Original Research Article

Serum uric acid level in acute ischemic stroke in eastern India

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ABSTRACT

Background: Present study was done to estimate the level of serum uric acid in acute ischemic stroke and to find out whether it is protective against or increases the risk for ischemic stroke and its effect on stroke outcome.
Methods: A total of 100 patients and 100 controls were taken randomly. Risk factors of stroke were considered such as hypertension, diabetes, adverse lipid profile, smoking and obesity. Serum uric acid level was measured in both cases and controls. Modified National Institute of Health (NIH) stroke scale score was calculated at the time of admission and discharge. Statistical analysis was done using SPSS 21.0 software.
Results: Out of 100 patients studied 65 were males and 35 were females. The mean serum uric acid level in stroke cases was 6.11±1.47 where as it was 4.85±1.12 in controls. SUA levels was higher among males than females. The mean SUA in hypertensive subjects (6.58±1.33) was significantly higher than in normotensive subjects (5.23±1.42). There was statistically significant difference between SUA levels in diabetic (6.66±1.26) and non-diabetic patients (5.63±1.49). Mean SUA among overweight patients was (7.0±1.16) where as it was (5.22±1.23) in patients with normal weight. The mean SUA in smokers (6.33±1.38) was higher than that in non-smokers (6.02±1.51). There was significant positive correlation between SUA an NIH stroke scale score(P<0.05). SUA levels were significantly higher in patients who succumbed as compared to those who were discharged from hospital.
Conclusions: SUA can be used as a marker for increased of stroke. Higher SUA is associated with a bad prognosis.

Keywords: Diabetes, Hypertension, Obesity, Smoking, Serum uric acid

INTRODUCTION

Uric acid is the final product of purine metabolism in human beings. For years, hyperuricemia has been thought to be the same as gout, but uric acid has now been identified as a marker for a number of metabolic and hemodynamic abnormalities.

Several large studies have provided conflicting results regarding the clinical significance of elevated serum uric acid levels in cardiovascular or cerebrovascular diseases. Many studies including the NHANES study concluded that uric acid is an independent risk factor for development of cardiovascular and cerebrovascular diseases.[1]

In contrast the Framingham heart study concluded that an association between hyperuricemia and cardiovascular diseases merely reflects the link between serum uric acid and other risk factors, including hypertension, renal disease, elevated lipoprotein levels and the use of diuretics.[2] Therefore it is unclear whether SUA promotes or protects against the development of cerebrovascular disease or simply acts as a passive marker of increased risk. If SUA would be identified as an etiological agent in the pathogenesis of vascular diseases, its therapeutically reduction could contribute to cardiovascular and cerebrovascular morbidity and mortality decrease. Amidst this controversy and lack of Indian data, it was decided to carry out the present study

with the aim of studying uric acid levels in patients of acute ischemic stroke.

METHODS

Setting-The work was carried out in the medical wards of MKCG Medical college and Hospital, Berhampur, Odisha.Case control study was design. The study was carried out from November 2014 to November 2016. The work was carried out after approval from the Institutional Ethics Committee of MKCG Medical College Hospital, Berhampur, Odisha, India. Study group (stroke cases): 100, control group: 100

Inclusion criteria

- Patients with stroke as defined by WHO criteria "a syndrome of rapidly developing clinical signs of focal or global neurological disturbance lasting for more than 24 hours.
- All patients who presented within 48 hours of onset of stroke and who gave consent were included.

Exclusion criteria

Patients with previous history of TIA/CVA, who are on thiazide diuretics and cytotoxic drugs, Pyrazinamide, ethambutol, nicotinic acid, levodopa, probenecid, allopurinol, losartan, atorvastatin, gout, alcohol abuse, chronic renal insufficiency, whose CT scan shows haemorrhage or other space occupying lesions, Patients who were known cases of cardiac diseases which could be the sources of emboli or whose echocardiogram shows evidence of emboli, patients with malignancy, hypothyroidism, active Infection, chronic inflammatory bowel disease.

