Serum uric acid level in patients with cerebrovascular ischemic stroke: relation to initial stroke severity and outcome.

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Abstract: Background: Ischemic stroke remains a major health care problem and a leading cause of morbidity and mortality. The role of serum uric acid (SUA) in cerebrovascular ischemic stroke (CVIS) is controversial. It is unclear whether it promotes or protects against the cerebrovascular disease or simply acts as a passive marker of increased risk. **Aim of the study:** to detect SUA level in acute CVIS patients and to investigate the relationship between it and stroke severity, outcome, and infarction size. **Methods and Results:** In this case control study, forty CVIS patients (26 males & 14 females) and twenty age matched control subjects were recruited for this study. Serum uric acid was estimated by Uricase method. Assessment of severity of stroke was done based on Canadian Neurological Scale. Assessment of outcome on discharge was done based on Barthel index score. In this study serum uric acid levels were raised in stroke cases when compared to controls on admission. The mean and standard deviation of uric acid were 7.5±2.15 in cases and 4.25±0.88 in controls with significant p value of < 0.001. Cases with high uric acid levels had low severity and outcome scores which indicate poor prognosis. Mean value of SUA level in 4 patients who died was significantly higher than other patients who survived with significant p value of < 0.001. Mean SUA level was higher among patients with large infarction size (mean value: 8.76 mg/dL). **Conclusion:** Elevated levels of serum uric acid can be used as one of the factors that predicts poor prognosis of ischemic stroke.

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Key words: Serum uric acid, acute cerebrovascular ischemic stroke.

1. Introduction

Stroke is one of the most common, fatal and debilitating neurologic diseases. Numerous risk factors are involved in the development of stroke, such as hypertension, cigarette smoking, hyperlipidemia and diabetes [(1)].

Recent studies indicate that there may be other factors influencing the development or course of the disease like serum level of uric acid.

Uric acid is the end product of purine catabolism in humans and is a powerful antioxidant whose generation is increased under ischemic conditions. However both clinical and experimental studies reveal a gradual exhaustion of antioxidant capacity after transient cerebral ischemia, and the magnitude of this consumption seems to be correlated with the extent of brain tissue injury, growth of infarction, severity of neurological impairment in the acute phase, and long-term function outcome [(2)].

Some studies have found that uric acid predicts the development of stroke, whereas others have failed to identify uric acid as a significant and independent risk factor after controlling for other atherosclerotic risk factors [(3)].

Considering this controversy, this study has been conducted to evaluate the serum level of uric acid in patients with acute cerebrovascular ischemic stroke in Benha, Egypt.

2. Patients and Methods:

This is a case control study, conducted from March 2015 to October 2015 in Benha University Hospital. Study subjects were informed of the possibility of using the data obtained for academic purpose. Confidentiality was assured to all participants and data used for this study were stripped of personally identifiable information.

***Patients*:**

Study participants were in the age group of 50-80 yrs. CVIS patients (n=40) and control subjects (n=20) were selected by considering strict inclusion and exclusion criteria. World Health Organization (WHO) defines stroke disturbance of cerebral function with symptoms lasting for 24 hours or longer or leading to death with no apparent cause other than of vascular origin [(40)]. Computed tomography (CT) brain imaging was done to confirm diagnosis of ischemic stroke. For comparison, age matched control subjects were

selected. Excluded were the patients with prior history of gout, renal impairment, liver disease, thyroid dysfunction, hematological malignancy, sepsis, neoplasms, coagulating disorders, patients with a known or possible cardiac source of embolism (atrial fibrillation, valvular heart disease), and patients who were on iron or vitamin supplements or on hyperuricemic drugs like thiazide diuretics, losartan, probenecid, fenofibrate, atorvastatin, ethambutol and allopurinol.

Methods:

All patients were subjected to the following: Thorough medical history taking, Full general and neurological examination, ECG, Blood sugar level. Serum electrolytes level, Liver function test, Kidney function test and Lipid profile.

Serum uric acid was estimated by Uricase method (enzymatic colorimetric test) .The reference range of uric acid is 3.4-7.2 mg/dl for men, and 2.4-6.1 mg/dl for women [(4)].

