Hyperuricemia in acute ischemic stroke: A prognostic marker

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Abstract:

Background: Stroke being the most incapacitating neurological disease with 2nd most common mortality worldwide. Hypertension, diabetes, smoking, hyperlipidaemia, cardiovascular disease and family history of stroke are some of the many risk factors for development of stroke. In addition to these there has always been a conflict in results over the influence of serum uric acid on neurological outcome of stroke.

Objective: The objective of this study was to develop an algorithm for prediction model for risk and output of Acute Ischemic stroke. To describe the level of serum uric acid level in patients reporting with acute ischemic stroke and to describe the association between the uric acid levels and severity of acute ischemic stroke.

Methodology: A longitudinal observational study was done among stroke patients. A detailed history and clinical examination along with relevant radiological examination was done for diagnosis of acute ischemic stroke and the serum uric acid level was monitored.

Results: The data of 60 patients who fulfilled the inclusion criteria was analysed. The mean age was 49.2±9.04 years (range 32- 64 years), with majority 60% being male. Hyperuricemia was found in 48.6%. Among the study participants 34(56.67%) had good outcome and 26(43.33%) had poor outcome. Statistically significant association was established between age, smoking, T2diabetes, hypertension and dyslipidaemia and the outcome of stroke. It was also seen that hyperuricemia is associated with people with poor prognosis.

Conclusion: Further research should be targeted on establishing a strong relationship between hyperuricemia and stroke by introduction of urate-lowering therapy, and thereby measuring the outcome to determine the exact association

Keywords:AIS, serum uric acid, stroke outcome, stroke risk factors.
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Introduction

Stroke, the most incapacitating disorder of the cerebro-vascular system tends to be the second leading cause of death and 3rd leading cause of both death and disability combined, globally. There is a substantial increase in global stroke burden in lower and lower middle-income countries accounting for almost 85.5% of total stroke deaths, which is almost seven times that in high-income countries. A metanalysis done in India determined the crude incidence of stroke ranged from 108 to 172/100,000 people per year, crude prevalence from 26 to 757/100,000 people per year, and one-month case fatality rates from 18% to 42%[1-4]. According to WHO, there are three types of strokes, transient ischemic attack, ischemic stroke and haemorrhagic stroke. It also estimates that ischemic stroke contributes to almost 87% of total stroke cases[3]. Hypertension, diabetes, smoking, hyperlipidaemia,

cardiovascular disease and family history of stroke are some of the many risk factors for development of stroke[5].

Uric acid, the end catabolite of purine nucleotide metabolism, is either produced from exogenous sources of high purine intake such as meat, seafood, animal organs or from endogenous sources like tissue catabolism and de novo synthesis of purines from RNA and DNA bases. It is also considered as an essential antioxidant in blood with a plasma concentration almost 10-fold higher than over antioxidants like vitamin C and E; and also uric acid is found to have much higher antioxidant capacity[6-9]. Thus serum uric acid being a natural antioxidant, and increased level have been associated with neuroprotective benefits in several neurodegenerative diseases and improvements in neuro immunity[10,11]. Hyperuricemia, uric acid greater than 6.8mg/dL, is related to pathophysiology of diseases like gout, renal disease, metabolic syndromes, stroke, cardiovascular disease, etc.,[12-16]. Platelet dysfunction, coagulopathy, endothelial dysfunction, increased oxidative stress, thrombosis, and inflammation were all often seen in patients with hyperuricemia, which suggestsit to be a poor prognostic factor for acute vascular events. Some studies even suggest hyperuricemia to be an independent risk factor for ACI and elevated Serum uric acid on admission predicts poor prognosis[17,18]. Thus there has always been a conflict in results over the influence of serum uric acid on neurological outcome of stroke over the last decades.

This study was aimed to determine the effect of hyperuricemia as a prognostic marker in ischemic stroke. The objective of this study was to develop an algorithm for prediction model for risk and output of Acute Ischemic stroke. To describe the level of serum uric acid level in patients reporting with acute ischemic stroke and to describe the association between the uric acid levels and severity of acute ischemic stroke.

