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Research Article

Serum uric acid level in patients of acute stroke

Chandan Prasad[1]*, Naresh Chandra Dwivedi[1], Poonam Gupta[1], Shailendra Kumar Shukla[1], Rita Shukla[2], Rakesh Kumar Yadav[1], Sujit Verma[1]

[1]Department of Medicine, MLN Medical College, Allahabad, Uttar Pradesh, India
[2]Department of Gynecology, MLN Medical College, Allahabad, Uttar Pradesh, India

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***Correspondence:**
Dr. Chandan Prasad,
E-mail: drchandankgmu05@rediffmail.com

ABSTRACT

Background: Controversial results regarding the association of serum uric acid (SUA) with acute stroke and its mortality outcome are consistently reported. Hence, present study was done to estimate SUA as a risk factor and its prognostic significance in patients of acute stroke.
Methods: Total 110 patients of acute cerebrovascular accidents admitted were studied and serum uric acid was measured within 48 hours of admission.
Results: The study comprised of 66 males and 44 females of whom 63 had hemorrhagic and 47 had ischemic stroke. Mean SUA of cases was 6.69±2.34mg/dl was significantly higher than age and sex matched controls. 50% of cases were found to be hyperuricemic. Mean SUA was greater in males, elderly (>60 years), diabetics, hypertensive, ischemic stroke patients, but their difference was not found to be statistically significant. However, mean SUA level in dyslipidemics (7.07±2.29) mg/dl was significantly higher. Prevalence of hyperuricemia was highest among patients with low HDL (58.33%).Mean SUA in expired cases was significantly higher than survived. Also among stroke subtypes, mean SUA was significantly higher in expired than survived ischemic stroke cases.
Conclusions: The study concludes that SUA level was significantly elevated in patients of acute stroke. Elevated SUA was associated with higher mortality, more in ischemic stroke patients. Hence, SUA can be considered as a risk factor and poor mortality outcome in patients of acute stroke.

Keywords: Uric acid, Cerebrovascular accident, Ischemic, Hemorrhagic, Stroke subtypes

INTRODUCTION

Stroke is the second most common cause of death worldwide after ischemic heart disease.[1] Stroke is one of the main clinical manifestation of cerebrovascular disease and studies investigating the relation between the uric acid and stroke have been inconsistent. Many studies including the NHANES study concluded that uric acid is an independent risk factor for development of cardiovascular and cerebrovascular diseases.[2] Some studies reported a positive independent relationship between uric acid and stroke whereas others demonstrated that uric acid did not relate significantly to stroke occurrence.[3] Therefore the role of uric acid as a risk factor for acute stroke is controversial and there is little information about it, so in this study we decided to determine serum uric acid levels in patients with acute stroke as a risk factor and its prognostic significance.

METHODS

The proposed cross sectional study is conducted in the Department of Medicine, S.R.N. Hospital, Allahabad, Uttar Pradesh, India.

Inclusion criteria

All patients 18 years of age or greater, presenting within 48 hours of stroke onset.

Exclusion criteria

Patients with a known or possible cardiac source of emboli, duration of symptoms more than 48 hours, patients receiving common drugs affecting serum uric acid level e.g. diuretics, losartan, allopurinol, probenecid, atorvastatin, fenofibrate, renal or liver disease, thyroid dysfunction, malignancy.

Detailed history, clinical examination and relevant laboratory investigations were done as per the proforma. All patients underwent CT scan brain (plain) to establish the ischemic lesion and hemorrhage stroke. Serum uric acid, blood urea, serum creatinine, fasting blood glucose, HbA1c, fasting lipid profile and free T3, T4, TSH were estimated. ECG, chest x-ray and echocardiogram were also done to assess the cardiac status. Age and sex matched healthy controls were selected and screened for stroke risk factors and assessed for serum uric acid.

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

Diabetes mellitus was defined as HbA1C >6.5 gm% or history of receiving treatment for diabetes mellitus or previously diagnosed diabetes mellitus.