Patients' initial stroke severity was assessed on admission by the Canadian Neurological Scale [(5)], Patients' stroke outcome was assessed on discharge by the Barthel ADL (activity of daily living) Index [(6)].

Statistical analysis:

The collected data were tabulated and analyzed using SPSS version 16 software (Spss Inc., Chicago, ILL Company). Categorical data were presented as number and percentages while quantitative data were expressed as mean ± standard deviation and range. Chi square test (X2), or Fisher's exact test (FET), were used to analyze categorical variables. Quantitative data were tested for normality using Kolmogorov–Smirnov test, and proved to be normally distributed, using Student, ANOVA and Person's correlation coefficient (r) for their analysis. ROC curve was used to determine cut off value of serum uric acid with optimum sensitivity and specificity in screening and prediction of infarct size, severity of stroke and outcome. The accepted level of significance in this work was stated at 0.05 (P<0.05 was considered significant).

3. Results:

In this study, 63.3% of the sample were males while 36.7% were females, with mean age of 67.1±8.1 years ranging from 50 – 80 years. 45% of the patient group (n=40) were non-smokers while 55% were smokers. 42.5% of the patients group were diabetic and 67.5% were hypertensive.

The mean values of TG & cholesterol were higher in patients group than that of control group. These results show high statistical significance (p<0.001).

The mean value of serum uric acid in patients group was higher than control group, 7.5±2.15 (range 3.2-11) and 4.25±0.88 (range 2.8-6.0) respectively, serum uric acid was normal in 30% of stroke patients while it was high in 70% of them, compared to controls who had normal SUA levels. These results were highly significant with p<0.001 (table 1).

Table (1): Comparing patients and controls regarding the levels of serum uric acid (SUA).

SUA			Group		Total	X2	P
			Patients	Controls			
	Normal	Count	12	20	32	26.3	<0.001**
		% within Group	30.0%	100.0%	53.3%		
	Increased	Count	28	0	28		
		% within Group	70.0%	0.0%	46.7%		
Total		Count	40	20	60		
		% within Group	100.0%	100.0%	100.0%		

The mean value of SUA level was higher in females than males and in non-smokers than smokers but these results were statistically non-significant (P>0.05), and it was higher among patients aging more than 70 years old compared to younger patients, this result was statistically significant (P<0.05) (table 2).

SUA level was higher in patients who died (with mean value 10.77± 0.263) than the 36 patients who survived (with mean value 7.14± 1.956) and this result showed high statistical significance (table 3).

In this study, 64.3% of patients with high SUA level had large infarction with mean value 8.76 mg/dL, 75% of them had severe stroke with mean

value 9.12 mg/dL and 83.3 % of them were severely dependent with mean value 8.38 mg/dL. While 83.3% of patients with normal SUA level had small infarction, all of them had mild stroke and 50 % of them were slightly dependent (table 4, 5) (figure 1).

Curve (1) shows that there was a negative correlation between SUA level and severity scores (the higher uric acid level, the lower severity score) and it was statistically high significant (P<0.001).

Curve (2) shows that there was a negative correlation between SUA level and outcome scores (the higher uric acid level, the lower outcome score) and it was statistically high significant (P<0.001).

Curve (3) shows that there was a positive correlation between SUA level and stroke size (the higher uric acid level, the larger stroke size) and it was statistically high significant (P<0.001).

Table (2): Comparing mean values of serum uric acid according to socio-demographic characters among the studied patients.

Variable		N.	S. uric acid		Test of sig.	P
			Mean	±SD		
Sex	**Male**	26	7.08	2.12	**St."t"= 1.72**	**0.09**
	Female	14	8.28	2.07		
Age	**50-60**	7	5.27	1.37	**ANOVA= 6.6**	**0.004***
	61-70	21	7.68+	2.21		
	>70	12	8.50+	1.49		
Smoking	**No**	18	7.89	2.07	**St."t"= 1.03**	**0.31**
	Yes	22	7.19	2.22		

+→ significance in comparison with "50-60" group.

Table (3): Comparing mean values of serum uric acid according to survival and mortality among the studied patients.

Variable		N.	S. uric acid		St. "t"	P
			Mean	±SD		
Survival	**Died**	**4**	10.77	0.263	**3.7**	**0.001****
	Survived	**36**	7.14	1.956		

Table (4): Serum Uric acid level among the studied patients according to disease characters.

