

ASSESSMENT OF SERUM URIC ACID LEVELS IN ACUTE ISCHEMIC STROKE

First and Corresponding Author:

Dr. Sheik Mohamed Raja

Assistant professor, Department of General Medicine, Tirunelveli Medical College,
Tirunelveli.

Second author

Dr. A. Vinoj

Assistant professor, Department of General Medicine, Tirunelveli Medical College,
Tirunelveli.

ABSTRACT

BACKGROUND: Cerebrovascular disease is the most common neurological disease of adult life. It has been reported that increased levels of uric acid are associated with established cardiovascular risk factor such as elevated serum triglyceride and cholesterol concentration, hypertension, obesity, insulin resistance and metabolic syndrome. The role of urate in ischemic stroke is poorly understood. Hence, our study is planned to estimate and to identify the correlation of serum uric acid level in patients with acute ischemic stroke, to find out its association with diabetes, hypertension, CAD and dyslipidemia.

METHODS: A cross section study was designed after institutional ethical clearance to screen acute ischemic stroke patients admitted to the hospital within 24 hours of onset of stroke who satisfied a rigid inclusion and exclusion criteria. The serum uric acid level was measured by uricase method. The data were entered in microsoft excel spread sheet and analysed statistically.

RESULTS: Hypertension constitutes the major risk factor in this stroke population. Mean uric acid in hypertensive population is 5.64mg/dl. The study *does not* shows any significant association between hypertension and uric acid. Diabetes mellitus constitutes 52% of study population. Mean SUA level of 5.96 mgs / dl among diabetics and 4.90 mgs / dl among non-diabetics there is a strong association between SUA and DM. Coronary artery disease constitutes 33% of study population Mean uric acid in stroke population with coronary artery disease is 6.40mg/dl and in those without coronary artery disease is 4.98mg/dl and this establishes a statistically significant relationship.

CONCLUSION: Elevated SUA is strongly associated with an increased risk for the development of acute ischemic stroke in this study population. The association between elevated SUA and ischemic stroke may need to be considered especially when treating elderly patients, diabetics and the population with coronary artery disease. Uric acid has been considered as a surrogate biochemical markers of oxidative stress in acute ischemic stroke.

Keywords: uric acid, stroke, ischemic.

INTRODUCTION

Cerebrovascular disease is the most common neurological disease of adult life. At least 50% of neurological disorders are cerebrovascular disease. After heart disease and cancer, stroke is the third most common cause of death. In the developed country approximately 700,000 cases of stroke – roughly 600,000 ischaemic lesions and 100,000 haemorrhages,

intracerebral or subarachnoid. Cerebrovascular disease is estimated to account for 7.8 million deaths yearly throughout the world and represents about 13% of all causes of death.¹ Due to increased morbidity and mortality, stroke has a high socio economic burden.² for primary prevention, at risk individual should be identified early.³

In humans, most abundant anti-oxidant is uric acid and it is the most important of all free radical scavengers in plasma and serve as a protective role by preventing lipid peroxidation.⁴ During acute oxidative stress and ischaemia local UA concentrations increases in organs and vascular bed, which helps in protection against free radical activity.⁵

Uric acid is the ultimate catabolite of purine metabolism in human and higher primates⁶. It exists in the extracellular compartment as sodium urate, and it is cleared from the plasma through the kidney⁷. Uric acid levels are influenced by age and sex. Prior to puberty, the average serum uric acid is 3.6 mg/dl for males and females. Following puberty, value rises to adult levels with women typically 1 mg/dl less than men. This lower level in women apparently reflects oestrogen related enhancement of renal urate clearance.

It has been reported that increased levels of uric acid are associated with established cardiovascular risk factor such as elevated serum triglyceride and cholesterol concentration, hypertension, obesity, insulin resistance and metabolic syndrome .On the other hand uric acid has been known to exert neuroprotective effects by acting as a free radical scavenger⁸. In humans, approximately one-half the antioxidant capacity of plasma comes from uric acid⁹.

The role of urate in ischemic stroke is poorly understood. A retrospective analysis of hospitalization data of 2495 patients in Glasgow suggested that higher serum urate on admission predicted poor outcome (dead or in care) and higher vascular event rate following ischemic stroke¹⁰. By contrast, a prospective hospital-based study involving 881 patients found that higher level of serum urate predicted better outcomes following stroke, suggesting that serum urate may be beneficial and protect against poor outcomes¹¹. In addition, an experimental study showed that uric acid administered early after thromboembolic stroke is neuroprotective in the rat brain and it extends the benefits of recombinant tissue plasminogen activator (rTPA)¹².

