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The Role of Serum Uric Acid in Acute Ischemic Stroke

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ABSTRACT

Ischemic stroke remains a major health care problem and a leading cause of disability, dementia and mortality. The role of serum uric acid remains controversial and is unclear whether it promotes or protects against the cerebrovascular disease. A case control study was undertaken from January 2012 to June 2012 to estimate uric acid levels in patients with acute ischemic stroke and to compare with controls. 30 cases of acute ischemic stroke were studied along with 30 age and sex matched healthy controls. Serum uric acid was estimated by Uricase method. Assessment of severity of stroke was done based on Glasgow coma scale (GCS). In this study serum uric acid levels were raised in cases when compared to controls. The mean and standard deviation of uric acid were 6.64±1.97 in cases and 4.42±1.11 in controls with significant p value of < 0.001. Cases with high uric acid levels had low GCS score which indicate poor prognosis. 57.1% of patients with raised uric acid levels had moderate GCS score (9-12) and 14.3% had severe GCS score (≤8). Elevated levels of serum uric acid can be used as one of the risk factor for stroke.

Keywords: Acute ischemic stroke, Uric acid, GCS, Uricase method.

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INTRODUCTION

Stroke is defined as per the World Health Organization (WHO) definition - a syndrome of rapidly developing clinical signs of focal or global neurological disturbance, with symptoms lasting for more than 24 hours or longer or leading to death, with no apparent cause other than of vascular origin. According to the estimates by the National Commission on Macroeconomics and Health, India, there will be 1.67 million stroke cases in 2015. Among all the neurologic diseases of adult life, stroke clearly ranks first in frequency and is the leading cause of morbidity and mortality [1, 2].

Ischemic cerebral infarction is the most common subtype of stroke [3]. Uric acid (2,6,8 trioxopurine) is an end product of purine metabolism and serves as important antioxidant by getting itself converted (nonenzymatically) to allantoin [4]. Uric acid is one of the major aqueous antioxidant in the human beings and constitutes approximately one half the antioxidant capacity of plasma [5, 6]. But it can work as a pro-oxidant under certain circumstances, particularly if the levels of other antioxidants (like ascorbate) are low [7] thus predisposes to the development of hypertension and vascular disease.

Elevated uric acid levels are injurious rather than protective in subjects with acute ischemic stroke.

Objectives:

To estimate uric acid levels in patients with acute ischemic stroke and to compare with controls, to find out the association between uric acid and severity of stroke.

MATERIALS AND METHODS

The study was conducted from January 2012 to June 2012 over a period of 6 months. The study was approved by the ethical committee of the institute and an informed consent was obtained from all subjects who took part in the study.

Study was conducted in patients admitted to Victoria hospital and Bowring & Lady Curzon hospital attached to Bangalore Medical College & Research Institute, Bangalore. Study comprised 30 inpatients of acute ischemic stroke with age between 30-90 years. [CT brain or MRI brain proved cases] and 30 age and sex matched healthy controls.

Patients with a known or possible cardiac source of emboli, past history of vascular disease, patients receiving drugs affecting serum uric acid levels, active infections, renal or liver disease, thyroid dysfunction and excessive alcohol consumption were excluded from the study.

Assessment of severity of stroke was done based on Glasgow coma scale (GCS). Normal score is 15, Severe GCS ≤ 8, Moderate GCS 9-12, Minor GCS ≥ 13 [8].

5 ml of venous blood was obtained by venepuncture under aseptic conditions, centrifuged and the separated serum was used for estimation. Serum uric acid was estimated by Uricase method (enzymatic colorimetric test) [4] using COBAS Integra 400 plus analyzer. All other biochemical measurements were performed as per standard procedures.

Statistical Methods:

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented as Mean ± SD (Min-Max, SD: Standard deviation) and results on categorical measurements are presented as Number (%). Significance is assessed at 5 % level of significance.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (inter group analysis on metric parameters). Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

Significant figures
+ Suggestive significance (p value: $0.05 < p < 0.10$)
* Moderately significant (p value: $0.01 < p \leq 0.05$)
** Strongly significant (p value: $p \leq 0.01$)

RESULTS AND OBSERVATIONS

In both the study groups 70% were males and 30% were females. The mean age for cases was 58.20years with SD 8.27 years and 57.97 years with SD 8.14 years for controls. The groups (cases and controls) were appropriately age and sex matched.

