Research Article

Renal Dysfunction in Ischemic Stroke Subjects

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Abstract | To determine whether decreased kidney function is a risk-factor in first-ever ischemic stroke. The study was conducted from Jan, 2013 to Jan, 2014 in Services and Jinnah Hospital Lahore, Pakistan. A total of 150 subjects were included in this study, divided into ischemic stroke group (n=100) and control (n=50). Kidney function estimation was done using serum creatinine and blood urea along with eGFR calculation by MDRD equation. Kidney dysfunction was defined as eGFR of <60 ml/min/1.73m^2. Statistical analysis was donedone by using SPSS. The serum creatinine of ischemic stroke patients was found to be 2.41 mg/dl compared to 0.93mg/dl in controls. The blood urea in ischemic stroke group was 67.3 mg/dl in contrast to 34.6 mg/dl in controls. The eGFR in ischemic stroke patients was calculated to be 54.62ml/min/1.73m^2, compared to 85.90 ml/min/1.73m^2 for controls. Prevalence of eGFR <60 ml/min/1.73m^2 in patients with stroke was 63%, significantly higher ($p<0.05$) than in controls. Moderate to severe reduction of eGFR in patients with ischemic stroke indicated renal impairment and kidney dysfunction. The risk of first ever ischemic stroke increases with low eGFR.

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1. Introduction

Stroke has been known to the third most common cause of death in the world, after cardiovascular diseases and all types of cancers (Banerjee et al., 2006). 15 million people suffer from stroke worldwide annually. Among these, 5 million die and 5 million suffer from a persistent disability resulting a huge burden on families and communities and only 5 million-people attain optimal recovery (Roger et al., 2012). About 80% strokes are ischemic stroke. Ischemic stroke is defined as severe disturbance of the blood to the specific parts of brain i.e. cerebellum, brain stem or spinal cord in a focal area leading to infarction. Ischemic stroke results in bland ischemia (non-hemorrhagic ischemia) and infarction in a typically vascular distribution. The vascular distribution is often very helpful in differentiating stroke from tumor or demyelination (Wityk et al., 2007).

The non-modifiable risk factors of stroke are age, gender, ethnicity and genetics. Whereas, cardiovascular diseases, hypertension, diabetes, hypercholesterolemia, smoking, alcohol consumption, drug users and inactive lifestyles are potentially modifiable risk factors for ischemic stroke (Carter et al., 2007).

The worldwide epidemic of chronic kidney disease (CKD) will result in a more kidney dysfunction affected individuals over the next decade (Coresh et al., 2007), doubling the number of end-stage renal disease patients (Golssteen et al., 2001) and a

subsequent increased morbidity and mortality rate in CKD complications. Increased mortality in elderly, hypertensive and myocardial infarction or stroke suffered patients has been found associated with elevated serum creatinine. Wannamethee et al., 1997 investigated the relationship between blood creatinine concentration and the risk of major ischemic heart disease, stroke events and all-causes of mortality in a general population of middle-aged men. Creatinine concentration was found to be correlated with a significant increase in stroke in both normal and hypertensive men.

Renal dysfunction has been suggested as risk factor and prognostic factors in cerebrovascular diseases. Regarding the association of renal dysfunction with stroke subtypes, conflicting results have been observed (Bos et al., 2007; Nakayama et al., 2007). The aim of the present study was to investigate the association of renal function with first-ever ischemic stroke patients.

2. Materials and Methods

2.1 Research design

The study was carried in different hospitals specifically Services hospital and Jinnah hospital, Lahore. The study period extended from January 2013 to January 2014. A total of 150 subjects were included in this study which were divided as control group (n=50) and ischemic stroke group (n=100). The control group was selected after examination by the physician and they were found healthy. They were included for comparison with ischemic stroke subjects.

Subjects with confirmed clinical diagnosis of stroke by physician were included and they were brought to the hospital within 48 hours. It had been made sure that the patients were first-ever ischemic stroke and did not have a previous stroke history. The data was collected with the help of questionnaire regarding the age, diabetes, hyperlipidemia, high blood pressure, heart diseases, personal and family history of stroke, obesity, smoking, and a sedentary lifestyle. The ethicsal permission was granted by the university board of Lahore College for Women University Lahore and by the ethical committee of the hospitals. After collection of the blood the serum was separated by centrifugation.

2.2 Calculation of eGFR

GFR was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) formula. This formula in the form of equations was developed in 1999 for the estimation of eGFR by routine measurement of serum creatinine, along with the readily available demographic variables age, gender and race (Levey et al., 1999).

