Original Research Paper

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A Clinical Case Study on Serum Uric Acid as an Independent Risk Factor in Acute Ischemic Stroke

Medicine

KEYWORDS : SUA, ischemic stroke

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ABSTRACT

The role of serum uric acid (SUA) levels as an independent risk factor for vascular disease has been questioned for decades. Evidence from epidemiological studies suggest that the elevated SUA levels may predict an increased risk for cerebrovascular (CV) events including stroke. SUA can work as pro-oxidant under certain circumstances, particularly if the levels of other antioxidants like ascorbic acid are low. Various studies have shown that uric acid can result in endothelial dysfunction which can lead to vascular disease. An association between SUA and inflammatory markers has also been discovered. Moreover therapeutic modalities with a SUA lowering potential have been shown to reduce CV disease morbidity and mortality.

INTRODUCTION:

Stroke is defined as "neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours" [1, It] was the second most frequent cause of death worldwide in 2011, accounting for 6.2 million deaths (~11% of the total) [2] . Early identification of individuals at risk could be of help in primary prevention strategies .

Uric Acid 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[3] . In a variety of organs and vascular beds, local uric acid concentrations increase during acute oxidative stress and ischemia, and the increased concentrations might be a compensatory mechanism that confers protection against increased free radical activity [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 a SUA lowering potential have been shown to reduce CV disease morbidity and mortality[6].

AIMS AND OBJECTIVES OF THE STUDY

1. To analyze the association between Serum Uric Acid (SUA) and acute ischemic stroke and to assess its risk factor potential using statistical analysis.
2. To also study the association between Serum Uric Acid (SUA) and other risk factors namely hypertension, Diabetes mellitus, CAD and adverse lipid profile.

The blood samples were taken within 24 hrs of onset of stroke and sent for biochemical analysis. The patients were further evaluated for presence of additional risk factors like Hypertension, Diabetes, Coronary artery disease, adverse lipid profile, smoking and alcoholism.

MATERIALS AND METHODS

INCLUSION CRITERIA:

1. Patients who were admitted in our hospital with first-ever-in life time acute ischemic nonembolic stroke with CT scan evidence of infarction within 24 hrs of onset of stroke.

EXCLUSION CRITERIA:

1. Patients with previous history of TIA / CVA
2. Patients who are on thiazide diuretics
3. Patients who are known cases of gout or show clinical evidences of gout.
4. Patients with chronic renal failure
5. Patients whose CT scan show haemorrhage or other space occupying lesions other than infarct.
6. Patients who were of known cardiac diseases which could be sources of emboli or whose echocardiogram shown sources of emboli.
7. Patients with haemotological abnormalities like leukemia or other myeloproliferative disorders.

All subjects gave informed consent and the study protocol was approved by the Ethical Committee.

The blood samples were taken within 24 hrs of onset of stroke and sent for biochemical analysis. The patients were further evaluated for the presence of additional risk factors such as hypertension, diabetes mellitus, coronary artery disease, dyslipdemia, smoking and alcoholism.

STATISTICAL TOOLS

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2002).

Using this software, frequencies, percentage, mean, standard deviation, x^2 and 'p' values were calculated. A 'p' value less than 0.05 is taken to denote significant relationship.

RESULTS

The observations made in this study are categorized, analysed and tabulated as under:

1. AGE DISTRIBUTION :

In this prospective study, 41 to 84 yrs old patients are included. Majority of this stroke population are between 50 to 69 yrs old, (61 % of the population) with 33 Males and 28 females. The elderly population, above 70 yrs old constitute 20 % of the population with 9 males and 11 females.

The mean age of the male population is 59.1 yrs and of the female population is 60.5 yrs. The overall mean age of the study population is 59.8 yrs.

2. RISK FACTORS:

Hypertension constitutes the major risk factor in this stroke population as 65 % of the population is hypertensive. 34 males and 31 females are hypertensives and form 68 % and 62 % in their respective population.

Diabetes mellitus ranks second as a risk factor, constitute 51% of the study population with 23 (46 %) males and 28 (56 %) females.

Coronary Artery Disease is associated in 32 % of the population with 15 (30 %) males and 17 (34 %) females.

34 % of the stroke population has adverse lipid profile and both sexes share equal number of hyperlipidemics (17 each).

Among the male population, 34 (68 %) are smokers and 16 (32 %) are alcoholics.