S. uric acid / Variable		Normal (N=12)		Increased (N=28)		X^2/ Fisher's test	P
		No.	%	No.	%		
Infarction size	**Small**	10	83.3	5	17.9	**FET= 14.2**	**<0.001****
	Moderate	0	0.0	5	17.9		
	Large	2	16.7	18	64.3		
Stroke Severity	**Mild**	12	100	2	7.1	**FET= 31.7**	**<0.001****
	Moderate	0	0.0	5	17.9		
	Severe	0	0.0	21	75.0		
Stroke Outcome	**Slightly dependent**	6	50.0	0	0.0	**FET= 22.0**	**<0.001****
	Moderately dependent	5	41.7	4	16.7		
	Severely dependent	1	8.3	20	83.3		

Table (5): Comparing mean values of serum uric acid according to disease characters among the studied patients.

Variable		N.	S. uric acid		ANOVA	P
			Mean	±SD		
Infarction size	**Small**	15	5.64	1.40	**16.3**	**<0.001****
	Moderate	5	8.06	1.04		
	Large	20	8.76	1.84		
Stroke Severity	**Mild**	14	5.04	1.11	**62.2**	**<0.001****
	Moderate	5	7.62	0.16		
	Severe	21	9.12	1.12		
Stroke Outcome	**Slightly dependent**	6	3.96	0.60	**45.0**	**<0.001****
	Moderately dependent	9	6.37	0.91		
	Severely dependent	21	8.38	1.17		

*→ significant results
**→ highly significant results

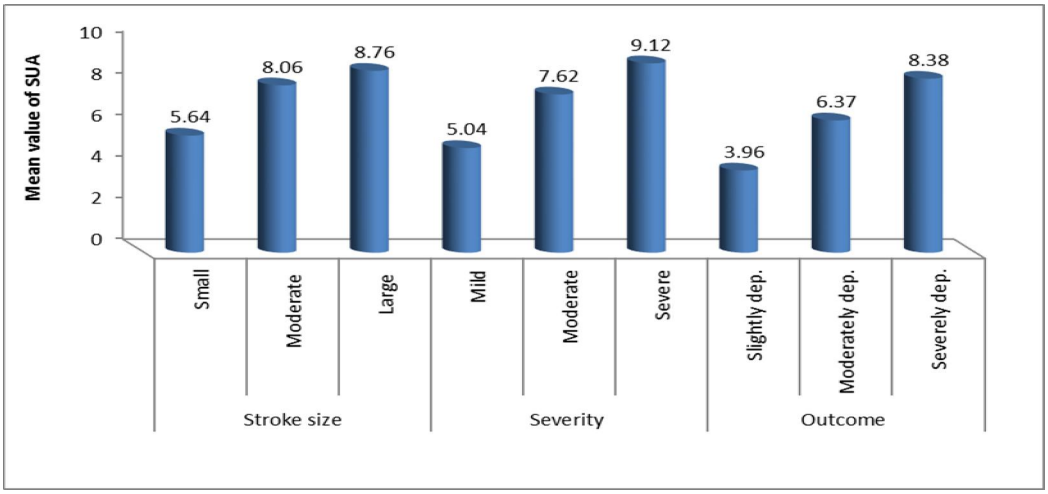
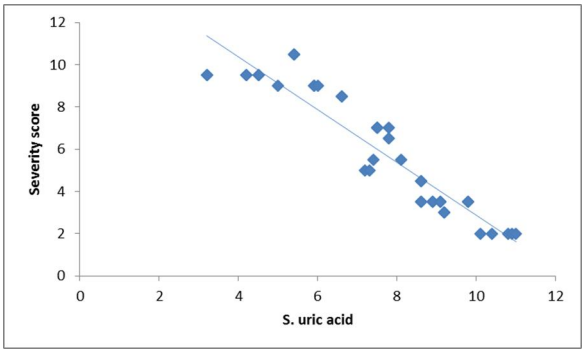
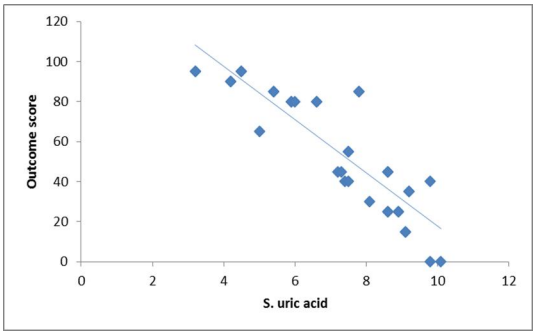