Hypertension was defined as a blood pressure of ≥ 140/90 mm of Hg on 2 or more occasion or ongoing treatment for systemic hypertension or previously diagnosed cases of systemic hypertension.

Diabetes mellitus was defined as fasting blood sugar of ≥126 mg/dl or history of receiving treatment for diabetes mellitus or previously diagnosed diabetes mellitus. Hypertriglyceridemia: Triglyceride ≥ 150 mg/dl or specific medications;

Person who smoked at least 10 cigarettes per day for 6 months/more or the one who has smoked daily for more than 1 year or more regardless of the number of cigarettes smoked per day was considered as smoker. A BMI (Body Mass Index) of ≥ 25 was taken as marker of obesity.

Statistical analysis

Statistical analysis was performed with the help of SPSS 21.0 software. It included the usual descriptive and univariate analysis. Student t test was used to compare continuous variables and X2 test was used to compare categorical variables. Unadjusted odds ratio with 95% confidence interval and P value were calculated. Multivariate analysis was performed to study the association of SUA with acute ischemic stroke in multivariate context. Ischemic stroke was taken as dichotomous independent outcome variable and conventional risk factors (e.g. hypertension, diabetes mellitus etc.) as dependent predictor variables. P value less than 0.05 was taken as significant.

Biochemical measurements

Serum uric acid was measured with the Uricase method. All other biochemical measurements were performed as per the standard procedures.

Modified National Institute of Health (NIH) stroke scale score was calculated for all the patients of stroke at the time of admission and before discharge from hospital.

RESULTS

Out of 100 patients studied, 63 were males and 37 were females. Male: female ratio was 1.7: 1. The controls were appropriately age and sex matched.

The mean age of cases was 60.05±9.98 and the range was 36 to 86, whereas the mean age of controls was 60.32±10.11 (with the range from 36 to 87 years). The difference between the two groups was not statistically significant (P = 0.85). Mean SUA level in cases was 6.48±1.92 mg/dl whereas it was 5.09±1.07 mg/dl for controls. Mean SUA level was significantly higher in cases as compared to controls (P = 0.00).

This analysis shows that hypertension, smoking, and obesity were found to be independently associated with ischemic stroke. It was also found that serum uric acid was also independently associated with ischemic stroke. The mean SUA was 6.42±1.42 mg/dl for males and 5.53±1.40 mg/dl for females. SUA values were higher among males as compared to females, but this difference was statistically significant (P = 0.003).

The mean SUA in hypertensive subjects (6.58±1.33 mg/dl) was higher than that in normotensive subjects (5.25±1.42 mg/dl). This difference was statistically significant (P<0.001). There was a statistically significant difference between SUA levels in diabetic (6.66±1.26 mg/dl) and non-diabetic patients (5.63±1.49 mg/dl) (P < 0.001). Mean SUA in overweight patients was 7±1.16 mg/dl whereas it was 5.21±1.23 in patients who had a normal weight. There was a statistically significant difference in SUA levels in obese and non-obese subjects (P < 0.001).

Table 1: Comparison of conventional risk factors for ischemic stroke (confounding variables) between cases and controls.

Variable		Cases	Controls	Total	Chi square	OR	CI	P value
Age		57.50	55.80					0.018
Hypertension	Yes	59	4	63	0.140	0.68	0.092-5.685	1.000
	No	41	96	137				
Diabetes	Yes	47	2	49	0.007	1.130	0.069-18.591	1.000
	No	53	98	151				
Hypertriglyceridemia	Yes	61	28	89	1.978	0.532	0.219-1.290	0.175
	No	37	72	111				
Smoking	Yes	28	9	37	1.140	1.320	0.306-5.686	0.486
	No	72	91	163				
Obesity	Yes	50	9	59	0.211	1.533	0.245-9.587	0.500
	No	50	91	141				

Table 2. An association of various risk factors with ischemic stroke in the multiple logistic regression analysis.