Table 1 : Risk Factors according to sex

Risk Factor	Cases			
	Males		Females	
	No.	%	No.	%
a) Hypertension				
Present	34	68	31	62
Absent	16	32	19	38
b) DM				
Present	23	46	28	56
Absent	27	54	22	44
c) Smoking (among males)				
Present	34	68	-	-
Absent	16	32	50	100
d) CAD				
Present	15	30	17	34
Absent	35	70	33	66
e) Hyper lipidemia				
Present	17	34	17	34
Absent	33	66	33	66
f) Alcoholism				
(among males)				
Alcoholic	16	32	-	
Non Alcoholic	31	62	50	100
Occasional Drinker	3	6	-	-

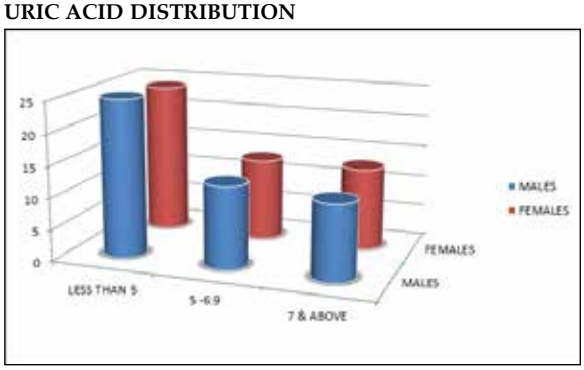
3. Uric acid levels in study population

The distribution of uric acid levels in the study population are as under:

- 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 5.41 mg / dl and in females it is 5.47 mg / dl.

GRAPH 1
URIC ACID DISTRIBUTION



4.AGE AND URIC ACID LEVELS

Age wise distribution of uric acid is found statistically significant. As age advances the uric acid level also rises with the 'P 'value of 0.0001. This significance is maintained even when male and female populations are considered separately. ('P' of 0.0056 for males and 0.0077 for females).

Table 2 : Age and uric acid according to sex

Age group	Uric Acid			
	Males		Females	
	Mean	S.D.	Mean	S.D.
40 – 49	4.19	1.72	4.48	0.7
50 – 59	5.0	1.54	4.92	1.3
60 –69	5.42	1.53	5.54	1.51
70 –79	7.1	2.1	7.04	1.45
80 & above	8.4	-	4.8	0.85
'p'	0.0056		0.0077	
	Significant		Significant	

The mean uric acid value for 40 – 49 yrs group is 4.36 mg / dl while the elderly agegroup of above 70 yrs has the mean value 7.07 mg / dl.

5 : SEX AND URIC ACID LEVELS

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 5.41 mg / dl and among female population it is 5.47 mg / dl.

6. HYPERTENSION AND URIC ACID LEVELS

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 5.06 mg/ dl.

There is no significant association found, also when males and females are considered separately. The mean uric acid levels for male hypertensives is 5.49 mg/ dl (non hypertensive males- 5.24 mg /dl) and in females is 5.82 mg /dl (non hypertensive females – 4.91 mg / dl).

7: DIABETES MELLITUS AND URIC ACID LEVELS

There is 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 is 5.98 mg / dl while among non diabetics it is 4.88 mg / dl.

This association is more significant among males (p value -0.0006) among whom the diabetics have 6.16 mg / dl as mean uric acid level compared to non diabetics, 4.76 mg / dl as mean value.

But, this association is not found significant in female population. The mean uric acid level in diabetic women is 5.83 mg / dl when compared to non diabetic women is 5.03 mg / dl.

8 :CAD AND URIC ACID LEVELS

In this study, mean uric acid level in this stroke population with CAD is 6.46 mgs / dl and in those without CAD is 4.96 mgs / dl and thus establishes a statistically significant relationship ('p' 0. 0004).

When males and females are considered, males have a significant association with a 'p' value of 0. 0003. Female population does not show such association. (See table)

9.HYPERLIPIDEMIA AND URIC ACID LEVELS

Mean uric acid level in hyperlipidemic stroke population is 5.75 mgs / dl and compared to 5.28 mgs / dl mean uric acid

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level in patients with out hyperlipidemia do not show any statistically significant relationship.

There is no statistically significant relationship even when males and females are analysed separately.

10. SMOKING AND URIC ACID LEVELS

Mean uric acid level in smokers is 5.14 mg / dl and among non-smokers is 5.96 mgs / dl. Thus in this study there is no statistically significant relationship between smoking and uric acid.

RISK FACTORS IN POPULATION WITH HIGH URIC ACID LEVEL (ie. > 7mgs / dl)

Table 3 : Risk Factors and uric acid levels < / > 7 mgs / dl

Risk Factor	Uric acid			
	< 7mg/dl		> 7mg/dl	
	No.	%	No.	%
a) Hypertension				
Present	45	60	20	80
Absent	30	40	5	20
'p'	0.1156			
	Not significant			
b) DM				
Present	34	45.3	17	68
Absent	41	54.7	8	32
'p'	0.0832			
	Not significant			
c) Smoking (among males)(50)				
Present	27	71.1	7	58.3
Absent	11	28.9	5	41.7
'p'	0.314			
	Not significant			
d) CAD				
Present	15	20	17	68
Absent	60	80	8	32
'p'	0.0001			
	Significant			