In acute brain injury of animal models, local UA concentrations increases significantly.¹³ It has been questioned for decades that for vascular disease the role of serum uric acid levels as an independent risk factor.⁷ Elevated SUA levels predict increased risk for cerebrovascular events.¹⁴ Therapeutic modalities with a SUA lowering potential shown to reduce CV disease morbidity and mortality.¹⁵

Diabetic individuals are at two to four time's greater risk of developing atherosclerotic vascular disease. In middle-aged individual with diabetes, hyperuricemia is a strong predictor of stroke events. SUA level is used as an serum marker in individuals who are at risk of developing stroke.¹⁶

SUA is also been associated with insulin resistance. In various epidemiological studies elevated serum uric acid levels, identified as an important risk factor for stroke.¹⁴ But it is not clear whether elevated SUA levels promote or protest against development of CV disease.¹⁴ In NHANES I studies, regardless of confounding factors such as sex, menopausal status, race, presence of CV disease, diuretic use have been established an independent association in subjects older than 45. Hence our study is planned to estimate and to identify the correlation of

serum uric acid level in patients with acute ischemic stroke, to find out its association with diabetes, hypertension, CAD and dyslipidaemia.

MATERIALS AND METHOD

In our study patients who have been diagnosed as acute ischemic stroke and admitted in ward of a tertiary care reaching hospital as a cross sectional, analytical hospital based study. The study was carried out for a period of two years. The stroke patients admitted within the above period and who satisfied the set criteria were included. The number of patients in the present study group was 100. Patients with previous history of TIA, previous history of CVA, presented after 24 hrs of onset of symptoms and who are on thiazide diuretics were excluded. All subjects gave informed consent and the study protocol was approved by the Ethical Committee.

After selecting the patients based on the above criteria, blood samples were taken within 24 hrs of onset of stroke and sent for biochemical analysis and were analyzed in our Biochemical Laboratory using standard analyzer. The serum uric acid level was measured in the stroke patients by the uricase method.

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using SPSS version 24 statistically. Using this software, frequencies, percentage, mean, standard deviation, χ^2 and 'p' values were calculated. A 'p' value less than 0.05 is taken to denote significant relationship.

RESULTS

In our study, majority of this stroke population are between 50 to 69 yrs old, (63 % of the population) with 35 Males and 28 females. The elderly population, above 70 yrs old constitute 19 % of the population with 8 males and 11 females. The mean age of the male population is 59.08yrs and of the female population is 60.5 yrs. The overall mean age of the study population is 59.8 yrs.

Hypertension constitutes the major risk factor in this stroke population as 64 % of the population is hypertensive. 34 males and 30 females are hypertensive's and form 68 % and 60 % in their respective population. Diabetes mellitus ranks second as a risk factor, constitute 52% of the study population with 24 (48 %) males and 28 (56 %) females. Coronary Artery Disease is associated in 33 % of the population with 16 (32 %) males and 17 (34 %) females.

In our study 33 % of the stroke population has adverse lipid profile with 16(32%) males and 17(34%) females. The distribution of uric acid levels in the study population is as below, less than 5 mg / dl – 49 % (25 males and 24 females), between 5 – 6.9 mg / dl - 26 % (13 males and 13 females) , above and equal to 7 mg / dl - 25 % (12 males and 13 females). Mean uric acid level in males is 5.42 mg / dl and in females it is 5.49 mg / dl. There is no statistically significant association is found in this study between sex and uric acid. The mean uric acid level among male population is 5.42 mg / dl and among female population it is 5.49 mg / dl.

Age wise distribution of uric acid is found statistically significant. As age advances the uric acid level also rises with the 'P' value of 0.001. This significance is maintained even when male and female populations are considered separately. ('P' of 0.008 for males and 0.005 for females). The mean uric acid value for 40 – 49 yrs group is 4.46 mg /dl while the elderly age group of above 70 yrs has the mean value 6.84 mg / dl.

This study does not show any significant association between hypertension and uric acid. The mean uric acid level in hypertensive population is 5.64 mg / dl and in non

hypertensive population is 5.11 mg/ dl. There is no significant association found, also when males and females are considered separately. The mean uric acid levels for male hypertensive is 5.48 mg/ dl (non-hypertensive males- 5.23 mg /dl) and in females is 5.77 mg /dl (non-hypertensive females – 5.02 mg / dl).