Among 30 patients 53.3% of cases were diabetic and 70% were hypertensive. Graph 1 shows the distribution of co-morbid conditions among patients.

Normal levels of serum uric acid in males were 3.4-7 mg/dL and in females were 2.4-5.7 mg/dL. 46.7% of patients had raised uric acid levels which are shown in table 1. Mean total cholesterol levels in cases were 201.33 mg/dL with SD 50.05 mg/dL and 177.43 mg/dL with SD 29.76 mg/dL in controls.

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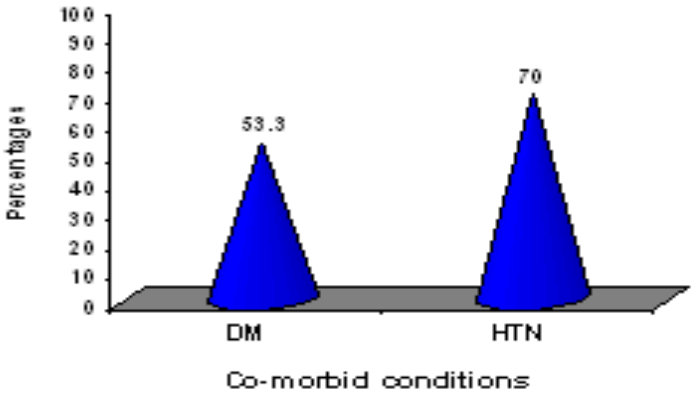


DM: Diabetes mellitus, HTN: Hypertension

Graph 1: Distribution of co-morbid conditions among patients

Table 1: Uric acid levels in patients

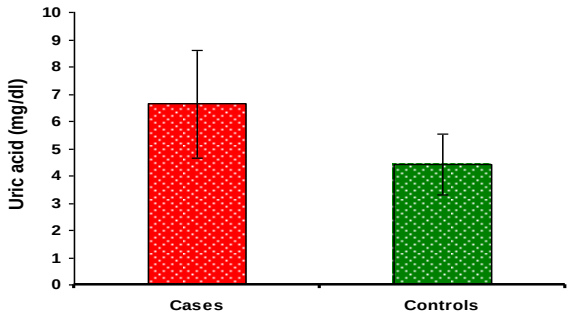
Uric acid (mg/dl)	Number of patients (n=30)	%
Normal Female:2.4-5.7 mg/dl Male :3.4-7.0 mg/dl	16	53.3
Raised Female: >5.7 mg/dl Male : >7.0 mg/dl	14	46.7

Table 2: Comparison of levels of uric acid in two groups

Uric acid (mg/dl)	Cases	Controls	P value
Min-Max	3.20 - 12.10	2.30 - 6.20	**t = 5.379;**
Mean ± SD	6.64 ± 1.97	4.42 ± 1.11	**p < 0.001****

** Strongly significant (p value: $p \leq 0.01$)

Graph 2: Uric acid levels in two groups



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From table- 2 and graph 2, the mean uric acid level in cases was 6.64 mg/dL with SD 1.97 mg/dL whereas it was 4.42 mg/dL with SD 1.11 mg/dL for controls with statistical significant difference in two groups.

Table 3: Association of clinical variables with uric acid levels in patients

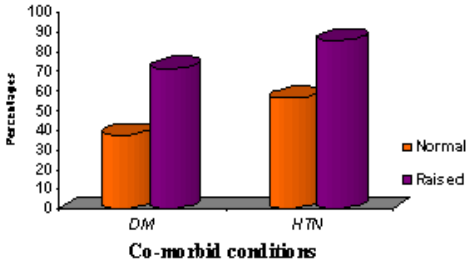
Clinical variables	Normal Uric acid (n=16)		Raised Uric acid (n=14)		P value
	No	%	No	%	
Age in years					
• 41-50	3	18.8	3	21.4	0.709
• 51-60	8	50.0	4	28.6	
• 61-70	4	25.0	6	42.9	
• >70	1	6.3	1	7.1	
Gender					
• Male	11	68.8	10	71.4	1.000
• Female	5	31.3	4	28.6	
Co-morbid conditions					
• DM	6	37.5	10	71.4	0.063+
• HTN	9	56.3	12	85.7	0.118
GCS score					
• Severe GCS	9	56.3	2	14.3	0.050*
• Moderate GCS	6	37.5	8	57.1	
• Minor GCS	1	6.3	4	28.6	

+ Suggestive significance (p value: 0.05< p <0.10)