Risk factor	Odds ratio	Z-value	95% CI	P value
Age	2.219	0.797	0.798-6.618	0.126
Hypertension	0.091	2.393	0.021-0.406	0.002
Diabetes Mellitus	0.081	4.040	0.003-0.090	0.001
Hypertriglyceridemia	0.459	0.779	0.97-1.499	0.167
Smoking	0.381	0.996	0.971-1.498	0.617
Serum Uric acid	0.112	2.193	0.31-0.397	0.001
Obesity	0.221	1.503	0.050-0.970	0.045

SUA levels were significantly higher among smokers as compared to non-smokers (6.38±1.38 versus 6.021±1.51, P = 0.318).

Mean SUA level was lower in the patients with lacunar stroke as compared to the patients with larger infarcts (5.31±1.03 mg/dl versus 6.741.03 mg/dl) and this difference was statistically significant as the (P <0.001).

The correlation between SUA and stroke outcome was studied based on NIHSS score. The mean SUA levels were higher in patients with poor outcome as compared to those with good outcome (P value<0.001).

Mean SUA for discharged patients (n = 91) was 6.16±1.68 mg/dl and it was 7.26±0.78 mg/dl for the patients who died in the hospital (n = 9). SUA levels were significantly higher in the patients who succumbed as compared to those who were discharged from the hospital (P = 0.014).

DISCUSSION

Several epidemiologic studies have reported a significant association between elevated SUA and increased cerebrovascular diseases. Although uric acid is one of the most important antioxidants in plasma/serum and appears to be neuroprotective in animal models, the results from human studies are controversial.

In the apolipoprotein mortality risk study (AMORIS) Holme et al, found increased uric acid to be a risk factor for myocardial infarction, congestive cardiac failure and stroke. A meta-analysis of 16 prospective cohort studies including 2,30,000 patients concluded that the elevated uric acid in adults.

Is associated with modest but statistically significant elevated risk of stroke and mortality. The authors have also suggested that the exact mix of prooxidant versus antioxidant properties for uric acid depends on a complex mix of transition metals and so forth.

In present study was found that the levels of SUA were significantly elevated in ischemic stroke within 24 hours after symptom onset. Early measurement of SUA increases the relevance of the study. There are limited studies on the association of SUA levels with stroke and the outcome of stroke. Hence the relevance of the study.

Out of the 100 cases taken in to study the male to female ratio was 1.8:1. The mean age of the cases was 56.35±9.95 years with the range of 30 to 70 years. These findings are consistent with the data published by Pandiyan et al who observed a male: female ratio of 1.9:1.[3]

The mean SUA levels were higher among males (6.42±1.42) than females (5.52±1.40) and this difference

was statistically significant (P value = 0.003). Longo-Mbenza et al found significantly higher SUA level in males (6.6±7 versus 5.8±6 mg/dl, P < 0.01).[4] Similar results were obtained in the study by Milionis et al and in the Rotterdam study (348 versus 302 μmol/L).[5,6] Framingham heart study also showed higher SUA levels in males.

In present study, most of the patients were in the age group of 50 years and above i.e 89% of patients.

Stroke occurs predominantly in the middle and late years of life. When serum uric acid level was compared between age groups ≥50 years and <50 years in cases and controls; even though the level was increased among older age group it was not statistically significant.

Uric acid levels were found to be significantly higher among patients with stroke than the control in this study. A study by Folsom HA et al also showed increased uric acid levels in patients with ischemic stroke.[7] Longo Mbenza et al in a study among African patients found that uric acid levels were elevated among stroke patients. In a study by Iribarreen, Folsom and Eckfeldt et al they tried to find the correlation between uric acid levels and asymptomatic carotid atherosclerosis.[8] They found a positive correlation between the two and that uric acid level can be used to predict future cerebrovascular events.

It was also found that SUA levels among hypertensive patients were significantly higher as compared to normotensive patients (6.58±1.33 versus 5.44±1.42 mg/dl, P < 0.001).