Table 1: Hypertension and uric acid

Hypertension	Uric Acid (mg/ dl)	
	Mean	S.D
Present	5.64	1.68
Absent	5.11	1.69
P	0.139 (Not significant)	

There is a statistically significant association (p value- 0. 002) found between the level of uric acid and Diabetes mellitus. Among diabetics the mean uric acid value is 5.96 mg / dl while among non diabetics it is 4.9 mg / dl. This association is more significant among males (p value -0.008) among whom the diabetics have 6.12 mg / dl as mean uric acid level compared to non diabetics, 4.73 mg / dl as mean value. But, this association is not found significant in female population. The mean uric acid level in diabetic women is 5.82 mg / dl when compared to non diabetic women is 5.02 mg / dl.

Table 2: DM and uric acid

DM	Uric Acid (mg / dl)	
	Mean	S.D
Present	5.96	1.64
Absent	4.9	1.60
P	0.002 (Significant)	

In this study, mean uric acid level in this stroke population with CAD is 6.40 mgs / dl and in those without CAD is 4.98 mgs / dl and thus establishes a statistically significant relationship (‘p’ 0. 001). When males and females are considered, males have a significant association with a ‘p’ value of 0. 001. Female population does not show such association.

Table 3: CAD and Uric acid

CAD	Uric Acid (mg / dl)	
	Mean	S.D
Present	6.40	1.86
Absent	4.98	1.40
P	0.001	(Significant)

Mean uric acid level in hyperlipidaemic stroke population is 5.79 mgs/dl and compared to 5.28 mgs / dl mean uric acid level in patients without hyperlipidemia do not show any statistically significant relationship.

Table 4: Hyperlipidemia and Uric acid

Hyperlipidemia	Uric Acid (mg / dl)	
	Mean	S.D
Present	5.79	1.91

Absent	5.28	1.57
P	0.164 (Not Significant)	

DISCUSSION

Stroke is defined as rapid onset of focal neurological deficit due to cerebrovascular disease. The mortality rate of stroke in the acute phase is as high as 20%. Stroke remains an important cause of morbidity and long-term disability; upto 40% patients are not independence with self-care and 25% unable to walk independently¹⁷.

Uric acid is a final end product of purine metabolism. Long been considered only in the pathogenesis of gout and uric acid stones. Its role in the pathogenesis of hypertension, cardiovascular, cerebrovascular and its anti-oxidant functions events are been considered of late. Serum uric acid levels in vascular events have proven its prognostic significance in recent studies. Uric acid is also been considered as a marker for atherosclerosis. An association between SUA and inflammatory markers has also been discovered¹⁸.

In a study by Iribarreen, Folsom and Eckfeldt et al.,¹⁹ found a positive correlation between uric acid levels and asymptomatic carotid atherosclerosis. Uric acid level can be used to predict future cerebrovascular events. A study by Hozawa A. Folsom et al²⁰ also showed increased uric acid levels in patients with ischemic stroke. In a study by Longo Mbenza, et al.²¹ among African patients found that uric acid levels were elevated among stroke patients.

The serum uric acid level was compared between male and female patients. Mean uric acid levels in males 5.42mg/dl and 5.49mg/dl in females. No statistically significant association found between gender and uric acid. However, in a study by Chamorro et al.²² serum uric acid levels were found to be higher in males. Regarding the association between risk factors and gender, CAD is significantly associated with high uric acid levels in both sexes whereas DM is associated only with males and not with females.

Age is the most common non-modifiable risk factor for the development of stroke. In our study majority of stroke population are between 50 to 69 yrs old constitute 63 % and elderly population, above 70 yrs old constitute 19%. The mean age of the male population is 59.08yrs and of the female population is 60.5 yrs. The overall mean age of the study population is 59.8 yrs. Age wise distribution of uric acid is found statistically significant. As age advances the uric acid level also rises with the 'P' value of 0.001 and the association was maintained even when both sexes are considered separately Our study is consistent with Milinois et al who found elevated SUA in individuals older than 70 years.¹⁵

Diabetes mellitus ranks second as a risk factor in our study, constitute 52 % of the study population. Mean SUA level is 5.96 mgs / dl among diabetics and 4.90 mgs / dl among non-diabetics found statistically significant. Further analysis shows stronger association among males (mean SUA in male diabetics -6.12 mgs / dl vs non-diabetic males- 4.73 mgs /dl) than females. Lehto et al.²³ prospective study revealed elevated uric acid in diabetics who develop stroke. In a study by Wang, Lim et al.²⁴ showed that hyperglycemia increases stroke mortality and another study by Yoon, et al.²⁵, found high blood glucose is associated with poor outcome after ischemic stroke.

