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Study of Correlation between Small Vessel Diseases of Brain With Cognitive Impairment in Indian Pre Dialysis Chronic Kidney Disease Patients

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ABSTRACT

Background: Chronic kidney disease (CKD) is a worldwide public health problem; its prevalence has increased in the past decade globally, attributed to increase in prevalence lifestyle disease and improved life expectancy. Small vessel disease (SVD) of brain is a syndrome of clinical and imaging findings that are thought to result from pathologies in perforating cerebral arterioles, capillaries and venules. There is increasing evidence suggesting (SVD) of brain have a role in development of cognitive decline.

Aim: Aim of this study was to study the relationship between SVD of brain and cognitive decline in pre-dialysis CKD patients.

Materials and Methods: 50 pre-dialysis CKD patients were enrolled in this study. SVD was evaluated by the presence and severity cerebral microbleeds (CMBs), lacunar infarcts and white matter hyperintensities (WMHs) on brain magnetic resonance imaging (MRI). Neuropsychological tests were assessed using battery of four validated cognitive tools.

Results: Using univariate and multivariate regression analysis most of correlations between SVD of brain with cognitive impairment came out to be positive and were statistically significant.

Conclusion: Patients with cerebral SVD had more cognitive impairment as compared to patients without having SVD. With increase in each presence and severity of CMB and WMH along with the lacunar infarcts, the patients perform poor in each test for cognition resulting in an overall decline in cognitive abilities.

Keywords: Cerebral microbleeds, Chronic kidney disease, Magnetic resonance imaging, Small vessel disease, White matter hyperintensities.

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem; its prevalence has increased in the past decade globally, attributed to increase in prevalence lifestyle disease and improved life expectancy. In India it is estimated that the age-adjusted incidence rate of ESRD to be 229 per million population (pmp), and >100,000 new patients enter renal replacement programs annually. Small vessel disease (SVD) of brain is a syndrome of clinical and imaging findings that are thought to result from pathologies in perforating cerebral arterioles, capillaries and venules. It is described on imaging as changes in the white matter and subcortical grey matter, including recent small

subcortical infarct, lacunes, white matter hyperintensities (WMHs), cerebral microbleeds (CMBs) and atrophy. In elderly, the SVD is also abundantly present in brain. SVD of brain is associated with increased risk of cognitive decline, dementia, mood disturbance and stroke(1).

Cognitive impairment is a well-known finding in CKD patient's and has also been linked to uremia. This is characterized by stupor, decreased intellect, sluggishness of manner, disorientation, behavioral abnormalities and drowsiness. There is increasing evidence suggesting that SVD of brain and other vascular abnormalities have a role in development of cognitive decline. SVD is now recognized as a major etiologic cause of cognitive deficit. There is a paucity of well published literature of its association with cognitive decline in CKD patients(2). Cognitive impairment has been reported to vary between 17-50% in CKD patients and >85% in patients of ESRD(3).

Yasumasa et al showed in their study on CKD patients that the presence of extensive SVD including severe WMHs and many lacunar infarcts were strongly associated with cognitive impairment in multivariate analysis. Moreover, CKD was also independently associated with severe WMHs and many lacunae. Accordingly, the significant relationship between cognitive impairment and CKD in this study is partly explicable by the hypothesis that extensive small vessel disease may represent an intermediate stage along the pathway from CKD to global cognitive impairment(4).

Cognitive Function

Were assessed using following tests.

1. 6 items cognitive impairment test.
2. MMSE
3. Trail making test – A
4. Trail making test - B

This study is an attempt to probe about the association of small vascular diseases of brain in chronic kidney disease patients with cognitive. With new emerging evidences claiming reversibility in the various components of cognitive impairment, early recognition of cognitive decline is very important. There is paucity of literature on all types of SVD of brain and cognitive impairment in CKD patients and there is no well published study on Indian patients.

Materials and Methods

A cross-sectional study was conducted on 50 patients having Chronic Kidney Disease, defined by K/DOQI guidelines (Kidney Disease Outcome Quality Initiative) with estimated GFR (eGFR) <60ml/min/1.73m2 for more than 3 months, who do not require renal replacement therapy at the time of presentation (hence called pre-dialysis chronic kidney disease patients). The patients were then subjected to detailed history and examination. The patients were then subjected to various biochemical and radiological investigations including MRI of the Brain.

