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# Serum Uric Acid as an Independent Risk Factor for Acute Ischemic Stroke

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## ABSTRACT

**Background**: Stroke is a neurological deficit due to acute focal injury of the central nervous system due to any vascular cause. The role of serum uric acid as a risk factor for acute stroke is an area of importance to many researchers. We in the current study tried to determine the levels of serum uric acid in cases of acute ischemic stroke and compare them with those in age and sex-matched controls.

**Methods**: This hospital-based case-control study was performed in the Department of General Medicine, Prathima Institute of Medical Sciences, Naganoor, Karimnagar. All the subjects were interviewed, examined, and investigated as per the predesigned and pre-tested proforma. Biochemical investigations included estimation of serum uric acid, serum triglycerides, fasting blood glucose, Renal function tests, and Liver function tests.

**Results**: Mean Serum Uric Acid level was lower in the patients with lacunar stroke as compared to the patients with larger infarcts (6.16 $\pm$ 1.68 mg/dl vs. 6.73 $\pm$ 2.07 mg/dl). Butthisdifference was not statistically significant as the p-value is >0.05.The correlation between SUA and NIHSS score was studied with the help of Spearman rank correlation. It was found that there was a significant positive correlation between SUA and NIH stroke scale score on admission as well as at the time of discharge ($p<0.05$ for both).

**Conclusion:** Elevated serum uric acid level is independently associated with acute ischemic stroke. It was observed that serum uric acid levels were correlated with hypertension, diabetes mellitus, smoking, obesity, and metabolic syndrome. It was found that cases with elevated serum acid levels had poor prognosis and overall mortality rate.

**KEYWORDS:** Serum uric acid, ischemic stroke, risk factors, metabolic syndrome

## INTRODUCTION

Stroke is commonly distributed across the world. It is an important cause of morbidity, mortality, and disability in developed as well as developing countries. There is a substantial difference in stroke incidence in different parts of the world. The higheststroke incidence is found in the 'stroke belt' region i.e. South Eastern states of the United-States with stroke mortality of 29-42 deaths per 1 lakh population. A WHO collaborative study in 12 countries showed a stroke incidence rate of 0.2-2.5 per thousand population years. Age-standardized rates for men were 2 per 1000 in Colombo and 4-8 per 1000 in European countries. [1]Analysis of the data from major urban hospitals in India suggests that nearly 2% of all hospital cases, 4.5% of Medical and 20% of Neurology unit admissions are from a stroke. [2] The prevalence rate of hemiplegia in South India is reported to be 56.9 per 1 lac population as compared to150-186 per 1 lac population in USA and Europe. The number of stroke patients is likely to increase as the population ages. It is estimated that, by the year 2025 in the USA, the portion of people above 65 years of age will increase to 18.4% as compared to 12.6% in 1995. [3]Most stroke deaths occur in low- and middle-income countries and middle-income countries and among non–western populations. [4] Black, Chinese, South Asian, and Japanese populations have a higher incidence of stroke compared with Caucasians. [5] In some Asian populations, the burden of cerebrovascular disease exceeds that of coronary heart disease. In China, for example, stroke is the second leading cause of death in urban areas [6] and it is estimated that three times as many Asian people die from stroke than from coronary heart disease [4]The impact of stroke on morbidity is also quite large. It seems prudent to view prevention as the most effective strategy to reduce the health and the economic consequences of stroke. Prevention is facilitated bya better understanding of predisposing host and the environmental factors. The relative impact of each of these factors must be studied for effective risk factor modification. 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 [7] study

concluded that uric acid is an independent risk factor for the development of cardiovascular and cerebrovascular diseases. In contrast, the Framingham Heart Study [8]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. Therefore, it is unclear whether uric acid promotes or protects against the development of cerebrovascular disease or simply acts as a passive marker of increased risk. Amidst this controversy and lack of Indian data, it was decided to carry out the present aimed to study uric acid levels in patients with acute ischemic stroke.

## MATERIAL AND METHODS

This hospital-based case-control study was performed in the Department of General Medicine, Prathima Institute of Medical Sciences, Naganoor, Karimnagar. Institutional Ethical committee permission was obtained for the study.

Inclusion criteria were Cases of acute ischemic stroke admitted to Medicine wards ,Confirmed cases with Computed Tomography (CT) brain or Magnetic Resonance Imaging (MRI) brain proved cases of acute ischemic stroke, Healthy age and sex-matched cases were included as controls.

Exclusion criteria were Patients with a known or possible cardiac source of emboli like atrial fibrillation ,valvular heart disease, patients receiving anticoagulant treatment, Duration of symptoms more than 48 hours, History of vascular disease (previous stroke, angina, myocardial infarction, revascularizations, peripheral artery disease), Patients receiving drugs affecting Serum Uric Acid (SUA) levels (diuretics, losartan, allopurinol, probenecid, atorvastatin, fenofibrate), Active infections, malignancy, Endocrine diseases , Renal or liver disease

Based on the inclusion and exclusion and sample size calculation using formula $n=Z^2pq/E^2$ if 5% of the population is affected and the approximate population size is 500,000 then the sample size was n=73 we have included n=100 cases. N=100 age and sex-matched healthy controls selected randomly were also enrolled in the study. All the subjects were interviewed, examined, and investigated as per the predesigned and pre-tested proforma.Biochemical investigations included estimation of serum uric acid, serum triglycerides, fasting blood glucose, Renal function tests, and Liver function tests.

