Original Research Article

Serum uric acid – An independent risk factor in acute non-embolic ischemic stroke

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Abstract

Background: A stroke, or cerebrovascular accident, is defined as an abrupt onset of a neurological deficit that is attributable to a focal vascular cause. The incidence of cerebrovascular diseases increases with age, and the number of strokes is projected to increase as the elderly population grows, with a doubling in stroke deaths in the United States by 2030. For India, community surveys have shown a crude prevalence rate for 'hemiplegia' in the range of 200 per 100,000 persons, nearly 1.5% of all urban hospital admissions, 4.5% of all medical, and around 20% of neurological cases.
Aim of the study: To also study the association between Serum Uric Acid (SUA) and other risk factors namely hypertension, Diabetes mellitus, CAD, and adverse lipid profile.
Materials and methods: The study was conducted in the year 2018, at Madha Medical College and Research Institute, Chennai. All subjects gave informed consent and the study protocol was approved by the Ethical Committee. The blood samples were taken within 24 hours of the onset of stroke and sent for biochemical analysis and were analyzed in our Biochemical Laboratory using a standard analyzer.
Results: Mean uric acid level in males was 5.41 mg/dl and in females, it was 5.47 mg/dl. This study did not show any significant association between hypertension and uric acid. The mean uric acid level in the hypertensive population was 5.64 mg/dl and in the non-hypertensive population was 5.06 mg/dl. There was a statistically significant association (p-value- 0. 0006) found between the level of uric acid and Diabetes mellitus. Among diabetics, the mean uric acid value was 5.98 mg/dl while among non-diabetics it was 4.88 mg/dl. In this study, the mean uric acid level in this stroke population with CAD was 6.46 mg/dl and in those without CAD was 4.96 mg/dl and thus establishes a statistically significant relationship ('p' 0. 0004). Mean uric acid level in the hyperlipidemic stroke population was 5.75 mg/dl and compared to 5.28 mg/dl mean uric acid level in patients without hyperlipidemia did not show any statistically significant relationship. Further analysis was done to analyze the relationship between uric acid levels less than and more than 7 mg/dl and the risk factors. This

analysis showed age more than 65 years and CAD had a statistically significant relationship with uric acid level.

Conclusion: 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. Elevated SUA can be considered as one of the risk factors for acute ischemic non-embolic stroke.

Key words

Serum Uric Acid, Hypertension, Diabetes Mellitus, Metabolic Syndrome, Cerebro Vascular Accident.

Introduction

Stroke also entails a high socio-economic burden due to increased morbidity and mortality. Ischemic strokes account for > 80% of total stroke events. Early identification of individuals at risk could be of help in primary prevention strategies [1]. UA is the most abundant aqueous antioxidant in humans and contributes as much as two-thirds of all free radical scavenging capacity in plasma. It is particularly effective in quenching hydroxyl, superoxide, and peroxynitrite radicals, and may serve a protective physiological role by preventing lipid peroxidation [2]. In a variety of organs and vascular beds, local UA concentrations increase during acute oxidative stress and ischemia, and the increased concentrations might be a compensatory mechanism that confers protection against the increased free radical activity [3]. The role of serum uric acid (SUA) levels as an independent risk factor for vascular disease has been questioned for decades [4]. Evidence from epidemiological studies suggests that the elevated SUA levels may predict an increased risk for cerebrovascular (CV) events including stroke [5]. Moreover, therapeutic modalities with an SUA lowering potential have been shown to reduce CV disease morbidity and mortality [6]. Subjects with NIDDM have a two-fold to four-fold greater risk of all manifestations of atherosclerotic vascular disease including stroke [7]. The increased risk of stroke is only partly explained by the adverse effects of NIDDM on classic risk factors or risk factors clustering with hyperinsulinemia. The USA has been recently associated with insulin resistance [8]. Although high SUA levels have been identified as an important risk factor for stroke in unselected populations in several epidemiological studies it is unclear whether high SUA levels promote or protect against the development of CV disease [9].