Hypertension is the most common modifiable risk factor for stroke. SUA is also commonly associated with hypertension. In our study, Hypertension constitutes the major risk factor, as 64 % of the stroke population is hypertensive. The mean uric acid level of

hypertensive patients is 5.64 mgs / dl and of non-hypertensive is 5.11 mgs / dl and thus this study does not show any statistically significant relationship between SUA and hypertension. In a study by Verdecchia P and Schillaci et al.,²⁶ proved a relation between serum uric acid and essential hypertension. A study by Franeesea Viazzi et al.,²⁷ found that cerebrovascular events was higher in hypertensives with increased uric acid level.

In our study, CAD is found in 33 % of stroke population. The mean SUA level in this CAD population is 6.40 mgs / dl comparing this to patients without CAD is 4.98 mgs / dl, which shows a strong statistical significance. Our study strongly favours Rotterdam study²⁸ and suggests SUA is a strong risk factor for myocardial infarction and stroke.

In our study, the mean uric acid level in hyperlipidemic patients is 5.79 mgs / dl and in patients without hyperlipidemia is 5.28 mgs / dl, which does not show any statistical significance. Various prospective studies²⁹ showed that higher levels of total cholesterol increase the risk of ischaemic stroke. In a meta-analysis study by Amerenco p et al³⁰ showed that administration of statins reduces the risk of stroke among patients with CAD.

CONCLUSION

Elevated SUA is strongly associated with an increased risk for the development of acute ischemic stroke in this study population. The association between elevated SUA and ischemic stroke may need to be considered especially when treating elderly patients, diabetics and the population with coronary artery disease. Uric acid has been considered as a surrogate biochemical markers of oxidative stress in acute ischemic stroke. Elevated uric acid among stroke patients concurred with previous publication. Lowering of SUA level can be considered as one of the preventory modalities for stroke while treating high risk population. It is also suggested that further studies are required to assess whether lowering of SUA level with drugs can actually reduce the risk of ischemic stroke.

REFERENCES:

1. Adam and Victor's principles of Neurology – 10th edition; Chapter 34; page 778-792.
2. Bonita R. Epidemiology of stroke. *Lancet* 1992; 339: 342–344.
3. Buckley BM. Healthy ageing: ageing safely. *Eur Heart J* 2001; (Suppl.3): N6– 10.
4. Squadrito GL, Cueto R, Splenser AE, Valavanidis A, Zhang H, Uppu RM, et al. Reaction of uric acid with peroxynitrite and implications for the mechanism of neuroprotection by uric acid. *Arch Biochem Biophys* 2000; 376: 333– 337.
5. Nieto FJ, Iribarren C, Gross MD, Comstock GW, Cutler RG. Uric acid and serum antioxidant capacity: a reaction to atherosclerosis? *Atherosclerosis* 2000; 148:131–139.
6. Barr WG. Uric acid. In: Walker HK, Hall WD, Hurst JW, editors. *Clinical Methods. The History, Physical, and Laboratory Examination*. 3rd ed. Boston: Butter worth; 1990. pp. 760–763.
7. Heo SH, Lee SH. High levels of serum Uric acid are associated with silent brain infarctivn. *Jaurnal of the Neurol Scien*. 2010;297:6–15.
8. Amaro S, Urra X, Gomez-Choco M. Uric Acid Levels Are Relevant in Patients With Stroke Treated with Thrombolysis. *Stroke*. 2011;42:28–32.
9. Ogbera A, Azenabor A. Hyperuricemia and the metabolic syndrome in type 2 DM. *Diabetol Metab Syndr*. 2010;2:24–30.