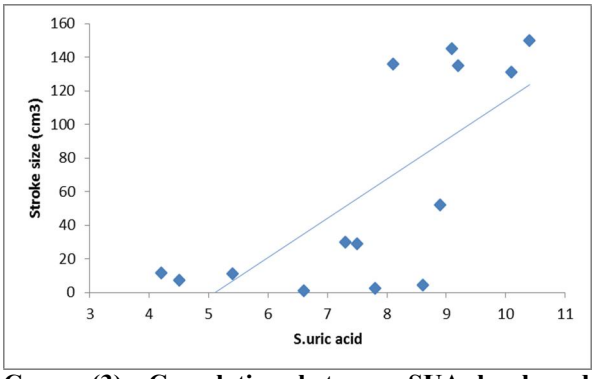
Fig. (1): Comparison of mean values of serum uric acid according to disease characters among the studied patients.



Curve (1): Correlation between SUA level and severity scores.



Curve (2): Correlation between SUA level and outcome scores.



Curve (3): Correlation between SUA level and stroke size.

4. Discussion:

Stroke is becoming an important cause of premature death and disability in low-income and middle-income countries [7]. Currently, a lot of studies features controversial reports on the relationship between SUA levels and acute CVIS. Studying the role of SUA in the pathogenesis of acute CVIS has been challenging because of various metabolic risk factors associated with this disorder [8].

This is a comparative cross-sectional study carried out in Neuropsychiatry department at Benha University Hospital on 40 stroke patients and 20 controls.

In this study the mean age of the studied sample was (67.3±8.2) years versus (66.7±8.3) years for stroke patients and controls respectively with significant increase of SUA level among older patients.

This result disagreed with *Reddy and Ghanekar,* and *Mehrpour et al.* who found a significant negative correlation between the age and SUA levels [8, 9].

The number of female patients with stroke in this study was 14 patients (35%) compared to 26 male patients (65%). With non-significant increase in SUA level in males than females.

This result was in line with *Iranmanesh et al.* who suggested that there were no significant relationship between gender and hyperuricemia in patients with stroke [23].

We found that increased levels of SUA was associated with several metabolic risk factors including hypertension, elevated triglycerides and total cholesterol. Therefore, we explained this as it is difficult to establish whether or not an independent association between SUA and CVIS exists. So, our data strongly suggest that increasing baseline SUA levels in CVIS patients positively correlated with these risk factors.

Reddy and Ghanekar have found that increased baseline levels of SUA was associated with hypertension, hypercholesterolemia, elevated levels of triglycerides, which was accordant with our results [8].

This finding also was in line with a large study in USA, which reported an independent and significant association between elevated UA with CVIS [10].

In this study, SUA levels were higher in non-diabetics and non-smokers, which was a non-statistical significant result.

This disagreed with *Momin et al.* who found that the mean uric acid level was higher in diabetic stroke patients (7.98±1.77mg/dl) compared to non-diabetic stroke patients (6.34±1.51mg/dl) [11].

In this study, there was a highly significant increase in SUA level within stroke patients with mean value 7.5±2.15 (range 3.2-11) compared to controls who showed normal SUA levels with mean value 4.25±0.88 (range 2.8-6.0).

Using Canadian Neurological Scale and Barthel Index Score, stroke severity and short term outcomes were determined and observed a highly significant correlation between elevated SUA levels and lower Canadian Neurological Scale score on admission, and also lower Barthel index score in stroke patients when assessed on discharge. Among the studied patients, patients who succumbed showed higher SUA levels (with mean value 10.77± 0.263) than patients who survived (with mean value 7.14± 1.956).

There was also a highly significant positive correlation between SUA levels and infarction size.