Dyslipidemia are generally characterized clinically by increased plasma levels of cholesterol (>200mg/dl), triglycerides (>150mg/dl), or both, variably accompanied by reduced levels of HDL (<40mg/dl) cholesterol.

Biochemical measurements

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

Statistical analysis

The graph pad software version 6.0 was used to analyze data. Assuming normal distribution, the numerical data was compared using t test while chi square test was used for categorical variables.

RESULTS

Out of 110 acute stroke patients 66 (60%) were males, 44 (40%) were females. Also 63 (57.27%) had hemorrhagic and 47 (42.72%) had ischemic stroke. Baseline characteristics of cases are mentioned in Table 1. The mean age of study population was 64.77±10.9 years (30-90 years). Mean age of males among cases was 64.69±12.89 years and that of females was 63.68±11.23 yrs. Mean SUA level in cases was 6.69±2.34 mg/dl whereas it was 4.72±0.9 mg/dl for controls. Mean SUA level was significantly higher in cases as compared to controls (P =0.0001) (Table 2) and 50% of acute stroke patients were found to be hyperuricemic**.**

Table 1: Baseline characteristics of cases.

Baseline parameters	Mean±SD
Age (years)	64.77±10.90
HbA1c	6.85±1.13
Cholesterol (mg/dl)	206.54±44.65
TG (mg/dl)	184.25±106.93
LDL (mg/dl)	120.03±35.52
HDL (mg/dl)	49.65±9.51
VLDL (mg/dl)	36.85±21.38
SBP (mmHg)	174.40±16.11
DBP (mmHg)	89.58±7.52
Uric acid (mg/dl)	6.69±2.34

Table 2: Comparison of mean SUA level among cases and controls.

Parameter	Cases (Mean± SD)	Controls (Mean± SD)	P value
SUA (mg/dl)	6.69± 2.34	4.72±0.9	0.0001*

*(P value <0.05)

Mean SUA of males was 6.77±2.24 mg/dl and that of females was 6.57±2.50 mg/dl. Although mean age of males was more than females but the difference was not found to be statistically significant (p value >0.05) (Table 3).

Table 3: Comparison of mean uric acid with different parameters among cases.

	SUA (mean±SD)	P value
Age (years)		
(>60) (n=68)	6.89± 2.40	0.2686
(<60) (n=42)	6.38± 2.23	
Sex		
Males (n=66)	6.77± 2.24	0.6629
Females (n=44)	6.57± 2.51	
Diabetics (HbA1C≥6.5)(n=75)	6.78± 2.35	0.5612
Non Diabetics (n=35)	6.50± 2.34	
Ischemic (n=47)	6.99 ±1.92	0.2504
Hemorrhagic (n=63)	6.47 ±2.6	
Dyslipidemic (n=79)	7.07± 2.29	0.0063*
Normal lipid (n=31)	5.73±2.22	
Hypertensive (n=50)	7.16± 2.31	0.054
Normotensive (n=60)	6.30± 2.31	

*(P value<0.05)

Mean SUA in hypertensive was 7.16±2.31 mg/dl and in normotensive was 6.30±2.31mg/dl. Although mean SUA in hypertensive was more than normotensive but the difference was not found to be statistically significant (p value >0.05) (Table 3).

Mean SUA in diabetics was 6.78±2.35 mg/dl and in non-diabetics was 6.50±2.34 mg/dl. Although mean SUA in diabetics was more than non-diabetics but the difference was not found to be statistically significant (p value>0.05) (Table 3).