Materials and methods

The study was conducted in the year 2018, at Madha Medical College and Research Institute, Chennai. All subjects gave informed consent and the study protocol was approved by the Ethical Committee.

Inclusion criteria: Patients who were admitted to our hospital with first-ever-in lifetime acute ischemic non-embolic stroke with or without CT Scan evidence of infarction within 24 hours of the onset of stroke.

Exclusion criteria: Patients with a previous history of TIA / CVA, Patients who were on thiazide diuretics, Patients who were known cases of gout or show clinical evidence of gout. Patients with chronic renal failure, Patients whose CT scan showed hemorrhage or other space-occupying lesions other than infarct. Patients who were of known cardiac diseases which could be sources of emboli or whose echocardiogram shown sources of emboli. Patients with hematological abnormalities like leukemia or other myeloproliferative disorders.

The blood samples were taken within 24 hours of the onset of stroke and sent for biochemical analysis and were analyzed in our Biochemical Laboratory using standard analyzer.

Statistical analysis

The collected data were entered in a Microsoft Excel spreadsheet and analyzed statistically

using the epidemiological Information package – 2008 developed by the centers for disease control and prevention, Significance has considered if the 'p' value was below 0.05.'t' test was used to find out whether or not there exists a mean difference. Using this software, frequencies, percentage, mean, standard deviation, $x^{2,}$ and 'p' values were calculated. A 'p' value less than 0.05 was taken to denote a significant relationship.

Results

Majority of this stroke population was between 50 to 69 years old, (61% of the population) with 33 Males and 28 females. The elderly population, above 70 years old constituted 20% of the population with 9 males and 11 females. The mean age of the male population was 59.1 years and of the female population was 60.5 years. The overall mean age of the study population was 59.8 years (**Table – 1**).

Table – 1: Age distribution.

Age in years	**Cases**	
	No	**No**
Less than 40	-	-
41- 49	19	19
50 – 59	26	26
60 – 69	35	35
70 – 79	16	16
80 & above	4	4
Total	100	100
Mean S.D	59.8 years 10.6	

Hypertension constitutes the major risk factor in this stroke population as 65% of the population was hypertensive. 34 males and 31 females were hypertensives and form 68% and 62% in their respective population. Diabetes mellitus ranks second as a risk factor, constituted 51% of the study population with 23 (46 %) males and 28 (56 %) females. Coronary Artery Disease was associated with 32% of the population with 15 (30 %) males and 17 (34 %) females. 34% of the stroke population has an adverse lipid profile and both sexes share an equal number of hyperlipidemias (17 each). Among the male population, 34 (68%) were smokers and 16 (32 %) were alcoholics (**Table – 2**).

Table – 2: Risk factors.

Risk Factor	**Cases**	
	No	**No**
a) Hypertension		
Present	65	65
Absent	35	35
b) DM		
Present	51	51
Absent	49	49
c) Smoking (among males)		
Present	34	68
Absent	16	32
d) CAD		
Present	32	32
Absent	68	68
e) Hyper lipid		
Present	34	34
Absent	66	66
f) Alcoholism (among males)		
Alcoholic	16	32
Non-Alcoholic	31	62
Occasional Drinker	3	6

Table – 3: Uric acid levels and their association with risk factors.

Uric Acid (mg/dl)	**Cases**			
	Males		**Females**	
	No.	**%**	**No.**	**%**
Less than 5	25	50	24	48
5 – 6.9	13	26	13	26
7 & Above	12	24	13	26
Total	50	100	50	100
Mean S.D.	5.41 1.88		5.47 1.53	
'p'	0.6586 Not significant			

The distribution of uric acid levels in the study population were as under: 1. Less than 5 mg / dl – 49 % (25 males and 24 females) 2.Between 5 – 6.9 mg / dl - 26 % (13 males and 13 females) 3.Above and equal to 7 mg / dl - 25 % (12 males and 13 females) as per **Table – 3**. Mean uric acid level in males was 5.41 mg/dl and in females, it

was 5.47 mg/dl. Age wise distribution of uric acid was found statistically significant. As age advances the uric acid level also rises with the 'P 'value of 0.0001. This significance was maintained even when male and female populations were considered separately ('P 'of 0.0056 for males and 0.0077 for females) as per **Table - 3**.

