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Uric acid in men with acute stroke

Bhadra J[1*], Mahor DS[1], Seth S[1], Ghalaut VS[1], Dhupper V[1], Kulshrestha MR[2]

[1] Department of Biochemistry, Pt. B. D.Sharma PGIMS, Rohtak, Haryana,India

[2]Department of biochemistry, Modern Institute of Medical Sciences, Madhya Pradesh, India

*Corresponding author: Bhadra J

Abstract

Higher levels of uric acid in men as compared to women can be a reason behind greater incidence of stroke in men. The objective of the present study was to evaluate the levels of uric acid in men with acute stroke and correlate with stroke severity.For the purpose of the study ,50 male patients of acute stroke admitted to the hospital and 50 age matched healthy controls were included in the study. Routine biochemical parameters including fasting blood glucose, uric acid and lipid profile were assessed in serum obtained from 5 ml of fasting blood sample. Patients with kidney or liver diseases, malignancies, diuretic use, alcohol intake, on iron or antioxidant therapy were excluded from the study. Initial stroke severity was measured by the National Institute of Health Stroke (NIHS) scale. It was found that , among the 50 cases, 38(76%) had ischemic stroke and 12(24%) had hemorrhagic stroke. Serum uric acid levels were very significantly higher in cases ($p<0.001$) than controls. There was strong positive correlation between uric acid levels and initial stroke severity ($p=0.006$, $r=0.386$). Also, serum uric acid showed a statistically significant correlation with fasting blood glucose, TG and VLDL and an inverse association with HDL in both cases and controls. The conclusion drawn was that the significantly higher levels of uric acid in men with stroke and the positive association of uric acid with stroke severity suggest a possible role of uric acid as a risk factor for stroke in men.

Keywords: Uric acid, Acute stroke, Men, Stroke severity

Introduction

Stroke is one of the leading causes of mortality and morbidity worldwide, afflicting approximately 20 million people each year and causing 5 million deaths. [1] Although the etiopathogenesis and risk factors have been elucidated to a great extent, one intriguing aspect of stroke is its higher incidence in men than women, suggesting that male sex is an important risk factor. Uric acid, which has higher levels in men as compared to women, may have an important role in this.

However, studies regarding role of uric acid in stroke have produced inconsistent results so far. Increased uric acid levels have been found to be associated with established risk factors of stroke such as hypertension, dyslipidemia, obesity and diabetes.[2] Also, significantly higher risk of stroke incidence and mortality was reported in cases of hyperuricemia.[3]In the general elderly population too, high uric acid levels were independently associated with increased incidence of fatal stroke.[4] But, contrary to this, other studies have advocated uric acid to be neuroprotective due to its antioxidant action.[5,6]There is also disagreement regarding the role of uric acid in stroke severity and outcome. While Weir et al reported that increased serum urate levels predicted poorer outcome in patients of stroke, other studies found higher levels of serum urate to be associated with better outcomes following stroke. [6,7,8] Considering these conflicting findings, our

study was undertaken to evaluate the serum uric acid levels in men with stroke and to correlate the levels with stroke severity.

Materials and methods

A case control study was carried out between December 2013 and May 2014 on 50 adult male patients (>18 years) of acute stroke admitted to the hospital and 50 age matched healthy controls. A stroke, or cerebrovascular accident, was defined by the abrupt onset of a neurologic deficit that is attributable to a focal vascular cause. [9] Patients with kidney or liver diseases, malignancies, diuretic use, alcohol intake, on iron or antioxidant therapy were excluded from the study. Patients with onset of stroke more than 72 hours before admission were also excluded. An informed written consent was obtained for each participant of the study. The study was approved by institutional ethics committee. Complete history and physical examination was done in cases and controls according to standardized procedure. In patients, these risk factors were taken into account: age, atrial fibrillation (if present on electrocardiogram obtained on admission), smoking (smoking of any kind of tobacco), hypertension (known or under treatment with antihypertensive drugs), diabetes (already known, taking hypoglycemic drugs, or fasting blood glucose on admission >126 mg/dL), dyslipidemia, history of ischemic heart disease and previous stroke. Information about the risk factors was obtained from health records or by asking the patients or relatives. Initial severity of stroke in cases was measured by the NIHS Scale which evaluates level of consciousness, orientation, best gaze, visual fields, facial motor function, upper-extremity motor function, lower-extremity motor function, limb ataxia, sensory function, language, articulation, extinction or inattention. [10] The level of stroke severity is measured as 0(no stroke); 1-4(minor stroke); 5-15(moderate stroke); 15-20(moderate to severe stroke) and 21-42(severe stroke). Computed tomography (CT) scan of brain and electrocardiography (ECG) was performed on patient's admission to hospital. 5 ml of fasting venous blood sample was collected under all aseptic conditions on the day after admission. . All samples were taken between 10 am and 4 pm. Serum separation was done by centrifugation and the sample was analyzed in Erba XL30i autoanalyzer for routine biochemical parameters including fasting blood glucose, uric acid and lipid profile. Uric acid was estimated by the enzymatic uricase method. [11]