Risk Factor	Uric acid			
	< 7mg/dl		> 7mg/dl	
	No.	%	No.	%
e) Hyper lipid				
Present	22	29.3	12	48
Absent	53	70.7	13	52
'p'		0.1436		
	Not significant			
f) Alcoholism (among males)				
Alcoholic	15	39.5	4	33.3
Non Alcoholic	23	60.5	8	66.7
'p'		0.6858		
	Not significant			
No risk factor	7	9.3	2	8
At least one risk factor	68	90.7	23	92
'p'		0.6008		
	Not significant			
Age				
>65	11	42.3	15	57.7
<65	64	86.5	10	13.5
'p'		0.0001		
	Significant			

Further analysis is done to analyse the relationship between uric acid levels less than and more than 7 mgs / dl and the risk factors. This analysis shows age more than 65 yrs and CAD have statistically significant relationship with uric acid level.

DISCUSSION

Our study was conducted on 100 Stroke patients of which males and females were equal in number and hence there is no sex bias. Mean age in males is 59.1 years and females 60.1 years. Mean uric acid levels in males 5.41mg/dl and 5.47mg/dl in females. Distribution of risk factors also is more or less in similar pattern (Hypertension: males-34, females-31; Diabetes mellitus: males-23, females-28; CAD: males-15 females-17 ; Hyperlipidemia ; males-17, females-17). Millinois et al and Waring et al found high levels of SUA in males, which is not seen in our study.[7].

However, in elderly population both sexes show high levels of SUA which has statistical significance. Our study is consistent with Milinois et al who found elevated .SUA in individuals older than 70 years.[7] Regarding the association between risk factors and both sexes, CAD is significantly associated with high uric acid levels in both sexes whereas DM is associated only with males and not with females.

In this study, most of the patients belongs to anterior circulation territory, especially of middle cerebral artery region with commonest presentation being hemiplegia. 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 [8]. In this study, 25 % of the patients are above 65 yrs with 12 males and 13 females. MIllinois et al studied .163 patients above 70 yrs studied for association of SUA and stroke concludes that SUA is associated with an increased risk for acute ischemic nonembolic stroke in elderly patients independently of concurrent metabolic derangements. This study also shows evidences for a significant association between SUA and elderly stroke population, and the association was maintained even when both sexes are considered separately. These findings are consistent with those in this study.

Hypertension is the most common modifiable risk factor for stroke . SUA is also commonly associated with hypertension [9,10]. 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 hypertensive patients is 5.64 mgs / dl and of nonhypertensive is 5.06 mgs / 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. Lehto s et al[11] conducted 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.

SUA levels are often increased in subjects with MetS [12-14]. In this study, with the mean SUA level of 5.98 mgs / dl among diabetics and 4.88 mgs / dl among non-diabetics there is a strong association between SUA and DM. Further analysis shows this association is more stronger among males (mean SUA in male diabetics -6.66 mgs / dl vs non-diabetic males- 4.76 mgs /dl)than females. Thus this study strongly favours for an association between SUA and acute ischaemic / nonembolic stroke in diabetic population.

SUA is significantly associated with cardiovascular mortality in certain

epidemiological studies .Rotterdam study[15] which had 4385 participants with follow up of 8.4 years showed that SUA is a strong risk factor for myocardial infarction and stroke. In this study CAD is found in 32 % of the patients with 15 males and 17 females. The mean SUA level in this CAD population is 6.46 mgs / dl comparing this to patients without CAD is 4.96 mgs / dl which shows a strong statistical significance. Among those 32 stroke patients with CAD 17 have SUA > 7 mgs / dl. This also shows a strong statistical significance with a 'p' value of 0.0001. Hence this study strongly favours Rotterdam study and suggests SUA is a strong risk factor for myocardial infarction and stroke.

Several prospective studies [16,17] have shown that higher levels of total cholesterol increase the risk of ischaemic stroke. Amerenco p et al conducted 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. In some studies [18,19] relating Met S and SUA, increased SUA levels correlated with low HDL-C levels.

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 low socio-economic group and are not found obese. In this study, the mean uric acid level in hyperlipidemic patients is 5.75 mgs / dl and in patients without hyperlipidemia is 5.28 mgs / dl and does not show any significant association between these variables. Out of 34 patients with hyperlipidemia in this study, only 12 are found to have SUA > 7 mgs / 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. This study also fails to show any statistically significant relationship between SUA and these risk factors when considered separately.

Further analysis between < 7mgs/dl and> 7 mgs / dl SUA groups also maintain the association between high SUA and the risk factors namely age and CAD.

CONCLUSION

This study shows that elevated SUA is strongly associated with an increased risk for the development of acute ischaemic/ non-embolic stroke in this study population.

The association between elevated SUA and ischaemic 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 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.

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