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STROKE: A CAUSE OF PROXIMAL TUBULAR DYSFUNCTION

Nephrology

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ABSTRACT

Background: AKI following stroke is associated with higher morbidity and mortality. Proximal tubular dysfunction as a measure of kidney dysfunction can predict acute kidney injury in patients of stroke. **Objectives:** To determine the association between stroke and proximal tubular dysfunction in non-CKD patients. **Methods:** This was a hospital based analytical cross-sectional study conducted in the outpatient department and/or inpatient wards of the Department of Internal Medicine, Swaroop Rani Nehru (SRN) Hospital associated with Moti Lal Nehru (MLN) Medical College, Prayagraj, Uttar Pradesh, India between June 2023 and May 2024. **Results:** The study analysed 120 stroke patients (47.5% males and 52.5% females) without CKD and any comorbidity, with a mean age of 63.37±13.58 years. Among total 120 patients 21.66% females and 8.33% males had proximal tubular dysfunction indicating female gender is more prone to develop proximal tubular dysfunction after stroke. 52.5% patients had ischemic stroke and 47.5% had haemmorhagic stroke. On the basis of TmP/GFR, Proximal tubular dysfunction was observed in 30% patients in which 17.5% patients had ischemic and 12.5% patients had haemmorhagic stroke (p value-0.320). However Ischemic stroke was noted in 52.5% and haemmorhagic stroke was found in 47.5%. **Conclusion:** Stroke can lead to significant dysfunction in the proximal tubules among patients of advanced age and longer illness duration. Therefore, our study clearly states that early detection of proximal tubular dysfunction in stroke cases with the help of TmP/GFR may have prognostic value and could be considered a suitable target for therapeutic intervention to reduce stroke related morbidity and mortality.

KEYWORDS

Acute Kidney Injury, Chronic Kidney Disease

INTRODUCTION

Stroke is the second leading cause of death worldwide, with 6.2 million dying from stroke in 2015, an increase of 830,000 since the year 2000.[1] The kidney and brain together regulate the sodium and water balance in the extracellular fluid to preserve normal homeostasis. Both organs exhibit several common physiological characteristics. They also get a significant amount of blood during the cardiac cycle and maintain constant perfusion in response to changes in arterial blood pressure.[2]

To date, research has focused on the role of kidney damage in causing brain dysfunction. However, the implications of brain damage on renal function remain largely unknown. This article explores the relation of kidney dysfunction following stroke.

Cerebrovascular diseases can impact kidney function because the brain regulates kidney activity through neural pathways. Organ cross talk refers to the mutual effects on distant organs through biological communication via central neural and peripheral humoral pathways.

The central pathway of brain–kidney interaction may be via the central autonomic network (CAN) and sympathetic nervous system.

The peripheral signaling pathways of brain kidney interaction may be regulated by auto regulation, inflammatory responses and neuroendocrine system. Therefore the objective is to determine the association between stroke and proximal tubular dysfunction in non-CKD patients.[2]

METHODS

Study Design: This was a hospital based analytical cross-sectional study conducted in the outpatient department and/or inpatient wards of the Department of Internal Medicine, Moti Lal Nehru (MLN) Medical College, Prayagraj, Uttar Pradesh, India between June 2023 and May 2024. All patients more than 18 years of age, of both gender, presenting with features suggestive of stroke (based on NCCT head) were included in the present study, However, patients with known renal dysfunction, with comorbidities, patients on drugs like mannitol, furosemide, and steroids that can cause kidney dysfunction were excluded from the study. Considering the alpha error to be 5% (type I error), beta error to be 20% (type II error; or 80% power), the minimum estimated sample size was rounded off to 120 patients with 95% confidence. We used nonprobability sampling technique – complete enumeration to enrol the patients. A predesigned, semi structured, pretested Performa was used to document the patient's socio demographic characteristics (including age, gender), detailed clinical history, presence or absence of co-morbidities, details of general physical examination, clinical examination, and laboratory investigations i.e., CBC, LFT, KFT, Serum Phosphorus, Urine Routine Microscopy, eGFR, Urinary Creatinine, Urinary Phosphorus, HbA1C, TmP/GFR, TRP, NCCT Head or NIHSS score. The proximal tubular dysfunction was assessed using Tubular Reabsorption of Phosphate (TRP) and the maximal tubular reabsorption of phosphate normalized to glomerular filtration rate (TmP/GFR). TRP [Formula: TRP = 1 - ((Up/Pp) x (Pcr/Ucr))] reflects the kidney's ability to reabsorb phosphate in the proximal tubule.[3,4] By analysing the ratio of urinary phosphate to plasma phosphate (Up/Pp) and comparing it to the ratio of plasma creatinine to urinary creatinine (Pcr/Ucr), TRP gives an estimate of how much phosphate is being reabsorbed versus excreted. A lower TRP might indicate impaired proximal tubular function, where phosphate reabsorption is compromised. TmP/GFR [Formula: TmP/GFR = Pp – (Up/Ucr) x Pcr] helps to assess the kidney's maximum capacity to reabsorb phosphate, adjusted for the glomerular filtration rate (GFR). It represents the point at which the proximal tubule becomes saturated with phosphate, beyond which any additional phosphate is excreted. TmP/GFR is crucial in understanding phosphate handling by the kidneys, especially in conditions that might lead to tubular dysfunction. A TmP/GFR level less than 2.6 mg/dl was considered as Proximal Tubular Dysfunction. Based on TmP/GFR, patients were divided into abnormal and normal groups and comparison was done with various parameters.

