, the study did not include a control group.

In conclusion, the present study documented that white matter hyperintensity involving periventricular area, temporal and parietal areas; atrophy of dorsolateral frontal lobe were associated with executive dysfunction. White matter (hyperintensity) is the most affected in comparison with gray matter (atrophy); most associated with executive dysfunction. Hypertension significantly contributes to predict the atrophy of temporal lobe and parietal lobe; and white matter hyperintensity of frontal area. Elevated HbA1c levels and smoking to WMH of basal ganglia; and alcohol ingestion to WMH of frontal area were significant predictors. It is understood that modifying and treating vascular risk factors can prevent progression of executive dysfunction and these findings emphasize the complex nature of the relationship between vascular risk factors, cognitive impairment, and brain structure. Further research with larger sample sizes and a more comprehensive approach is needed to confirm and expand upon these findings.

DISCLOSURE

Ethics: Study was approved by institutional ethical committee, SMS Medical College and attached hospitals, Rajasthan, Jaipur, India. Written Consent from study participants were taken before study participation.

Data availability: The datasets generated and/or analysed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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Conflict of interests: None

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