Sample Size

Total sample size taken was 50.

Formula used is:-

$$ME = Z^* \sqrt{\frac{p(1-p)}{N}}$$

Where Z is value of Z at two-sided alpha error of 5%, ME is margin of error and p is prevalence rate.

Observation and Results

Table 4: MRI findings in study population

MRI	No.	Percentage
No evidence of SVD	24	48.00%

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CMB, WMH	1	2.00%
CMB. LI	2	4.00%
Isolated CMB	1	2.00%
Isolated WMH	3	6.00%
WMH, LI	6	12.00%
CMB, WMH, LI	13	26.00%
Total	50	100.00%

All patients had undergone MRI brain for evidence of cerebral SVD. 24 patients (48%) were found to have no evidence of SVD on MRI. The MRI of 26 patients (52%) was suggestive of some SVD of the brain. 17 patients (34%) had CMBs, Isolated CMB seen in 1 patient (2%). WMHs were seen in 23 patients (46%). Isolated WMH were present in 3 patients (6%). Lacunar infarcts were seen in 21 patients (42%). Out of 50 cases none of our patients had overt clinical neurological deficit and MRI defined stroke.

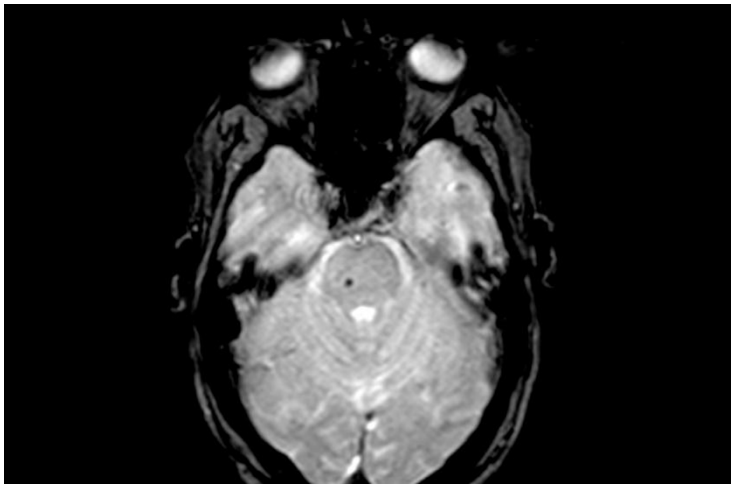

Figure 1: Cerebral microbleeds

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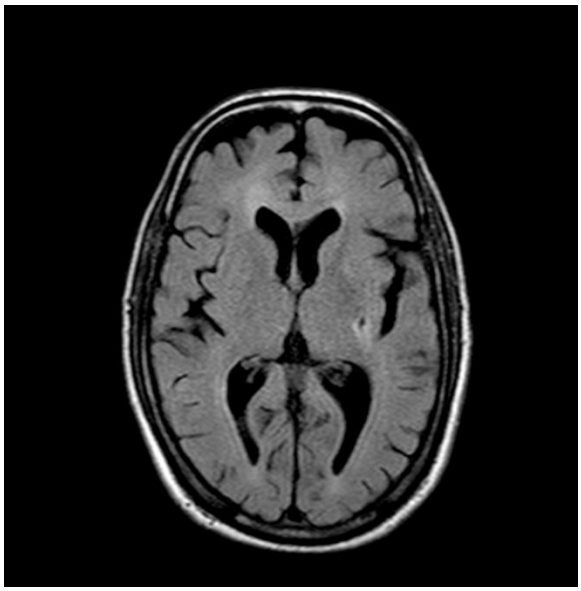