For creatinine in mg/dl:

$$eGFR = 186 \times Serum\ Creatinine^{-1.154} \times Age^{-0.203} \times (0.742\ if\ female) \times (1.212\ if\ black).$$

According to the National Kidney Foundation definition, CKD is a kidney damage reflected by an estimated GFR of <60mL/min/1.73 m^2 of body surface area. CKD was further classified into moderate reduction of GFR of 45 to 60 and severe reduction of <45 mL/min/1.73 m^2. This further categorization is a Modification of National Kidney Foundation classification scheme chosen based on prior studies in patients with cardiovascular disease. Higher values i.e. >60 were not further categorized because the MDRD equation have substantial errors for GFR estimates in the normal – high range (Stevens et al., 2007; Brosius et al., 2006; Rule et al.,2004).

2.3 Statistical analysis

The data was then analyzed statistically using statistical software package SPSS version 13.0 for windows. The comparison of clinical characteristics and renal parameters between the ischemic stroke and control groups was performed with Students T- test.

3. Results and Discussion

It was observed that there were 48% females and 52% males in the studied groups.

The average age of ischemic stroke subjects was 62.3 ± 1.48 yrs. and that of controls was 60.6 ± 1.79 yrs. with non-significant difference between the two groups ($p \geq 0.05$). The average calculated BMI of ischemic stroke and control subjects was 26.4 ± 0.32 kg/m^2 and 26.36 ± 0.45 kg/m2 respectively with non-significant difference between the groups ($p \geq 0.05$).

Diabetes was frequent in 43% of the subjects. The frequency of Irregular heart beat due to hypertension in ischemic stroke subjects was 38%, whereas, other heart diseases or problems found in the subjects was 22%. 56% of the subjects took excessive oily or high

cholesterol food on regular basis. 32% of the subjects with ischemic stroke smoked as well. About 71% of the subjects had sedentary life style, while 29% did walk or other moderate activity for at least 30 minutes a day or at least 3 hours a week.

The demographic and clinical parameters of both groups were presented in Table 1. As compared with controls, subjects with ischemic stroke had a lower eGFR and were older. The prevalence of an eGFR (<60 ml/min/1.73m^2) in patients with stroke was 63% significantly higher than in controls.

The subjects was further categorized into 3 categories on the basis of CKD and its severity i.e. stage 1 (including patients with normal GFR), stage 2 (patients with moderate reduction of GFR) and stage 3 (patients with severe reduction of GFR). Baseline clinical features of these groups estimated by MDRD equation were shown in Table 2. On the basis of the formula of renal function estimation 16% of ischemic stroke subjects had moderate reduction of eGFR ranging within 45 to 60 ml/min/1.73m^2 and 45% of the patients had severe reduction of eGFR that was <45 ml/min/1.73m^2. The rest of 39% ischemic stroke patients had eGFR >60 ml/min/1.73m^2. The differences of age and gender were also seen in the three groups. Subjects with extremely low GFR were older and were more likely to be women (Tables 1 and 2).

In our study, subjects were from single ethnicity and from the same area. It was observed that there was a relationship between kidney dysfunction and future risk of ischemic stroke and it has been confirmed that subjects with ischemic stroke have reduced kidney function or greater prevalence of CKD when compared to controls. In other studies, the relationship between ischemic and hemorrhagic types of stroke has been carried out but no study has been carried out with ischemic stroke. This study was carried out on homogenous sample (ischemic group) to reduce confounding factors.

Our central finding is that, low eGFR and the presence of CKD is a strong predictor of first-ever stroke. The correlation between renal function and stroke has previously been noted in a study in UK[7], whereas high normal serum creatinine levels or low eGFR were a risk factor for stroke in general population. Renal function as assessed by blood urea showed an association similar to that observed with creatinine, with significantly elevated blood urea concentration in ischemic stroke patients when compared to controls. A slightly weaker association between blood urea and risk of stroke was observed by Wannamethee et al., 1997.

Table 1: Clinical characteristics of ischemic stroke and control subjects.

Sr. no.	Mean	Groups		P value
		Ischemic stroke	Controls	
1	Age (yrs)	62.3 ± 1.48	52.6 ± 1.79	0.11**
2	Serum Creatinine (mg/dl)	2.41 ± 0.244	0.93 ± 0.28	0.001**
3	Blood Urea (mg/dl)	67.3 ± 5.77	34.6 ± 1.25	0.001**
4	eGFR (ml/min/1.73m^2)	54.62 ± 4.55	85.90 ± 4.34	0.001**
5	eGFR <60 ml/min (%)	63%	6%	0.001**

GFR, glomerular filtration rate; **p≤0.001--- Highly significant.

Table 2: Mean renal functional parameters in different stages.