These findings agreed with other studies, *Milionis et al.* 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, $p<0.001$) [12], and *Koppula et al.* found that serum UA levels were significantly elevated in stroke patients with 54.9% of the patients versus 24.7% of controls had high levels of serum UA (>6mg/dL). The significance remained even after adjusting for known risk factors of stoke. Also they noticed that high levels of serum UA were associated significantly with poor outcome in patients independently of other prognostic factors. The recurrence of stroke and death rate were also high in patients with high levels of serum UA in comparison with patients with low levels of serum UA [13].

Lamani and Vishwanath [14] showed that severe and moderate stroke 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.

An Egyptian study carried out in Benha university hospital in 2004 by *fathy et al.* reported that uric acid was significantly increased in ischemic stroke patients with DM, this high level of uric acid could contribute to the deleterious effect of the cerebrovascular insult [15].

It also reported that Allopurinol could act as a free radical scavenger directly through inhibition of XO enzyme. This enzyme leads to increase the amount of production of uric acid, superoxide ions, and NO, and thus impairing the activity of antioxidants indirectly [15].

Another Egyptian study in 2006 carried out by *Abdul-Fattah et al.* showed that serum uric acid levels were significantly higher in stroke patients than controls [16].

A prospective study carried out by *Logallo et al.* [17] revealed that increased serum UA levels associated with bad outcomes in ischemic stroke patients. Another recent study carried out by *Miedema et al.* [18] also confirmed these findings.

Chamorro et al. [19] reported that the addition of uric acid to thrombolytic therapy did not increase the proportion of patients who achieved excellent outcome after stroke compared with placebo, but it did not lead to any safety concerns.

SUA is considered by some researchers as an independent predictive factor, or an adverse cardiovascular outcome marker, or even an independent cardiovascular factor [20].

On the other hand, some studies reported that low SUA level during the first week after onset of stroke correlates with more severe stroke, unfavorable stroke evolution, and poor long-term stroke outcome [21, 22].

No significant relationship was found between occurrence of acute ischemic non-embolic stroke and high serum level of uric acid. Moreover, no significant relationship was observed between stroke risk factors and hyperuricemia [23].

According to the Framingham study, SUA is not a cardiovascular risk factor, there is no association between its level and cardiovascular mortality or stroke, and gout is not a cardiovascular risk factor [24].

Amaro et al. [25] showed that increased levels of uric acid were associated with better outcome in patients with stroke treated with reperfusion therapies. The effects of raising circulating uric acid concentrations, by direct administration, have also been studied in vivo in a rat model of acute ischemic stroke, involving transient occlusion of one middle cerebral artery for 2 hours.

Administration of uric acid, prior to ischemia or during the subsequent reperfusion period, caused a significant reduction in infarct volume, and led to improved behavioral outcome. These findings suggest that early elevation of uric acid, during or shortly after acute ischemic stroke, could confer significant protection against neurological deficit [26].

Liu et al. also found that increased SUA levels were associated with excellent outcomes in Chinese patients with acute ischemic stroke treated with intravenous thrombolysis, giving additional support to administration of exogenous UA as an adjuvant to thrombolysis [27].

Bandyopadhyay et al. reported that high serum uric acid level is associated with small infarction size and good neurological outcome at the time of hospital discharge in patients with acute ischemic stroke [28].

The role of SUA in short- and long-term outcomes is still controversial. A possible explanation for the varying effects of SUA in the acute phase of ischemic stroke could be that different outcome measures, study size and population are used in the different studies, thereby hampering the comparison of the findings [29].

UA is a weak organic acid that is naturally produced in the human body as the end result of purine catabolism from xanthine and hypoxanthine and it has long been considered an anti-oxidant reagent [30].

Because of Its significant capacity as an antioxidant, it behaves as a free radical scavenger, and therefore, may have a protective role in vascular inflammation and dysfunction [31].

The size of the ischemic infarct and consequently the severity of the stroke event have been found to be greater in patients with diminished antioxidant activity. Since the level of free radicals is extremely difficult to measure in the human body, UA can be taken as a potential biomarker of the free radical level, which has been established as an accurate measure of the amount of free radicals generated in the body [13].