Table – 4: Hypertension and uric acid.

Hypertension	**Uric Acid (mg/ dl)**	
	Mean	**S.D.**
Present	5.64	1.7
Absent	5.06	1.68
p	0.0793 (Not significant)	

Table – 5: Diabetes mellitus and uric acid.

DM	**Uric Acid (mg / dl)**	
	Mean	**S.D.**
Present	5.98	1.66
Absent	4.88	1.59
p	0.0006 (Significant)	

Table - 6: CAD and uric acid.

CAD	**Uric Acid (mg / dl)**	
	Mean	**S.D.**
Present	6.46	1.87
Absent	4.96	1.4
p	0.0004 (Significant)	

Table – 7: Hyperlipidemia and uric acid.

Hyperlipidemia	**Uric Acid (mg / dl)**	
	Mean	**S.D.**
Present	5.75	1.9
Absent	5.28	1.59
p	0.2541 (Not significant)	

Table – 8: Smoking and uric acid.

Smoking	**Uric Acid (mg / dl)**	
	Mean	**S.D.**
Present	5.14	1.8
Absent	5.96	1.98
p	0.0978 Not significant	

This study did not show any significant association between hypertension and uric acid. The mean uric acid level in the hypertensive population was 5.64 mg/dl and in the non-hypertensive population was 5.06 mg/ dl. There was no significant association found, also when males and females were considered separately. The mean uric acid levels for male hypertensives were 5.49 mg/ dl (non-hypertensive males - 5.24 mg / dl) and in females was 5.82 mg/dl (non-hypertensive females – 4.91 mg /dl) as per **Table - 4**.

There was a statistically significant association (p-value- 0. 0006) found between the level of uric acid and Diabetes mellitus. Among diabetics, the mean uric acid value was 5.98 mg/dl while among non-diabetics it was 4.88 mg/dl. This association was more significant among males (p-value -0.0006) among whom the diabetics had 6.16 mg/dl as mean uric acid level compared to non-diabetics, 4.76 mg/dl as the mean value. But, this association was not found significant in the female population. The mean uric acid level in diabetic women was 5.83 mg/dl when compared to non-diabetic women was 5.03 mg/dl (**Table – 5**).

In this study, the mean uric acid level in this stroke population with CAD was 6.46 mg/dl and in those without CAD was 4.96 mg/dl and thus establishes a statistically significant relationship ('p' 0. 0004). When males and females were considered, males have a significant association with a 'p' value of 0. 0003. The female population did not show such an association (**Table - 6**).

Mean uric acid level in hyperlipidemic stroke population was 5.75 mg/dl and compared to 5.28 mg/dl mean uric acid level in patients without hyperlipidemia did not show any statistically significant relationship. There was no statistically significant relationship even when males and females were analyzed separately (**Table – 7**).

Mean uric acid level in smokers was 5.14 mg/dl and among non-smokers was 5.96 mg/dl. Thus in this study, there was no statistically significant

relationship between smoking and uric acid. Further analysis was done to analyze the relationship between uric acid levels less than and more than 7 mg/dl and the risk factors. This analysis showed age more than 65 years and CAD have a statistically significant relationship with uric acid level (**Table – 8**).

