

Original Research Article

Serum uric acid as a prognostic indicator in acute ischemic stroke

Chandana Kaspa*, Shankar Govindu

Department of General Medicine, Government General Hospital, Guntur, Andhra Pradesh, India

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***Correspondence:**

Dr. Chandana Kaspa,

E-mail: dr.chandana.2k2@gmail.com

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ABSTRACT

Background: Association between serum uric acid (SUA) and the outcome of acute ischemic stroke is debated and needs to be evaluated. The present study was conducted to study the serum uric acid concentration as an indicator of outcome among acute ischaemic stroke and to determine the role of serum uric acid as a risk factor for acute ischemic stroke.

Methods: An observational study where 50 patients who presented within 48 hours of onset of stroke admitted to medical wards of government general Hospital Guntur were selected for the study.

Results: Out of 50 patients included for the study, 6 belonged to the age group of 30-40 years. Majority were male (66%) and 44.5% of the males and 76.5% of females showed raised serum uric acid levels. 25 out of 50 patients were diabetic (i.e. 50%) Among them 16 had serum uric acid >6 mg% (ie.64%), 56% of the patients were hypertensive and among them 71% were found to have uric acid levels greater than 6mgs%, 38 out of 50 patients had bad outcome, with elevated uric acid levels found 30 among them. In the present study, BMI and outcome of Stroke were significantly associated with Serum Uric acid levels.

Conclusions: Serum uric acid levels can be used as a prognostic indicator as a marker for increased risk of stroke. Elevated serum urate concentration may stratify risk of death after acute stroke.

Keywords: Ischemic stroke, Prognosis, Serum uric acid

INTRODUCTION

Stroke is defined by the World Health Organization as a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin.¹ Stroke is classified broadly into three categories; ischemic stroke, haemorrhagic stroke and subarachnoid haemorrhage. Ischemic stroke occurs due to blockage of blood vessel which limits the blood supply to the brain whereas haemorrhagic stroke occurs due to rupture of blood vessel leading spillage of blood in the intracranial cavity.² Depending on the site of blood spillage the haemorrhagic stroke could be classified as

intracerebral haemorrhage or subarachnoid haemorrhage. Approximately 60-80% of all strokes is ischemic.³

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.⁴

Cerebral ischemia initiates a complex cascade of metabolic events, generating nitric oxide and free oxygen radicals.⁵ These free radicals and reactive oxygen species (ROS) mediate a great part of injuries appearing after a

transitory ischemic attack or during permanent ischemia, modifying macromolecules especially DNA, initiating apoptosis and necrosis.⁶

Uric acid is the final product of purine metabolism. Different genetic mutations, which probably occurred later in the evolution, reduced the activity of uricase in higher primates and completely inactivated the gene activity in humans.⁷

SUA is a major natural antioxidant and increased levels have been associated to a slower progression of several neurodegenerative disorders but also to an improvement in neurological and immune functions.⁷

The role of Serum Uric Acid (SUA) in the acute phase of ischemic stroke (IS) is investigated. SUA concentrations increase in the first hours after Ischemic Stroke and decrease to baseline levels in the following days.⁸ Animal models seem to confirm a neuroprotective role for SUA in the setting of IS. In humans, an association between higher SUA levels and better outcomes after Ischemic Stroke has also been described.⁹

However, several mechanisms including platelet dysfunction, coagulation disorders, endothelial dysfunction, increased oxidative stress, thrombus formation, have been observed in hyperuricemic subjects, suggesting an association between SUA and worse prognosis after acute vascular diseases.

Therefore the role of uric acid as a risk factor for acute ischemic stroke is controversial.

Hence the present study was conducted to study the serum uric acid concentration as an indicator of outcome among acute ischaemic stroke and to determine the role of serum uric acid as a risk factor for acute ischemic stroke.

METHODS

The present study was an observational study conducted at Medical wards government general Hospital Guntur during January 2019 to July 2019 where all stroke patients admitted within the above period and who satisfied the inclusion and Exclusion criteria were included.

Inclusion criteria

Patients with stroke as defined by WHO criteria

Rapidly developing clinical signs of focal or global (coma) neurological deficit lasting more than 24 hrs or leading to death with no apparent cause other than vascular origin. All patients who presented within 48 hours of onset of stroke and who gave informed consent to participate in the study were included

Exclusion criteria

- Patients with sub arachnoid haemorrhage, extradural Haemorrhage, subdural haemorrhage and intra cerebral haemorrhage were excluded by CT.
- Patients with previous history or TIA/RIND were excluded.
- Patients with gout were excluded
- Patients who were alcoholics were excluded.
- Patients taking drugs causing hyperuricemia were excluded from the study(eg.) drugs like:
 - Loop diuretics
 - Anticancer drugs (Cisplatin, cyclosporine, Cyclophosphamide)
 - ATT (Pyrazinamide, Ethambutol)
 - Aspirin, Pentamidine, Theophylline, Ketoconazole, Levodopa, isotretinoin.
- Patients with previous history of coronary vascular events were excluded.