**Statistical analysis**: Statistical analysis was performed with the help of SPSS19.0 software on Windows format. Statistical analysis included the usualdescriptive and univariate analysis. Student t-test was used to compare continuous-variables and the test was used to compare categorical variables. Unadjusted odds ratio with 95% confidence interval and p-value were calculated.In addition to this, multivariate analysis was also performed to study the association of SUA with acute ischemic stroke in a multivariate context. Ischemic stroke was taken as the 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.

## RESULT

Out of n=100 patients studied, n=63 were males and n=37 were females. Thus, there was a male preponderance in the present study. Male: female ratio was 1.7: 1. The controls were appropriately age and sex matched. The mean age of cases was 60.05 $\pm$ 9.98 and the range was 36 to 86, whereas the mean age of controls was 60.32 $\pm$ 10.11 (with the range from 36 to 87 years). The difference between the two groups was not statistically significant (p = 0.85).

In this study, on univariate analysis, there was a significant correlation between systemic hypertension and stroke ($X^2$= 37.40, OR = 8.42, 95% C.I.=4.02-17.63, p=0.00).N=23 patients were diabetic whereas N=77 were non-diabetic among cases. In the controls group, n=11 people were diabetic and the remaining 89 were non-diabetic. On univariate analysis there was significant association between diabetes and ischemic stroke ($X^2$= 5.103, OR = 2.41, 95% C.I.= 1.10 – 5.27, p = 0.023)Table 1

| Risk Factors present | Cases | Controls | P value |
|---|---|---|---|
| Age (Mean$\pm$SD) | 60.1$\pm$10 | 60.3$\pm$10 | 0.85 |
| Hypertension | 51 | 11 | 0.00* |
| Diabetes mellitus | 23 | 11 | 0.023* |
| Metabolic syndrome | 40 | 8 | 0.00* |
| Smoking | 2 | 8 | 0.014* |
| Obesity | 44 | 6 | 0.000* |
| BMI (Mean$\pm$SD) | 25.1$\pm$3.1 | 22.9$\pm$2.9 | 0.00* |

* significant

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

Among cases, n=20 patients were smokers and n=80 were non-smokers. In the controls group, the number of smokers was n=8, and the remaining 92 controls were nonsmokers. On univariate analysis there was significant association between smoking and ischemic stroke ($X^2$= 5.98, OR = 2.87, 95% C.I. = 1.20 -6.88, p =0.014) given in Table 1 . In the present study, the mean serum uric acid (SUA) level in cases was 6.48 $\pm$ 1.92 mg/dl whereas it was 5.09 $\pm$ 1.07 mg/dl for controls. This shows that the mean serum uric acid level was significantly higher in cases as compared to controls and this difference was statistically significant depicted in Table 2 .

| Serum Uric Acid (SUA) | Cases | Controls | P-value |
|---|---|---|---|
| Mean±SD | 6.5±1.9 | 5.1±1.1 | <0.001 |
| Range | 2.1 - 12 | 2.1 – 8 | |
| Median | 6.55 | 4.9 | |

**Table 2: Comparison of serum uric acid levels in cases and controls**

Table 3 Shows the association of various risk factors with ischemic stroke in the multiple logistic regression analysis. This analysis shows that hypertension (OR= 0.152, 95% C.I. = -2.82 to -0.947, z = -3.39, p = 0.00), smoking (OR = 0.405, 95%C.I. = -1.80 to -0.003, z = -1.966, p = 0.049), and obesity (OR = 0.116, 95% C.I. = -3.321 to -0.995, z = -3.63, p = 0.00) were found to be independently associated with ischemic stroke. It was also found that serum uric acid was also independently associated with ischemic stroke (OR = 1.487, 95% C.I. = 0.182 to 0.611, z = -3.625,p = 0.00).

| Risk Factor | Odds Ratio | 95% CI of OR* | | P-value |
|---|---|---|---|---|
| Hypertension | 0.15 | -2.82 | -0.95 | 0.000 |
| Diabetes Mellitus | 0.96 | -1.34 | 1.26 | 0.951 |
| Metabolic syndrome | 0.66 | -1.74 | 0.90 | 0.530 |
| Smoking | 0.41 | -1.81 | -0.03 | 0.049 |
| SUA | 1.49 | 0.18 | 0.61 | 0.000 |
| Obesity | 0.12 | -3.32 | -0.99 | 0.000 |

* 95% CI of OR= 95% Confidence Interval of Odds Ratioe.