Discussion

A transient ischemic attack (TIA) is defined as stroke symptoms and signs that resolve within 24 hours. There are limitations to these definitions. 'Brain Attack' is sometimes used to describe any neurovascular event (NICE Clinical Guidelines). Various risk factors are involved in the development of stroke, like hyperlipidemia, hypertension, diabetes, and smoking, etc. [10]. Recent studies show that there may be other factors causing the development of the disease like serum uric acid level. Identification of potential prognostic factors for ischemic stroke may enable better prediction for the outcome and conducting early interventions may improve the prognosis [11]. Uric acid is an end product of purine metabolism in humans, is known to be a relation to many systemic risk factors of stroke, such as hypertension, diabetes mellitus, insulin resistance, and obesity. In this study, most of the population belongs to anterior circulation territory, especially of the middle cerebral artery region with the commonest presentation being hemiplegia, except in one patient with bilateral cerebellar infarct evidenced in MRI scan [11]. As most of the posterior circulation strokes have masquerading clinical presentations and often lack CT scan evidence of infarction, they are not included in this study to avoid inclusion bias. Age is the most common non-modifiable risk factor for the development of stroke [12]. Gu L, et al. has stated 25% of the population are above 65 years with 12 males and 13 females. One pilot study of 163 patients above 70 years studied the association of SUA and stroke concludes that SUA is associated with an increased risk for acute ischemic/ non-embolic stroke in elderly patients independently of concurrent metabolic derangements. This study also shows evidence for a significant association between SUA and the elderly stroke population, and the association was maintained even when both sexes are considered separately [13]. Thus this study supports the association of high SUA and acute ischemic/ non-embolic stroke. Hypertension is the most common modifiable risk factor for stroke. The USA is also commonly associated with hypertension [14]. Elevated SUA level is an independent predictor of hypertension in 25% of patients with new-onset, untreated primary hypertension. In this study, H**y**pertension constitutes the major risk factor as 65% of the stroke population is hypertensive. The mean uric acid level of the hypertensive population is 5.64 mg/dl and of the non-hypertensive is 5.06 mg/dl and thus this study does not show any statistically significant relationship between SUA and hypertension. Diabetes mellitus ranks second as a risk factor in this study, constitute 51 % of the study population [15]. One population-based study involving 1017 persons with NIDDM, concludes that hyperuricemia is a strong predictor of stroke events in middle-aged persons with NIDDM, independently of other CV risk factors. Levels are often increased in subjects with MetS (47-49) [16]. The mean SUA level in this CAD population is 6.46 mg/ dl comparing to patients without CAD is 4.96 mg/dl which shows a strong statistical significance. Among those 32 stroke patients with CAD 17 have SUA > 7 mg/dl. This also shows a strong statistical significance with a 'p' value of 0.0001 [17]. Hence this study strongly favors Kang DH et.al study and suggests SUA is a strong risk factor for myocardial infarction and stroke. Several prospective studies have shown that higher levels of total cholesterol increase the risk of ischemic stroke [17]. Furthermore, a meta-analysis of 90000 patients showed that administration of statins reduces the risk of stroke among patients with CAD and that this risk reduction is primarily related to the extent to which LDL-C levels are lowered [18]. In some studies relating Met S and SUA, increased SUA levels correlated with low HDL-C levels [19]. In our study, Hyperlipidemia is considered separately and not as a part of Met S. Moreover,

most of our patients in this study population are from a low socio-economic group and are not found obese [20]. In this study, the mean uric acid level in hyperlipidemic patients is 5.75 mg/dl and in patients without hyperlipidemia is 5.28 mg/dl and does not show any significant association between these variables [20]. Out of 34 patients with hyperlipidemia in this study, only 12 are found to have SUA > 7 mg/dl. Among the other risk factors like smoking and alcoholism, they are not considered as separate risk factors in many pilot studies of this kind [21]. This study also fails to show any statistically significant relationship between SUA and these risk factors when considered separately. Further analysis between < 7 mg/dl and > 7 mg/dl SUA groups also maintain the association between high SUA and the risk factors namely age and CAD [22, 23].

Conclusion

This study shows that elevated SUA is strongly associated with an increased risk for the development of acute ischemic/ non-embolic 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. Elevated SUA can be considered as one of the risk factors for acute ischemic non-embolic stroke. Lowering of SUA level can be considered as one of the preventive modalities for stroke while treating a high-risk population. It is also suggested that further studies are required to assess whether the lowering of SUA level with drugs can reduce the risk of ischemic stroke.