10. Weir CJ, Muir SW, Walters MR, et al. Serum Urate as an independent predictor of poor outcome and future vascular events after acute ischemic stroke. *Stroke*. 2003;34:1951–1956.
11. Chamorro A, Obach V, Cerrera A, et al. Prognostic significance of uric acid serum concentration in patients with acute ischemic stroke. *Stroke*. 2002; 33:1048–1052.
12. Romanos E, Planas AM, Amaro S, et al. Uric acid reduces brain damage and improves the benefits of rtPA in a rat model of the thrombo-embolic stroke. *J cereb Blood Flow Metab*. 2007; 27:14–20.
13. Tayag EC, Nair SN, Wahhab S, Katsetos CD, Lighthall JW, Lehmann JC. Cerebral uric acid increases following experimental traumatic brain injury in rat. *Brain Res*1996; 733:287–291
14. Daskalopoulou SS, Athyros VG, Elisaf M, Mikhailidis DP. Uric acid levels and vascular disease. *Curr Med Res Opin* 2004; 20: 951–954.
15. Milionis HJ, Kalantzi KJ, Goudevenos JA, Seferiadis K, Mikhailidis DP, Elisaf MS. Serum uric acid levels and risk for acute ischaemic non-embolic stroke in elderly subjects. *J Intern Med* 2005; 258: 435 – 441.
16. Rathmann W, Funkhouser E, Dyer AR, Roseman JM. Relations of hyperuricemia with the various components of the insulin resistance syndrome in young black and white adults: The CARDIA study [Coronary Artery Risk Development in Young Adults]. *Ann Epidemiol* 1998; 8: 250 – 261.
17. Hariklia VD, Apostolos H, Haralambosk. The role of uric acid in stroke. The issue remains unresolved. *The Neurologist* 2008;14; 238-242.
18. Aduff GW, Atkins E, Malawista SE. The fever of gout; urate crystals activate endogenous pyrogen production from human and rabbit mononuclear phagocytes. *Trans Assoc Am Physician*. 1983; 96: 234-245.
19. Iribarren C, Folsom AR, Eckfeldt JH, MC Govern PG, Nieho FJ. Correlates of uric acid and its association with asymptomatic carotid atherosclerosis; the ARIC study; Atherosclerosis Risk in communities. *Stroke*, 1999; 29 : 635-639.
20. Hozawa, A. Folsom AR. Uric acid is an independent predictor of ischemic stroke among subjects not using diuretics. *Atherosclerosis*, 2006, 187(2): 401-407.
21. Longo Mbenza B, Luila EL, Mbete P, Vita EK. Is hyperuricemia a risk factor of stroke and coronary heart disease among Africans. *Int. J. Cardiol.*, 1999, 71(1) : 17-22.
22. Chamorro A, Obach V, Cervera A, Revilla M, Deulofeu R, Aponte JH. Prognostic significance of uric acid serum concentration in patients with acute ischemic stroke. *Stroke* 2002; 33: 1048– 1052.
23. Seppo Lehto, Leo Nishkanen and Ronnema et al. Serum uric acid is a strong predictor of stroke in patients with NIDDM. *Stroke*, 1998; 29: 635-639.
24. Wang Y, Lim JL, Levic, Hella RF, Fishen J. Influence of hyperglycemia on stroke mortality. *J. Stroke Cerebrovasc. Dis.*, 2001, 10(1) : 108-110.
25. Yoon SS, Zheng ZJ. Elevated total WBC count with high blood sugar is an indicator of poor outcome after ischemic stroke. *J. Stroke Cerebrovasc. Dis.*, 2005, 14(2): 88-93.

26. Verdecchia, Schillaci, Reboldi G, Santensanio F, Posullati. C Brunelti. P. Relation between serum uric acid and risk of cardiovascular disease in essential hypertension. The PIUMA study, *Hypertension*, Dec., 2000; 36(6) : 1072-1078.
27. Franeesea Viazzi, Denise Parodi and Giovanna Leoneini, Elena Ratto. Serum uric acid and target organ damage in essential hypertension. *Hypertension*, 2005; 45 : 991-996.
28. Bos MJ, Koudstaal PJ, Hofman A, Witteman JC, Breteler MM. Uric acid is a risk factor for myocardial infarction and stroke: The Rotterdam study. *Stroke* 2006; **37**: 1503–1507.
29. Zhang X, Patel A, Horibe H, Wu Z. Asia Pacific Cohort Studies Collaboration. Cholesterol, coronary artery disease and stroke in the Asia Pacific Region. *Int J Epidemiol* 2003; 32: 563-572.
30. Amarenco P, Labreuche J, Lavallée P, Touboul P-J. Statins in stroke prevention and carotid atherosclerosis: Systematic review and metaanalysis. *Stroke* 2004; **35**: 2902–2909.