Figure 2: Lacunar infarcts

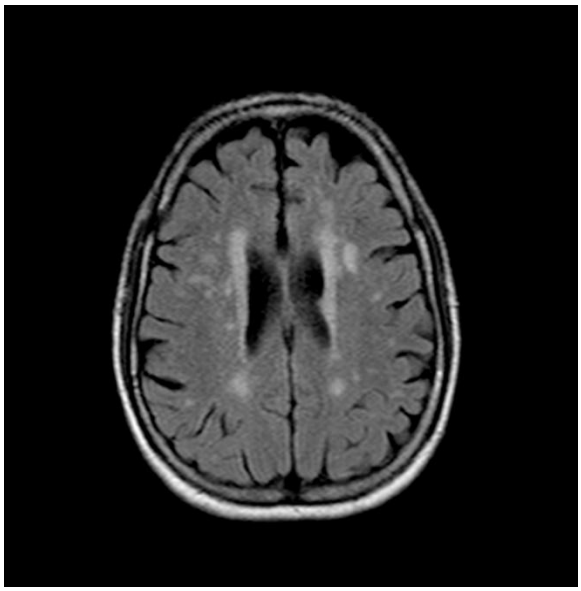

Figure 3: White matter hyperintensities

Discussion & Conclusion

This study was undertaken with an aim of evaluating the characteristic of cerebral small vessel disease (SVD) and to study its various clinical subtypes including CMBs, WMHs, lacunar infarcts in pre-dialysis CKD patients and its effect on cognitive domains.

Following conclusions were drawn from this study-

- There was increased prevalence of cerebral SVD in CKD patients (52%)., CMBs were found in 34% of patients, WMHs were present in 46% of patients, lacunar infarcts were present in 42% of patients.
- Patients with cerebral SVD had more cognitive impairment as compared to patients without having SVD.
- There was significant correlation between CMB grade and cognitive impairment with a p - value of <0.0001 for 6CIT, MMSE, TRAIL B and 0.0003 for TRAIL A and correlation coefficient (r) 0.672 (6 CIT), -0.677 (MMSE), 0.778 (TRAIL A) and 0.755 (TRAIL B).
- There was statistically significant correlation between WMH grade and cognitive impairment with a p- value of <0.0001 for 6 CIT, MMSE, TRAIL A and TRAIL B) and correlation coefficient (r) 0.769 (6 CIT), -0.76 (MMSE), 0.728 (TRAIL A) and 0.739 (TRAIL B).
- There was significant correlation between lacunar infarcts (0-4) and cognitive impairment with a p - value of < 0.0001 for MMSE, TRAIL A, TRAIL B and p = 0.0001 for 6 CIT) and correlation coefficient (r) 0.72 (6 CIT), -0.71 (MMSE), 0.77 (TRAIL A) and 0.781 (TRAIL B)..
- Using univariate regression analysis most of correlations between SVD of brain (CMBs, WMHs, lacunar infarcts) with cognitive impairment (using 6 CIT, Modified MMSE, TRAIL A and TRAIL B) came out to be positive and were statistically significant, implying that with an increase in each of the CMB and WMH grades along with the lacunar infarcts, the patients perform poor in each test for cognition resulting in an overall decline in cognitive abilities.

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- Using multivariate regression analysis with 6 CIT test, CMB and WMH grade showed statistical correlation with cognitive impairment as evident by the p value of 0.0176 and 0.0156 respectively while the correlation of lacunar infarcts (0-4) was not significant supported by a very high p-value of 0.5491. Multivariate analysis with other tests for cognition namely MMSE, TRAIL A and TRAIL B and SVD the correlation was inconsistent and statistically insignificant, thus suggesting that the SVDs of brain do not work in a synergistic manner and rather affect the cognitive abilities to deteriorate independently.

In this study it was demonstrated that there was increased prevalence of cerebral SVD including CMBs, WMHs and lacunar infarcts in pre-dialysis CKD patients more so in advanced CKD with relatively lower eGFR. This study strengthens the premise that CKD is a risk factor for cognitive decline even in pre-dialysis patients. It was also found that patients with SVD of brain had more cognitive impairment as compared to CKD patients without having any SVD of brain on MRI. Further work on the subject is needed to discover new modalities that can help us provide better treatment regimens for the patients targeting at SVD of brain. Screening for cognitive decline should be an integral part of CKD patient assessment. Early assessment and intervention may lower the disease burden of vast majority of CKD patients.

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