Statistical analysis

Assumption of normal distribution for continuous variables was tested by the Kolmogorov-Smirnov statistics. Data was expressed as mean ± SD or median and interquartile range. Comparison between two groups was done by independent samples T-test in normally distributed variables and Mann-Whitney U test in non-normally distributed variables. Pearson and Spearman's test were used for correlation as applicable. r was reported for correlation tests. Level of significance was considered as $P< 0.05$.

Results

Among the 50 cases, 38(76%) had ischemic stroke and 12(24%) had hemorrhagic stroke. No significant difference in uric acid level was found between cases of ischemic and hemorrhagic stroke. The percentages of cases having mild, moderate, moderate to severe and severe strokes according to NIHS scale were 8%, 32%, 42% and 18% respectively. The demographic and clinical characteristics of cases and controls are shown in Table 1.

Table 1:Comparison of demographic and clinical characteristics of cases and controls			
Characteristic	Case	Control	P value
Age, years, mean(SD)	59.28(12.31)	59.88(12.06)	0.806
Systolic blood pressure, mm Hg, median(IQR)	130(33)	120(10)	0.018
Diastolic blood pressure, mm Hg, median(IQR)	84(20)	80(7)	0.124
Fasting blood glucose, mg/dL, median(IQR)	119.5(58)	89.5(26)	<0.001
Triglyceride, mg/dL, mean(SD)	191.9(67.31)	102.06(31.32)	<0.001
Total cholesterol, mg/dL, mean(SD)	173.03(50.85)	123.4(39.56)	<0.001
HDL, mg/dL, mean(SD)	34.89(8.7)	36.93(9.16)	0.257
LDL, mg/dL, mean(SD)	131.31(46.83)	81.9(33.12)	<0.001
VLDL, mg/dL, mean(SD)	37.72(13.57)	20.32(6.23)	<0.001
Uric acid, mg/dL, mean(SD)	5.68(1.94)	3.72(0.96)	<0.001

*SD indicates standard deviation; IQR indicates interquartile range

Some of the patients had more than one risk factor for stroke. 38(76%) patients had smoking history while 24(48%) had diabetes. Hypertension was present in 24(48%) patients. 15(30%) had history of previous stroke. Ischemic heart disease and atrial fibrillation was present in 9(18%) and 2(4%) respectively. No significant difference in uric acid levels was found between patients with or without these risk factors. But serum uric acid showed statistically significant correlations with fasting blood glucose, triglycerides (TG), HDL and VLDL in both cases and controls (Table 2).

Table 2:Correlation of serum uric acid with various parameters in cases and controls					
		Fasting blood glucose	TG	HDL	VLDL
Coefficient(r)	Case	0.299	0.998	-0.290	0.965
	Control	0.807	0.869	-0.474	0.856
P value	Case	0.035	0.000	0.041	0.000
	Control	0.000	0.000	0.001	0.000

A significant association was found between serum uric acid levels and initial stroke severity as assessed by the NIHS scale(r=0.386, P=0.006).

Discussion

Our study results suggest a significant association between serum uric acid levels and stroke in men. Also higher uric acid levels lead to increased initial stroke severity, as assessed by the NIHS scale. These findings are in agreement to those of Mehrpour et al who found a higher prevalence of hyperuricemia in patients of acute stroke as compared to the normal population.[12]A large scale population-based, prospective survey of the general population of Tromsø, Norway also found that increase in serum uric acid was significantly associated with increased risk for ischemic stroke in men.[13] Similar conclusion was drawn by Kim et al in their systematic review and meta-analysis of 16 prospective cohort studies. The study included 238449 adults and evaluated the association between hyperuricemia and risk of stroke incidence and mortality. They found that high uric acid levels cause a modest but statistically significant increase in the risk of both stroke incidence

and mortality even after adjusting for known risk factors of stroke like age, hypertension, diabetes mellitus, and cholesterol.[14] The AMORIS study suggested uric acid as an important marker of cardiovascular risk in general population. Higher levels of uric acid were found to be associated with an increased incidence of stroke in middle-aged subjects without prior cardiovascular disease. Also, these associations rose gradually from lower to higher levels of uric acid.[15] Weir et al found an independent relation between urate levels and poor outcomes in stroke patients. This relation was true even after correction for the presence of established cardiovascular and cerebrovascular risk factors such as hypertension, diabetes mellitus, and hyperlipidemia.[7] Similar results of worse outcomes with high uric acid levels are described by other studies.[16,17]