Mean SUA level was found to be higher in patients who had elevated serum total cholesterol (>200mg/dl), triglycerides (>150mg/dl), LDL (>130mg/dl) and low HDL (<40mg/dl) than those with normal lipid profile but the difference was not statistically significant. According to this study, 79 were found to be dyslipidemic (cholesterol >200 mg/dl and TG >150 mg/dl) and out of which 41 (51.89%) were found to be hyperuricemic. Mean serum uric acid level of dyslipidemics acute stroke patients was 7.07±2.29 mg/dl and that of patients with normal lipid was 5.73±2.22 mg/dl. Mean serum uric acid level was higher in dyslipidemics than normal lipid acute stroke patients and the difference was found to be statistically significant (0.0063) (Table 3). However, prevalence of hyperuricemia was highest among patients with low HDL (58.33%) (Table 4).

Table 4: Comparison of mean uric acid between normal and dearranged parameters of lipid profile in cases.

	Serum uric acid (mg/dl) (mean±SD)	P value
S. Cholesterol (>200mg/dl) (n=56) (<200mg/dl) (n=54)	7.01± 2.35 6.36±2.30	0.1457
TG (>150mg/dl) (n=65) (<150mg/dl) (n=45)	6.98± 2.34 6.27±2.29	0.1174
LDL (>130mg/dl) (n=37) (<130mg/dl) (n=73)	7.04± 2.24 6.51± 2.38	0.2630
HDL (<40mg/dl) (n=12) (>40mg/dl) (n=98)	7.38± 3.21 6.61± 2.21	0.2826
Dyslipidemic (A+B) (n=79) Normal lipid (n=31)	7.07± 2.29 5.73±2.22	0.0063*

*(P value<0.05)

Among 110 cases 21 got expired during hospital stay, out of which 8 were ischemic and 13 were hemorrhagic stroke patients. Mean SUA in acute stroke patients who got expired (7.60±2.83 mg/dl) was higher than those who survived (6.48±2.17mg/dl) and the difference was statistically significant (p=0.0476). Also among stroke subtypes, mean SUA was found to be higher with both ischemic and hemorrhagic stroke who got expired than survived but statistically significant difference exist only with ischemic stroke patients (Table 5).

Table 5: Comparison of mean uric acid with mortality among stroke subtype.

	Expired (mean±SD) (n=cases)	Survived (mean±SD) (n=cases)	P Value
Ischemic stroke (47)	8.96±2.40 (8)	6.59±1.56 (39)	0.0009*
Hemorrhagic stroke (63)	6.76±2.83 (13)	6.39± 2.56 (50)	0.651
Total cases	7.60±2.83 (21)	6.48±2.17 (89)	0.0476*

DISCUSSION

In this study we determined the role of serum uric acid in acute stroke and its prognostic significance on stroke outcome. Mean SUA level was 6.69±2.34 mg/dl and half of them were hyperuricemic. The prevalence of hyperuricemia among the patients, attending Nobel Medical College was 28.33% (male 30.06%, female 26.61%).[4] Another large study in Bangkok population showed that prevalence of hyperuricemia is 24.4%.[5] According to these studies prevalence of hyperuricemia is significantly higher in patients with acute stroke than normal population.

In this study, majority of patients belong to age group between 60-79 years with male preponderance. In the German dataset, a maximum male preponderance was found for patients aged between 55 and 64 years (proportion of male patients 0.67 [95% CI: 0.66-0.67]), whereas patients older than 84 years revealed a strong overbalance of females (0.27 [0.26-0.28]).[6] Both in China and India, a strong preponderance of male stroke patients was found for the majority of age categories with a maximum proportion of male patients of 0.82 in the 35-44 years age group.[6] Arjundas D et al studied 77.8% of acute stroke patients who were between 50 and 79 years of age.[7]

The male to female ratio was 1.5:1. The mean age of the cases was 64.77±10.90 years. Arjundas D et al found male to female ratio 1.9:1 with mean age 61.7±13.4years. The findings about age and sex distribution were concordant with previous studies but subtypes of stroke was not concordant i.e. hemorrhagic patients were more in number in this study, which might be due to more admission of patients with hemorrhagic stroke as compared to patients with ischemic stroke and so our sample size was small for ischemic stroke.[8]