**Table 3:** Multiple logistic regression analysis showing association of various risk factors with ischemic stroke

Mean Serum Uric Acid level was lower in the patients with lacunar stroke as compared to the patients with larger infarcts (6.16 ± 1.68 mg/dl vs. 6.73 ± 2.07 mg/dl). But this difference was not statistically significant as the p-value is >0.05.

| **Size of Infarct** | **Lacunar Infarct (N=44)** | **Large vessel infarct (n = 56)** | **P-value** |
|---|---|---|---|
| SUA (Mean±SD) | 6.16±1.7 | 6.73 ±2.1 | 0.15 |
| Range | 2.3 - 9.9 mg/dl | 2.1 - 12 mg/dl | |

**Table 4: Relationship between Serum Uric Acid and size of the infarct**

The correlation between SUA and NIHSS score was studied with the help of Spearman rank correlation. It was found that there was a significant positive correlation between SUA and NIH stroke scale score on admission as well as at the time of discharge (p<0.05 for both). Out of n=13 deaths, the mean SUA for discharged patients was 6.16±1.68 mg/dl and it was 8.60 ±2.16 mg/dlfor the patients who died in the hospital. SUA levels were significantly higher in the patients who succumbed as compared to those who were discharged from the hospital (p = 0.00)Table 4

## DISCUSSION

Stroke is a major cause of mortality and morbidity in developed as well as developing countries. The well-recognized risk factors like age, smoking, diabetes, hypertension, and metabolic syndrome explain only a part of the cases.In this study, there were n=63 male and n=37 female patients. The male to female ratio was 1.7:1. The mean age of the cases was 60.05+ 9.98 years with the range of 36 to86 years. These findings are consistent with the findings of D Arjundaset al.,[8]They observed a male: female ratio of 1.9:1 and the mean age of stroke patients as 61.7 ± 13.4 years. In the present study, the serum uric acid (SUA) levels increased with increasing age with a correlation coefficient of r = 0.059 but this difference was not statistically significant. The mean SUA levels were higher among males as compared to females but this difference did not attain statistical significance (5.94 ± 1.72 vs. 5.51 ±1.64 mg/dl).Pearce et al.,[9] observed higher SUA values in males as comparedto females (5.28 ± 0.66 vs. 4.47 ± 0.78 mg/dl). B. Longo-Mbenza et al.,[10] found significantly higher SUA levels in males (6.6 ± 7 vs. 5.8 ± 6 mg/dl,). Similar results were obtained in the study by Milionis et al.,[11]the Study by Karagiannis et al.,[12]also showed significantly higher levels of SUA among males as compared to females (5.8 mg/dl vs. 5.2 mg/dl, p<0.05). Higher SUA levels in males were also observed by TuhinaNeogi et al., [13] In our study, out of n=100, n=51 cases were hypertensive as compared to n=11hypertensive patients among controls. This difference was statistically significant on univariate analysis. In the multiple regression analysis also, there was a significant correlation between stroke and hypertension. These findings are following the findings by D Arjundaset al.,[8]of 72% hypertensives among stroke patients in the Chennai population. Per Harmeson et al.,[14] who studied the different risk factors in the Swedish population noted that systemic hypertension is a risk factor for stroke. In our study, there were n=23 diabetic subjects among cases. In the controls group, n=11 subjects were found to be suffering from diabetes.Karagiannis et al.,[12]observed lower SUA levels in diabetic subjects as compared to those without it. This discrepancy between our and other studies maybe because of the different ethnicity of the study population.In this study, there were n=20 smokers and n=80 non-smokers in the cases group while N=8 subjects in the controls group were smokers. These findings are following the observations made by

D Arjundaset al., [8]who found a prevalence of 23.6% smokers among stroke patients. PerHarmeson et al., [14] noted that smoking is a risk factor for stroke. In our study, we found a significant inverse correlation between SUA levels and HDL cholesterol and a positive correlation between SUA and serum triglyceridelevels. Lehto et al., [15]concluded that SUA was significantly associated with HDL cholesterol and triglyceride levels.Bansal et al. [16]found a significant correlation between SUA and triglyceride($p<0.05$). Results from the PIUMA study [17] showed that mean HDL cholesterol levels were significantly lower and triglyceride levels were higher in the patients in the highest uric acid quartile as compared to those in the lowest quartile. In our study, we used the National Institute of Health Stroke Scale (NIHSS) to quantify stroke severity. It has been proved in earlier studies that a higher NIHSS score portends a poor prognosis following stroke. [18, 19] In the present study there was a significant correlation between SUA level and NIHSS score on admission. NIHSS. Scores on discharge also correlated significantly with SUA levels.SUA levels were also higher in patients with large artery stroke as compared to those with lacunar stroke but this difference was not found to be statistically significant.

**Limitations of the study:** It is difficult to determine the cause and effect of serum uric acid in stroke patients. We cannot determine whether the patients who suffered a stroke had higher levels of serum uric acid before stroke because such samples were out of scope in this study therefore, it will be difficult to determine whether higher levels of uric acid were the result of the stroke. The results of this study must be applied keeping in mind the above limitations.

## CONCLUSION

Elevated serum uric acid level is independently associated with acute ischemic stroke. It was observed that serum uric acid levels were correlated with hypertension, diabetes mellitus, smoking, obesity, and metabolic syndrome. It was found that cases with elevated serum acid levels had poor prognosis and overall mortality rate.

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