Milionis et al observed that SUA levels were higher in hypertensive subjects compared with non-hypertensives (5.4±1.6 mg/dl versus 5.0±1.6 mg/dl, P = 0.04) Lehto et al also found that the prevalence of hypertension among hyperuricemic subjects was higher as compared to the patients with SUA levels in the normal range (67.3% versus 41.2%, P < 0.001).[9]

Study found that SUA levels in patients suffering from diabetes mellitus were significantly higher as compared to those in non-diabetic subjects (6.66±1.26 versus 5.63±1.49 mg/dl, P < 0.001). Our findings are in accordance with the findings of Longo-Mbenza et al who observed significantly higher frequency of hyperuricemia among diabetic patients.[4] Lehto et al studied uric acid levels in diabetic's patients prospectively and showed that it was more elevated in the diabetics who developed stroke.[9]

In this study, it was shown that hyperglycemia is associated with poor outcome. Among the stroke patients, outcome in diabetic and non-diabetic was analysed, diabetics had higher percentage of poor outcome (60%) than good outcome (40%), and statistically significant association (P = 0.009) was seen. A study by Wang, Lim et al showed that hyperglycemia increases stroke mortality.[10] In yet another study by Yoon, et al they found high blood glucose is associated with poor outcome after ischemic stroke.[11]

In this study, serum uric acid level in obese stroke cases (7.004±1.16) were higher than in non-obese stroke cases (5.21±1.23) and it was statistically significant (p value <0.001). Milionis et al also found significantly higher levels of SUA among overweight patients (BMI > 25) as compared to non-obese patients (5.4±1.6 versus 4.9±1.5 mg/dl, P = 0.004).

In this study, it was observed that mean SUA level in smokers was higher as compared to non-smokers (6.33±1.38 versus 6.021±1.51 mg/dl, P = 0.318) but it was not statistically significant.

Similarly, Strasak et al also observed a positive correlation between SUA and smoking (r = 0.11, P < 0.001).[12] Mozos et al also found that SUA levels were significantly higher in smokers as compared to non-smokers (5.7±1.3 versus 5.0±1.1 mg/dl, P < 0.05).

In this study, we found a positive correlation between SUA and serum triglyceride levels (P < 0.001 for triglycerides) Bansal et al found a significant correlation between SUA and triglyceride (P < 0.05) our findings correlate with the above-mentioned studies.[13]

On multiple regression analysis, correlation of SUA with ischemic stroke was found to be independent of other major risk factors for stroke as shown in. These findings are in accordance with most of the data published worldwide.

We used National Institute of Health Stroke Scale (NIHSS) to quantify stroke severity. It has been proved in earlier studies that higher NIHSS score portends poor prognosis following stroke. In the present study, there was a significant correlation between SUA level and NIHSS scores on discharge (P value<0.001).

SUA levels were also higher in patients with large artery stroke as compared to those with lacunar stroke and this difference was found to be statistically significant (6.74±1.34 versus 5.305±1.23 mg/dl, P < 0.001).

In this study, out of 100 patients, 9 patients died and remaining 91 patients were discharged from the hospital. The mean SUA levels were significantly higher in the patients who succumbed as compared to the patients who were alive at discharge (7.256±0.78 versus 6.16±1.68 mg/dl, P = 0.014).

Karagiannis et al found an independent relationship between higher SUA levels on admission and death (OR = 1.37, 95% C.I. = 1.13 - 1.67, P = 0.001). Weir et al noted that higher serum urate value was significantly associated with bad outcome (OR = 0.78 per additional 0.1 mmol/L; 95% C.I. = 0.67 - 0.91).

Mozos et al, also found that the patients who died had a significantly higher SUA values as compared to those who were discharged home (9.5±3 mg/dl versus 6.9±4 mg/dl, P = 0.003). The findings of this study were in accordance with studies mentioned above.

CONCLUSION

From the above discussion, it is concluded that SUA levels are associated with increased risk for stroke as well as with poor prognosis after stroke. Further long term prospective studies are needed to establish the role of SUA in ischemic stroke. Also, trial of SUA lowering drugs in stroke patients as well as in those at increased risk of stroke can be worth considering.

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