In this study mean SUA level was found to be higher in patients who had elevated serum cholesterol (>200mg/dl), triglycerides (>150mg/dl) and LDL (>130mg/dl) than those with normal lipid profile but the

difference was not significant. Mean serum uric acid level was higher in dyslipidemic than normal lipid acute stroke patients and the difference was found to be statistically significant (<0.05). Bonora et al studied 957 young men and demonstrated that there was a significant positive correlation between serum uric acid levels and levels of serum triglyceride, total cholesterol and LDL cholesterol.[9] Another study including healthy people in developing countries showed a closely association between serum uric acid level and amount of serum triglyceride.[10] Moreover, Chammaro et al reported the association between serum uric acid level and amount of serum triglyceride.[11] However, percentage of hyperuricemia was highest among patients with low HDL (58.33%). The mechanism of this association between serum uric acid levels and dyslipidemia is still poorly understood. Most of researchers believed that hyperuricemia and dyslipidemia may reflect the patient's life style as a part of metabolic syndrome.[10]

We found that mean SUA levels was significantly higher among cases than controls (6.69±2.34mg/dl, 4.72±0.9 mg/dl, P <0.05). Milionis et al observed that the SUA levels were significantly higher in stroke patients compared with controls (5.6±1.7 mg/dl versus 4.8±1.4 mg/dl, P < 0.001).[12] Srikrishna R and Suresh DR found that serum uric acid levels were significantly higher in cases as compared to controls.[13]

Mean SUA in acute stroke patients who had expired (7.60±2.83 mg/dl) was higher than that those who survived (6.48±2.17mg/dl) and the difference was statistically significant (p=0.0476). Conclusion was drawn by Kim et al in their systematic review and meta-analysis of 16 prospective cohort studies. The study included 238449 adults and evaluated the association between hyperuricemia and risk of stroke incidence and mortality. They found that high uric acid levels cause a modest but statistically significant increase in the risk of both stroke incidence and mortality even after adjusting for known risk factors of stroke like age, hypertension, diabetes mellitus, and cholesterol. Weir et al noted that higher serum urate value was significantly associated with bad outcome (OR = 0.78 per additional 0.1 mmol/L95% C.I. = 0.67 - 0.91).[14] 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 vs. 6.9±4 mg/dl, P = 0.003).[15]

UA acts as metabolically inert, yet it can exert harmful effects as a result of crystallization. Studies have shown hyperuricemia to be a risk factor for several cardiovascular diseases associated with metabolic syndrome (Johnson et al, Feig et al, and Kim et al).

Various studies have shown that uric acid can result in; (1) endothelial dysfunction which can lead to vascular disease (2) promotes LDL cholesterol in vitro (3) increase in inflammatory markers.[16-18]

Role of xanthine oxidase [19, 20]

- Higher serum uric acid level reflects an increased activity of xanthine oxidase.
- Xanthine oxidase leads to generation of superoxide anions and the reactive oxygen species in human vasculature.
- Allopurinol, a xanthine oxidase inhibitor, was found to reduce inflammatory markers in stroke survivors.

There is a great debate regarding role of uric acid in stroke. Increased uric acid levels have been found to be associated with established risk factors of stroke such as hypertension, dyslipidemia, obesity and diabetes. [21] In the general elderly population, high uric acid levels were independently associated with increased incidence of fatal stroke. [22]

Significantly higher risk of stroke incidence and mortality was reported in cases of hyperuricemia.[23] But, contrary to this, other studies have advocated uric acid to be neuroprotective due to its antioxidant action.[24,25]

CONCLUSION

The study concludes that serum uric acid level was significantly elevated in patients of acute stroke, significantly associated with dyslipidemia, and had significant higher mortality association with hyperuricemic ischemic stroke patients and hence it can be considered as risk factor and poor mortality outcome. However further evaluation is needed with larger study for this fact to establish.

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