Statistical Analysis:

The data obtained was manually entered into Microsoft Excel and analysed using Statistical Package for Social Sciences (SPSS) v23. All the categorical variables were summarised using frequencies and percentages. Continuous variables were summarized using mean (standard deviation) and/or median (inter quartile range) (based on the results of data normality, tested using Kolmogorov–Smirnov test and the Shapiro–Wilk test). The correlation between various parameters like hemoglobin, age, sex with levels of TRP and TmP/GFR were assessed using Pearson's correlation coefficient. Statistical significance was considered at p value less than 0.05.

RESULTS

Out of 120 patients, 47.5% of subjects were males and 52.5% of subjects were females. The mean age of study population was 63.37±13.45 years. The mean duration of illness of the study

population was 5.18± 2.52 months. Out of 120 patients of stroke, 52.5% patients were of ischemic stroke and 47.5% patients were of haemorrhagic stroke. Total 30% patients developed proximal tubular dysfunction i.e., 17.5% of ischemic and 12.5% of haemorrhagic stroke. The mean TmP/GFR was 2.97± 1.25 which was not statistically significant (p value 0.320).

Age showed a significant negative correlation with function in the abnormal group ($r = 0.646$, $p < 0.001$), indicating that older age was strongly associated with reduced tubular function. Duration of illness had a significant negative correlation with function in the abnormal group ($r = 0.458$, $p = 0.005$), suggesting that a longer illness duration was associated with poorer function.

There was significant positive correlation with Hemoglobin levels in both the normal ($r = 0.357$, $p = 0.001$) and abnormal groups ($r = 0.454$, $p = 0.005$), with a strong correlation ($r = 0.368$, $p < 0.001$), indicating that higher hemoglobin levels were associated with better function.

There was a significant positive correlation with S. Phosphorus in all groups (normal: $r = 0.844$, $p < 0.001$; abnormal: $r = 0.603$, $p < 0.001$; overall: $r = 0.936$, $p < 0.001$).

U. Phosphorus had a significant positive correlation in the normal group ($r = 0.416$, $p < 0.001$) and overall ($r = 0.295$, $p = 0.001$), but not in the abnormal group ($r = -0.141$, $p = 0.413$).

We found a significant positive correlation with TRP in all groups (normal: $r = 0.283$, $p = 0.009$; abnormal: $r = 0.533$, $p = 0.001$; overall: $r = 0.408$, $p < 0.001$) respectively.

Table 1 and Figure 1 proportion of stroke Type in normal and abnormal tubular function in study participants (n= 120) while Table 2 depicts correlation of TmP/GFR with biochemical parameters according to their proximal tubular function status.

Table 1: Proportion Of Stroke Type In Normal And Abnormal Tubular Function In Study Participants (n= 120)

Type Of Stroke	Total Number of Patients (Percentage)	Normal Tubular Function (percentage)	Abnormal Tubular Function (percentage)
Ischemic Stroke	63(52.5%)	42(35.00%)	21(17.5%)
Hemorrhagic Stroke	57(47.5%)	42(35.00%)	15(12.5%)

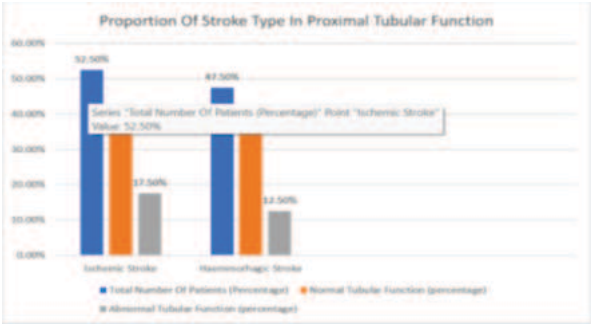

Figure 1: Proportion Of Stroke Type In Normal And Abnormal Tubular Function In Study Participants (n= 120)

Table 2: Correlation Of TmP/GFR With Biochemical Parameters According To Their Proximal Tubular Function Status.