Method of collection of data

A CT scan head was taken within 48 hours after stroke onset for all patients with first ever stroke admitted in Guntur Medical College and hospital. The lab values of serum uric acid at the time of admission of all patients who satisfied the above criteria from January 2019 to June 2019 was studied. A sample size of 50 patients were randomly selected by simple random sampling, from the table of random numbers satisfying the inclusion criteria. Serum uric acid was measured when the patient was admitted and was correlated with functional recovery of the patients after 4 weeks. patients were reviewed 4 weeks after onset of stroke and were stratified using Glasgow Outcome Scale (GOS). GOS was used to assess the functional outcome and residual neurological deficits. A detailed history, clinical examination and relevant laboratory investigations were done as per proforma.

In present study, uric acid was determined within 48 hours after the onset of stroke. Ischaemic stroke was confirmed by CT scan 50 patients who fulfilled the criteria were taken under study. None of the patients underwent Thrombolysis. They were treated with antiedema, anti-platelet drugs and physiotherapy. Outcome noted by Glasgow outcome scale

Laboratory assessment of uric acid (uricase method)

A reagent kit is available at the central biochemistry laboratory, GGH. This reagent kit is for quantitative estimation of uric acid in serum or plasma.

Preparation of working solution

A working solution is prepared by dissolving the content of vial labeled 1. uric acid (enzyme) with the quantity of 2. Uric acid (buffer). The two solutions are mixed gently.

Procedure

- The sample and working solution should be brought to room temperature prior to use.
- 25µl of the sample is mixed with 1 ml of working reagent. The solution is incubated at 37°C for 5min or 10 min at room temperature. The wavelength of the solution and that of the blank reagent solutions are compared at 520 nm or with green filter.
- Mix and incubate for 5 min at 37°C and read absorbance of the test and standard against reagent blank at 520 nm or with green filter.

Calculations

$$\text{Uric concentration mg/dl} = \frac{\text{Absorbance of test} \times 5}{\text{Absorbance of standard}}$$

To convert uric acid concentration from mg/dl to µmoles/L, the following equation is used

$$\mu\text{moles/L} = 59.5 \times \text{mg/dl}$$

$$\text{mmoles/L} = 0.0595 \times \text{mg/dl}$$

Statistical analysis

The data was tabulated in Excel 2013 and analysed using SPSS software version 16. Quantitative and Qualitative variables were expressed in terms of Descriptive statistics

like (mean±standard deviation), frequencies and percentages.

Each data variable was correlated with other variables wherever required using parametric and non-parametric statistic i.e. t test and chi square analysis respectively with various outcomes that were noted in the study.

The p value <0.05 was considered as statistically significant in this study.

RESULTS

Out of 50 patients, 6 belonged to the age group of 30-40 years.

Table 1: Age and gender distribution.

Age	Males	Females	Total	Percentage
<30	1	0	1	2%
30-40	2	4	6	12%
41-50	5	3	8	16%
51-60	12	4	16	32%
61-70	10	6	15	30%
>70	3	0	3	6%
Total	33	17	50	100%

Most of the patients were in the age group of 51-60 years (Table 1).

Table 2: Distribution of uric acid levels based on gender.

Sex	Uric acid <6mgs%	%	Uric acid >6 mgs%	%	Total
Males	15	45.5%	18	44.5%	33
Females	4	23.5%	13	76.5%	17

Chi-Square Value- 2.29, df= 1, p value- 0.130 (not significant)

Table 3: Uric acid and its association with risk factors.

	Uric acid <6mgs%	%	Uric acid >6 mgs%	%	Total
Diabetic	9	36%	16	64%	25
Non diabetic	10	40%	15	60%	25
Chi-Square Value-0.085, df= 1, p value- 0.771 (not significant)					
	Uric acid <6mgs%	%	Uric acid >6 mgs%	%	Total
Hypertensive	8	28.6%	20	71.4%	28
Non hypertensive	11	50%	11	50%	22
Chi-Square Value- 2.40, df= 1, p value- 0.121 (not significant)					
	Uric acid <6mgs%	%	Uric acid >6 mgs%	%	Total
BMI <25	19	59.4%	13	40.6%	32
BMI >25	0	0%	18	100%	18
Chi-Square Value-17.2, df= 1, p value- <0.001(significant)					
	Uric acid <6mgs%	%	Uric acid >6 mgs%	%	Total
Good outcome	11	91.6%	1	8.4%	12
Bad outcome	8	21%	30	79%	38
Chi-Square Value- 19.3, df= 1, p value- <0.001(significant)					

They constitute about 32% of the patients totally studied. Among the acute stroke patients 33 (66%) were males, 17 (34%) were females, 44.5% of the males and 76.5% of females showed raised serum uric acid levels (p value-0.130) (Table 2).