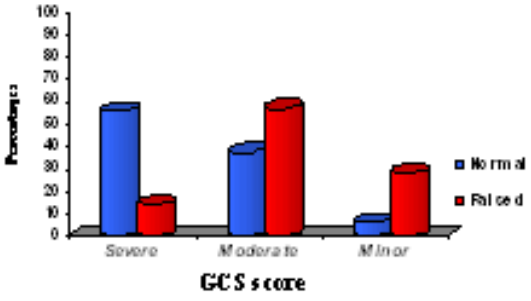
* Moderately significant (p value: 0.01< p ≤ 0.05)

From table-3 and graph 3, 4 - 71.4% of patients with diabetes had raised uric acid level which was suggestive of statistical significance. 14.3% of patients with severe GCS and 57.1% of moderate GCS patients had increased levels of serum uric acid with significant p value indicating the effect of uric acid on the severity of the disease.

Graph 3: Co-morbid conditions and uric acid levels



Graph 4: GCS scores and uric acid levels



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DISCUSSION

Stroke is a growing disease and becoming the common cause of disability and dementia. The well recognized risk factors like diabetes, hypertension, metabolic syndrome and smoking explain only a part of the cases. Additional knowledge about factors that contribute to morbidity and mortality after stroke is important for instituting therapies to lower the disability and mortality. This study was conducted to study the role of serum uric acid in acute ischemic stroke and its effect on stroke outcome.

The mean age of cases was 58.20±8.27 years; this finding was in consistent with the data published by Tushar B Patil et al [9] where the age range of stroke patients was 36 to 86 years with mean age of 60.05±9.98 years. 71.4% of patients with diabetes had raised uric acid level which was suggestive of statistical significance. This is in accordance with study of Longo-Mbenza et al [10] who observed significantly higher frequency of hyperuricemia among diabetic patients.

The mean uric acid level in cases was 6.64 mg/dL with SD 1.97 mg/dL whereas it was 4.42 mg/dL with SD 1.11 mg/dL for controls ($p<0.001$). These findings are in accordance with other studies, Milionis et al [11] observed that serum uric acid levels were significantly higher in stroke patients compared with controls (5.6±1.7 mg/dL vs 4.8±1.4 mg/dL, $p<0.001$). Shrikrishna R and Suresh DR [12] and The Rotterdam study [13] also found that high serum uric acid levels were associated with the risk of stroke.

In present study the severity of stroke was assessed by GCS score. 14.3% of patients with severe GCS and 57.1% of moderate GCS patients had increased levels of serum uric acid with significant p value indicating the effect of uric acid on the severity of the disease and poor prognosis. Weir et al [14] noted that higher serum urate value was significantly associated with bad outcome (OR=0.78 per additional 0.1 mmol/L; 95% C.I. = 0.67-0.91). Karagiannis et al [15] found an independent relationship between higher serum uric acid levels on admission and death (OR=1.37, 95%bC.I. = 1.13-1.67, p= 0.001).

A study done by Chammoro et al [16] found that higher levels of serum uric acid at admission were associated with better outcome after stroke.

Serum uric acid is one of the major antioxidant. So it should have a protective role in patients with stroke. But in most of the studies it is found that high uric acid levels are injurious rather than protective. Under certain circumstances, particularly if the levels of other antioxidants (like ascorbate) are low the original antioxidant properties of uric acid become paradoxically pro-oxidant [7]. Various studies showed that increased serum uric acid can result in endothelial dysfunction which can lead to vascular diseases [17, 18].

Increased uric acid levels lead to oxygenation of LDL cholesterol and facilitate lipid peroxidation[19]. Higher uric acid levels might reflect an increased activity of xanthine oxidase. The action of xanthine oxidase leads to generation of superoxide anions and reactive oxygen

species in human vasculature causing oxidative stress [20, 21]. In the presence of pre-formed lipid hydroperoxides, uric acid may accelerate the peroxidation of human LDL triggered by copper, even in the presence of endogenous antioxidants [22].

Limitations of our study were small sample size and the oxidant-antioxidant status was not assessed. Further long term prospective studies are needed to establish the role of uric acid in ischemic stroke.

CONCLUSION

Elevated levels of serum uric acid can be used as one of the risk factor for ischemic stroke. Thus serum uric acid levels could be of value in identifying subjects who are at risk of developing ischemic stroke and judiciously selecting drugs which will produce hyperuricemia so as to reduce the morbidity and mortality.

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