References

1. Abuja PM. Ascorbate prevents prooxidant effects of urate in the oxidation of human low-density lipoprotein. FEBS Lett., 1999; 446: 305–308.
2. Bagnati M, Perugini C, Cau C, Bordone R, Albano E, Bellomo G. When and why a water-soluble antioxidant becomes pro-oxidant during copper-induced low-density lipoprotein oxidation: A study using uric acid. Biochem J., 1999; 340: 143–152.
3. Boogaerts MA, Hammerschmidt DE, Roelant C, Verwilghen RL, Jacob HS. Mechanisms of vascular damage in gout and oxalosis: Crystal induced, granulocyte mediated, endothelial injury. Thromb Haemost., 1983; 50: 576– 580.
4. Buckley BM. Healthy aging: aging safely. Eur Heart J, 2001; (Suppl. 3): N6–10.
5. Cannon PJ, Stason WB, Demartini FE, Sommers SC, Laragh JH. Hyperuricemia in primary and renal hypertension. N Engl J Med., 1966; 275: 457–464.
6. 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.
7. Cherubini A, Polidori MC, Bregnocchi M, Pezzuto S, Cecchetti R, Ingegni T, et al. Antioxidant profile and early outcome in stroke patients. Stroke, 2000; 31: 2295–2300.
8. Daskalopoulou SS, Athyros VG, Elisaf M, Mikhailidis DP. Uric acid levels and vascular disease. Curr Med Res Opin., 2004; 20: 951–4.
9. DeFronzo RA, Ferrarini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic vascular disease. Diabetes Care, 1991; 14: 173–194.
10. Duff GW, Atkins E, Malawista SE. The fever of gout: Urate crystals activate endogenous pyrogen production from human and rabbit mononuclear phagocytes. Trans Assoc Am Physicians, 1983; 96: 234– 245.
11. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality. The NHANES I epidemiologic follow-up study, 1971–1992. JAMA, 2000; 283: 2404–10.
12. Gariballa SE, Hutchin TP, Sinclair AJ.

Antioxidant capacity after acute ischaemic stroke. Q J Med., 2002; 95: 685– 690.

13. Gu L, Okada Y, Clinton SK, Gerard C, Sukhova GK, Libby P, et al. Absence of monocyte chemoattractant protein-1 reduces atherosclerosis in low-density lipoprotein receptor-deficient mice. Mol Cell, 1998; 2: 275–281.
14. Hoieggen A, Alderman MH, The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int., 2004; 65: 1041–9.
15. Jossa F, Farinaro E, Panico S, et al. Serum uric acid and hypertension: the Olivetti Heart Study. J Hum Hypertens., 1994; 8: 677–81.
16. Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T, et al. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. Hypertension, 2003; 41: 1287– 1293.
17. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, et al. A role for uric acid in the progression of renal disease. J Am Soc Nephrol., 2002; 13: 2888– 2897.
18. Kondo N, Nomura M, Nakaya Y, Ito S, Ohguro T. Association of inflammatory marker and highly sensitive C-reactive protein with aerobic exercise capacity, maximum oxygen uptake, and insulin resistance in healthy middle-aged volunteers. Circ J, 2005; 69: 452 – 457.
19. Lehto S, Niskanen L, Ronnemaa T, Serum uric acid is a strong predictor of stroke in patients with non-insulin-dependent diabetes mellitus. Stroke, 1998; 29: 635–9.
20. Leinonen JS, Ahonen JP, Lonnrot K, Jehkonen M, Dastidar P, Molnar G, et al. Low plasma antioxidant activity is associated with high lesion volume and neurological impairment in stroke. Stroke, 2000; 31: 33– 39.
21. Maxwell SR, Lip GY. Free radicals and antioxidants in cardiovascular disease. Br J Clin Pharmacol., 1997; 44: 307– 317.
22. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, et al. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension, 2001; 38: 1101 – 1106.
23. Messerli FH, Frohlich ED, Dreslinski GR, Suarez DH, Aristimuno GG. Serum uric acid in essential hypertension: An indicator of renal vascular involvement. Ann Intern Med., 1980; 93: 817– 821.