In the present study, 25 out of 50 patients were diabetic (i.e. 50%) Among them 16 had serum uric acid >6 mg% (i.e.64%). Among non diabetics 15 out of 34 patients were found to have elevated serum uric acid >6mg% (i.e.) 60% (p value- 0.771). The study identified 22 out of 25 diabetic patients had poor outcome i.e.88% (Table 3).

Data wise 56% of the patients were hypertensive and among them 71% were found to have uric acid levels greater than 6mgs% (p value 0.121) (Table 3).

Based on the Body mass index, out of 50 patients, 18 patients have BMI >25 (obese) constituting 36%, associated with increased uric acid levels (p value-<0.001) (Table 3).

In the present study, patients with age of 60 years and above were 19 i.e.,38% Among them, 12 have elevated uric acid levels (p value- <0.895)

Statistically 38 out of 50 patients had bad outcome, with elevated uric acid levels found 30 among them. This finding was statistically significant as the p value- <0.001 statistically significant (Table 3).

DISCUSSION

Uric acid which is an end product of purine metabolism has long been considered only in the pathogenesis of gout and uric acid stones. Its anti-oxidant functions and its various role in the pathogenesis of hypertension, cardiovascular and cerebrovascular events are considered now only. Various studies conducted during recent years on serum uric acid levels in vascular events have proven its prognostic significance.

Uric acid is also been considered as a marker for atherosclerosis. But the exact pathogenesis and whether it is the cause or effect of atherosclerosis remains to be elucidated. Most of the patients were in the age group of 50 years and above i.e., 68% of patients.

Stroke occurs predominantly in the middle and late years of life. Age group of the patients has been found to have no correlation with serum uric acid levels in this study as per the statistical analysis by chi-square test, p value was not significant. Statistically 66% of the patients were males in the study, males show higher incidence of stroke as compared to females, 45% of males have raised serum uric acid levels more than 6 mgs% and 76 % of the female patients had raised uric acid levels.

In a study by Chamorro et al, male sex showed raised serum uric acid levels.⁹ In this study most of the patients

were males and a low number of females may falsely project them as patients with raised uric acid levels than males.

Total 25 out of 50 patients had diabetes (50%) as diagnosed by Fasting Blood Sugar more than 125 mg%. 16 diabetic patients had a poor outcome (64%). One of the bad prognostic factor in the outcome of stroke is the presence of associated diabetes mellitus. In this study 64% of diabetics had poor outcome.

The tests of significance didn't find any correlation between uric acid and diabetes. In a study by Nishkanen et al, serum uric acid levels was a strong predictor of stroke in Type II diabetes.¹⁰ Studies have suggested that hyperuricemia may have a pathogenetic role in the obesity metabolic syndrome.¹¹⁻¹⁴ Thus, an elevated uric acid was found to predict the development of both obesity and hyperinsulinemia in normal subjects and an elevated uric acid is universally present in the metabolic syndrome.

In this study 28 patients were hypertensive i.e.,56%. Among them 20 had raised serum uric acid levels i.e., 71 % of the hypertensive patients.

The tests of significance didn't find any correlation between uric acid and hypertension, because of small sample size, the correlation between uric acid level in hypertensive patients requires metacentric analysis

In a study on healthy Chinese participants by Cheng W et al, SUA concentration was positively associated with hypertension only in the 41-50 year old group.¹⁵ Lowering uric acid in this age group may help to reduce the incidence of hypertension.

Buzas R et al, reported that increased SUA levels are associated with arterial hypertension and with suboptimal BP control in treated hypertensive subjects.¹⁶

In this study, 18 patients were obese BMI >25 (43%). These patients had elevated uric acid levels. A statistically significant difference was observed between SUA and BMI (p<0.05). Study by Wang et al, reported that the prevalence of hyperuricemia remained approximately 2.98 times greater among individuals with overweight, and 5.96 times greater among obesity, compared to individuals with underweight.¹⁷

In this study, 78% of the total patients under study group had poor outcome. Out of which 79% had raised serum uric acid levels. A statistical significance with p value <0.05 was observed between poor outcome and raised uric acid levels in present study.

Study by Kaur et al, reported that Patients with poor GCS had higher mean serum uric acid levels as compared to patients with mild or moderate GCS score which was statistically significant(p =0.0426).¹⁸ Prasad et al,

reported that Mean SUA in expired cases was significantly higher than survived.¹⁹

CONCLUSION

Serum uric acid levels can be used as a prognostic indicator for increased risk of stroke. Elevated serum urate concentration may stratify risk of death after acute stroke. Anti oxidants can be added as a part of treatment protocol in patients with acute ischaemic stroke. Also, trial of serum uric acid lowering drugs in stroke patients as well as in those at increased risk of stroke can be worth considering. Further long term prospective studies are needed to establish the role of serum uric acid in ischemic stroke.

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