Proximal tubular function	Normal			Abnormal			Total		
	r	p value	N	r	p value	N	r	p value	N
TmP/GFR	1		84	1		36	1		120
Bilirubin Total	-0.326	**0.002**	84	0.530	**0.001**	36	-0.039	0.673	120
Bilirubin (Direct)	-0.305	**0.005**	84	0.382	**0.021**	36	-0.161	0.078	120
Bilirubin (Indirect)	-0.274	**0.012**	84	0.652	**<0.001**	36	-0.078	0.414	120
SGOT	-0.295	**0.006**	84	-0.358	**0.032**	36	-0.101	0.273	120
SGPT	-0.027	0.807	84	-0.164	0.340	36	0.168	0.067	120
Protein	0.169	0.080	84	-0.055	0.752	36	0.140	0.128	120
Albumin	0.069	0.531	84	0.060	0.729	36	0.127	0.168	120
Urea	-0.228	**0.037**	84	-0.243	0.154	36	0.015	0.871	120
Creatinine	-0.225	**0.039**	84	0.211	0.216	36	0.179	**0.051**	120
eGFR	0.403	**<0.001**	84	0.109	0.526	36	0.118	0.200	120
HbA1c	-0.033	0.764	84	-0.043	0.805	36	0.045	0.623	120
Serum phosphorus	0.844	**<0.001**	84	0.603	**<0.001**	36	0.936	**<0.001**	120
Urine Phosphorus	0.416	**<0.001**	84	-0.141	0.413	36	0.295	**0.001**	120
TRP	0.283	**0.009**	84	0.533	**0.001**	36	0.408	**<0.001**	120

DISCUSSION

Our study revealed males 47.5% and females 52.5%. The mean age of participants was 63.37±13.58 years with median age of 65 years. This finding aligns with global reports showing a higher prevalence of stroke among elder persons (Ruo Li Chen et al 2010).[5] Among total 120 patients 21.66% females and 8.33% males had proximal tubular dysfunction indicating female gender is more prone to develop proximal tubular dysfunction after stroke. Out of total 120 patients, 52.5% patients had ischemic stroke and 47.5% had haemorrhagic stroke. On the basis of TmP/GFR, proximal tubular dysfunction was observed in 30% patients out of 120 patients of which 17.5% patients had infarct (ischemic stroke) and 12.5% patients had bleed (Haemorrhagic stroke) although which is not statistically significant (p value0.320). Leticia Alejandra Olguín Ramírez et al 2017 showed that ischemic stroke is more associated with AKI than haemorrhagic stroke.

In our study patients were divided into two groups 1) one with normal proximal tubular function (TmP/GFR>2.6 mg/dl) 2) other with abnormal proximal tubular function (TmP/GFR<2.6 mg/dl).

In patients having Proximal tubular dysfunction there was significant association between age and sex with more number of patients having dysfunction with increasing age i.e., 50%, 33.3% and 8.3% in the age above 70 years, 60-69 years and 40-49 years respectively and Females (72.2%) being more prevalent than males (27.8%). Kamil Chwojnicki et al 2016[6] demonstrated that decreased eGFR (<60 mL/min/1.73m2 according to MDRD or CKD-EPI) or ACR≥30mg/g were detected in 40.38% (23.07% Men, 55.32% Women; P<0.01) among post stroke survivor patients.

S. phosphorus was significantly lower in the abnormal group (2.10 mg/dL) compared to the normal group (3.86 mg/dL) ($p < 0.001$), and TRP was significantly lower in the abnormal group (74.74%) compared to the normal group (99.15%) ($p = 0.001$) signifying that dysfunctional proximal tubules will not be able to absorb phosphorus to their maximal capacity thereby lowering the values of both TRP (Tubular Reabsorption of Phosphate) and TmP/GFR. Johanna E. Emmens et al 202261 demonstrated that TmP/GFR can be used as a marker of proximal tubular dysfunction.

Other parameters like duration of illness, total leukocyte counts, platelet counts, liver enzymes including SGOT and SGPT and markers of renal function such as serum urea, serum Creatinine and estimated glomerular filtration rate were not significantly associated with abnormal Proximal tubular dysfunction.

In assessing proximal tubular function, age showed a significant negative correlation with function in the abnormal group ($r = -0.646$, $p < 0.001$), indicating that older age was strongly associated with reduced function.

Duration of illness had a significant negative correlation with function in the abnormal group ($r = -0.458$, $p = 0.005$), suggesting that a longer illness duration was associated with poorer function.

There was found to be significant positive correlation with Hemoglobin levels in both the normal ($r = 0.357$, $p = 0.001$) and abnormal groups ($r = 0.454$, $p = 0.005$), with a strong overall correlation ($r = 0.368$, $p < 0.001$), indicating that higher hemoglobin levels were associated with better function.

A significant positive correlation was observed with S. Phosphorus in all the groups (normal: $r = 0.844$, $p < 0.001$; abnormal: $r = 0.603$, $p < 0.001$; overall: $r = 0.936$, $p < 0.001$). Urine Phosphorus had a significant positive correlation in the normal group ($r = 0.416$, $p < 0.001$) and overall ($r = 0.295$, $p = 0.001$), but not in the abnormal group ($r = -0.141$, $p = 0.413$).

We observed a significant positive correlation with TRP in all groups (normal: $r = 0.283$, $p = 0.009$; abnormal: $r = 0.533$, $p = 0.001$; overall: $r = 0.408$, $p < 0.001$).

CONCLUSION

Stroke can lead to significant dysfunction in the proximal tubules among patients of advanced age and longer illness duration. Therefore, our study clearly states that early detection of proximal tubular dysfunction in stroke cases with the help of TmP/GFR may have prognostic value and

could be considered a suitable target for therapeutic intervention to reduce stroke related morbidity and mortality.

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