There have been reports suggesting a sudden increase in the UA level at the onset of an ischemic attack [32], which might be a mechanism to combat the generation of large quantities of free radicals. The idea of increased serum urate contributing to elevated stroke risk suggested by a few studies [33], has not been supported with sufficient evidence.

Although an increased severity of brain damage has been correlated with elevated levels of UA (hyperuricemia) in the body [34], there are no consistent results to prove this. An initial increase in urate levels can act as a predictor of ischemic brain injury, but cannot be considered as a cause of brain damage [35].

There has been considerable debate whether UA is neuroprotective as an antioxidant or neuro-toxic as a pro-oxidant. The antioxidant properties of urate have long been known. The issue originated in two complementary reports suggesting urate as both a primate evolutionary substitute for ascorbate and as a pro-oxidant [36].

It has been stated that in addition to being a potent antioxidant, urate mediates radical oxidations and likely, oxidative- stress-related diseases. *Proctor* [36] has suggested that, "The well-established

association between high urate levels and atherosclerosis could be a protective reaction (antioxidant) or a primary cause (pro-oxidant)". He has also suggested that the exact mix of pro-oxidant verses antioxidant properties for uric acid depends on a complex mix of concentration, oxygen availability, electronically active species, other pro- and antioxidant enzymes, transition–series metals and so forth.

In conditions of extraordinary oxidative stress the balance between the pro- and antioxidant properties of uric acid may shift in favor of tissue protection. This is particularly so because urate scavenges oxidants such as peroxy nitrites, where normal background levels are low, except in pathogenic processes [(36)].

Therefore, it has been suggested that a low level of chronic, sometimes pathogenic oxidative stress may be the price paid for the protective presence of urate when things go bad acutely [(13)].

The present study does not address the mechanisms by which SUA can associate with stroke related morbidity and mortality. However, the available study revealed that SUA is known to contribute to endothelial dysfunction by impairing nitric oxide (NO) production. SUA has been shown to be inversely correlated with the measures of functional capacity and maximal oxygen intake [(37)]. Therefore, it is believed that elevated SUA levels in stroke patients may lead to endothelial damage and increased vascular permeability [(8)].

Another putative mechanism likely to be involved is association of xanthine oxidase (XO) and cyclooxygenase systems with ischemic stroke in the presence of elevated SUA levels, which cause neuronal death [(38)].

The action of XO leads to generation of superoxide radical anions and the reactive oxygen species (ROS) as supported by the fact that knockout mice for mitochondrial superoxide dismutase (mSOD) genes display larger brain lesions after focal ischemia. The increased levels of ROS can make the brain more susceptible to oxidative stress [(39)].

At present, it is unclear whether high SUA levels promote or protect against the development of CVIS, or simply act as a passive marker of increased risk in stroke patients [(8).]

Limitations met while conducting this study were: (1) This is not a population-based study. It is a single-center case control study restricted to a local hospital, based on the data collected from a small number of ethnically homogeneous CVIS patients, which may not accurately reflect the majority of other population. (2) The oxidant-antioxidant status was not assessed. (3) The greater risk of acute stroke events attributable to hyperuricemia in this study challenges the antioxidant properties shown by UA. (4) SUA was measured only once at baseline, and repeated measurement may be necessary to evaluate the kinetics of SUA levels after acute ischemic stroke onset.

Conclusion and recommendation:

The relationship between SUA and acute CVIS is controversial. The present results revealed that: (a) There is highly significant increase in SUA level within stroke patients. (b) High SUA level was associated with severe stroke, large infarction size and bad outcome. (c) A significant positive correlation was observed between the age of CVIS patients and their SUA levels. (d) Increased levels of SUA was associated with several metabolic risk factors including hypertension, elevated triglycerides and total cholesterol. Based on these results, Elevated levels of serum uric acid can be used as one of the factors that predicts poor prognosis of ischemic stroke.

Taking into account, all the limitations of the study and the previous studies on the prevalence of CVIS, we recommend that Patients with high levels of SUA on admission should be closely monitored for CVIS associated complications, Serum uric acid levels could be of value in identifying subjects who are at risk of developing ischemic stroke, Individuals with risk factors of stroke such as hypertension, elevated TG and high cholesterol should be monitored for SUA level and further studies are necessary to confirm these results with a larger group of patients from many different areas/regions.

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