Contrary to these reports, the Syst-Eur trial found no significant relationship between serum uric acid levels and fatal and non fatal strokes after proper adjustments for confounding variables. [18] Other studies have also postulated absence of any role for urate in vascular disease.[19] Chen et al followed up 226 patients on hemodialysis for 18 months out of which 43 patients experienced acute ischemic stroke. Serum uric acid was found to have an weak but significant inverse relation with risk of ischemic stroke.[20]Also in a prospective study done on 317 stroke patients, an inverse correlation was found between the levels of uric acid and the volume of the infarction at follow-up brain CT scan while lower UA levels were associated with a greater incidence of malignant MCA infarctions and hemorrhagic transformation.[6]Similarly Chamorro et al in their study found that for each milligram per deciliter increase of uric acid there was 12% increase in the chances of better clinical outcome. [8]

In our study, serum uric acid showed a significant correlation with fasting blood glucose, TG and VLDL. An inverse association between HDL and uric acid levels was also found. Chammaro et al had also reported an association between serum uric acid level and amount of serum triglyceride.[8] Bonora et al studied 957 young men and demonstrated that there was a significant positive correlation between serum uric acid levels and levels of serum triglycerides and fasting insulin levels.[21] Derangements in lipid profile and blood glucose levels have been implicated in development of atherosclerosis.[9] Since a major factor in development of stroke is atherosclerosis of blood vessels, it can be postulated that high uric acid levels in men can predispose to stroke.

In addition to the interactions between uric acid and surrogate markers of stroke, uric acid may have a direct affect on atherogenesis or the clinical course of cerebrovascular disease by various other possible mechanisms.

Uric acid is the breakdown product of purines. In this process hypoxanthine is converted by the enzyme xanthine oxidase to xanthine and further to uric acid. Both steps induce the release of free radicals. [22] Increased uric acid levels promote oxygenation of low-density lipoprotein cholesterol and facilitate lipid peroxidation.[23] Uric acid may stimulate vascular smooth cell proliferation, and reduce vascular nitric oxide production. [24] Moreover, higher uric acid levels may be associated with increased platelet adhesiveness predisposing to thrombus formation.[25] UA has also been found to stimulate the synthesis of pro-inflammatory factors like monocyte chemoattractant protein-1, interleukin-lβ, interleukin-6, and tumor necrosis factor-α.[26] Experimental findings indicate that uric acid might have a role in the development of hypertension through stimulation of the renin-angiotensin system and induction of sodium sensitivity.[27,28] In rats, uric acid has been shown to mediate renal disease development by causing glomerular hypertension and hence renal hypertrophy, glomerulosclerosis, and interstitial fibrosis.[29,30] Uric acid also induces renal arteriolar thickening independently of its effect on blood pressure.[31]

Each of these factors can play a pivotal role in the progression of atherosclerosis. As compared to control coronery artery walls, urate crystals are more abundant in diseased atherosclerotic plaques.[32]

It has been suggested that serum uric acid may cause endothelial dysfunction. Vannorsdall et al. reported that even a mild elevation of serum uric acid was associated with cerebral ischemia among community-dwelling adults. It was suggested that impaired vascular tone and endothelial dysfunction could contribute to ischemic changes, because they permit cerebrospinal fluid to cross the blood-brain barrier and cause areas of edema. [33] Certain intervention studies have shown that the xanthine oxidase inhibitor Allopurinol lowered blood pressure in hypertensive adolescents and had anti-ischemic effects in patients with angina pectoris.[34,35] Allopurinol also reduced cardiovascular and hospitalization risk in a small study of patients with renal failure.[36]Although the precise role of uric acid in each of these mechanisms has yet to be established, it is clear that these effects provide a potential basis for uric acid as a primary cardiovascular risk factor.

Our study has certain limitations. Firstly, we could only observe the prevalence and temporarily associated factors. Second limitation was the small sample size which limited the ability of the study to draw any strong conclusions regarding role of uric acid in stroke. As such further large scale prospective studies are warranted to support the concept of involvement of uric acid in pathogenesis of stroke in men and its contribution to stroke severity.

In conclusion, our study shows significantly higher levels of uric acid in men with stroke as compared to control population. Also, serum uric acid showed a significant correlation with fasting blood glucose, TG and VLDL and an inverse association with HDL. Uric acid levels also correlated significantly with stroke severity, with increased uric acid levels being associated with greater initial stroke severity. Higher uric acid levels in men can thus be considered as a contributor to stroke but more large scale scientific and clinical research is needed before the role of uric acid as a risk factor in stroke can be established.

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