Characteristics	Stage 1 (>60)	Stage 2 (45 – 60)	Stage 3 (<45)	P-value
Total Percentage (%)	39%	16%	45%	
Age (yrs)	60.97 ± 2.14	59.3 ± 5.37	64.62 ± 1.97	0.361
Female (%)	43.6% (17)	31.25% (5)	57.8% (26)	
Male (%)	56.4% (22)	68.75% (11)	24.2% (19)	
Serum Creatinine (mg/dl)	0.88±0.045	1.36±0.05	4.10±0.42	0.00**
Blood Urea (mg/dl)	40.21±4.17	51.25±7.19	96.49±10.54	0.001**
eGFR (ml/min/1.73m^2)	95.22±7.36	53.19±1.51	19.95±1.6	0.001**

**p ≤ 0.001 --- Highly significant.

Glomerular filtration rate is of central importance for measuring renal function. Serum creatinine concentration is mainly determinant of the glomerular filtration rate and is used as an index of renal function (Waller et al., 1991). However, inference of renal dysfunction from the serum creatinine level is complicated by the differing rates of creatinine production among individuals, as muscle mass vary. This is why; women and the elderly people often have low serum creatinine levels (Maaravi et al., 2007; Froissart et al., 2005). There are substantial errors for GFR estimation by MDRD in the normal high range[11], and creatinine-based estimations are not reliable with particularly low creatinine generation.

There are number of evidences regarding the correlation between renal dysfunction and cerebrovascular morbidity (Bos et al., 2007; Nakayama et al., 2007) CKD is also found to be associated with increased risk of ischemic stroke (Koren-Morag et al., 2006).

Mechanisms under investigation showed that under the impact of renal dysfunction risk of cerebro-cardiovascular diseases increases. The continual increase in cerebrovascular risk with increased GFR was associated with decrease renal function, oxidative stress, inflammation and conditions that promote clotting (Johnson et al., 2007; McCollough et al., 2007; Soriano et al., 2007; Valkonen et al., 2001). Which leads to atherosclerosis and endothelial dysfunction.

We identified a significant prevalence of kidney dysfunction in patients presenting early to the hospital with ischemic stroke (<24 h) by using the eGFR. A study conducted by Mc Walter *et al*, also reported similar results (Mc Walter et al., 2002). In our study the higher frequency of renal dysfunction may be because our 80% of subjects were hypertensive.

In this study, patient with an eGFR of <45 ml/min were most significantly associated with stroke. This is in contrast to most other studies in which mild reduction of eGFR of 45 – 60 ml/min was associated significantly with stroke (Losito et al., 2011; Tsagalis et al., 2008). In these studies the eGFR distribution was normal with large number of patients having normal to mild lowering GFR. In our study, on the other hand, a sharp lowering of GFR was observed in many patients.

The cause and effect relationship between kidney dysfunction and ischemic stroke is vague until now. In this study low eGFR (estimated glomerular filtration rate) is correlated with an increased risk of future ischemic stroke. This result is in consistent with the study conducted in America (USRDS Annual Data Report, 2009). A relationship of mild to severe renal disease to long-term mortality in persons with self-reporting stroke has also been found recently (Ani et al., 2010). Our population differs from this as method of enrolment, hospital setting and type of stroke analyzed. Also, unlike other studies it was not a long-term follow-up study.

The clinical implication of this study indicates that people suffering from kidney dysfunction may be at high risk for future ischemic stroke. Patients with early stages of kidney dysfunction need close surveillance.

Our study has several probable limitations. First, the study is hospital based, so stroke patients treated at home were not included. Secondly, although the use of the MDRD equation is a quite reliable mean of estimating GFR, as has been previously used in many clinical trials but it tends to overestimate GFR in high levels of renal function and is also affected by age. Finally, another limitation of our study was the absence of follow-up or mortality data; therefore, we were not able to interpret the effect of renal dysfunction on mortality. Despite these limitations, our study has strong basis to reinforces the belief that there is a strong correlation between renal impairment and first-ever ischemic stroke and that renal function proves an important independent risk factor for first symptomatic stroke events.

Conclusion

In this study, kidney function found to be significantly associated with ischemic stroke. A reduced eGFR showed renal dysfunction in few ischemic stroke patients (16%) while a severely reduced eGFR was observed in 45% patients. This suggests that estimated GFR associated to the other known prognostic factors as kidney dysfunction or CKD was an independent risk factor for ischemic stroke.

Author's Contribution

SS: Conceived idea and designed the project &writing

of Manuscript
FM: Analysis & writing of manuscript
TF: Analyzed the results
SN: helping in experimental work & writing manuscript
RT: data collection and did experimental work.

Conflict of interest

The authors have declared no conflict of interest.

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