Methodology

A longitudinal study was done among the adult patients admitted in a tertiary care centre in Trichy. The study was done over a period of 3 months. All adult patients (20 to 65 years of age) diagnosed and admitted with acute ischemic stroke based on clinical findings, CT-brain, MRI brain study and consented were included in the study. Those patients with history of Gouty arthritis, Chronic Renal failure, alcoholics, patients on thiazide and loop diuretics, cyclosporine, pyrazinamide, lead toxicity, known case of myeloproliferative disorders, Psoriasis, lactic acidosis were excluded from the study. Consecutive sampling technique was used to recruit the patients by complete enumeration. A total of 60 patients who fit into the eligibility criteria participated in the study. A detailed history and clinical examination along with relevant radiological examination was done for diagnosis of acute ischemic stroke and the serum uric acid level was monitored. Serum uric acid levels was measured with Cobas C311 analyser by the principle of enzymatic calorimetric analysis on day 0, day 2 and day 7 post admission. The level of serum uric acid was corrected using The National Institutes of Health Stroke Scale (NIHSS)on day 0, day 2 and day 7. NIHSS is composed of 11 components, each of which scores between 0 and 4, thus having a maximum and minimum score of 42 and 0 respectively after summing up the individual scores.

Operational definition: Those patients meeting two or more of the following criteria were considered to have ischemic stroke-Glasgow coma scale score < 15, inability to move one or more limbs, and a CT scan showing a hypodense area. Uric acid > 7 mg/dL for male patients or >6 mg/dL for female were considered as hyperuricemia. Hypertension was defined as patients with systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg and treated for more than five years. Glycatedhemoglobin> 6.5% were type 2 diabetic. Patients with any one of the following were considered as having dyslipidemia: total cholesterol > 200 mg/dL, serum triglyceride levels > 150 mg/dL, low-density lipoprotein (LDL) > 100 mg/dL, or high-density lipoprotein (HDL) < 40 mg/dL. Patients who smoke at least five cigarettes per day for at least one year were deemed as smokers, and patients who had quit smoking for at least one year after being a smoker or those who had never smoked were deemed as non-smokers.

The study was started after obtaining the institution ethical committee clearance. The purpose of the study was well explained to the participants and an informed written consent was obtained before including the participants into the study. The right to withdraw form the study at any given point of time without any loss or penalty was explained to the patients. The data was collected and entered in MS excel. SPSS software version 23 was used for the analysis. Mean and standard deviation was used to express the quantitative variable; frequency and percentage for qualitative variables. Chi-square was used for determining the association and liner regression

used for independent variable analysis.

Results

Table 1: Socio-demographic characteristic of the study population

Socio-demographic characteristics		Frequency N(%)
Age	<50 years	34(56.67)
	>50 years	26(43.33)
Sex	Male	36(60)
	Female	24(40)
Socioeconomic status	Lower class	16(26.67)
	Middle class	28(46.66)
	Upper class	16(26.67)
Body mass index	<24.9	23(38.33)
	>25	37(61.67)
Smoking	Yes	32(53.33)
	No	28(46.67)

Table 2: Distribution of metabolic syndrome among the study participants

Metabolic syndrome		Frequency N(%)
Type 2 diabetes mellitus	Yes	41(68.33)
	No	19(31.67)
Hypertension	Yes	39(65)
	No	21(35)
Dyslipidaemia	Yes	36(60)
	No	24(40)

Table 3: Association of baseline characteristics with hyperuricemia

Characteristics		HyperuricemiaN(%)		p value	Chi square value	OR	CI
		Present (n=29)	Absent (n=31)				
Age in years	<50	17(50)	17(50)	0.775	0.086	1.164	0.4195, 3.245
	>50	12(46.15)	14(53.85)				
Sex	Male	21(58.33)	15(41.67)	0.032	3.544	2.8	0.954, 8.217
	Female	8(33.33)	16(66.67)				
BMI	<24.9	13(56.52)	10(43.48)	0.167	0.984	1.706	0.597, 4.876
	>25	16(43.24)	21(56.76)				
Smoking	Yes	19(59.38)	13(40.62)	0.037	3.292	2.63	0.923, 7.491
	No	10(35.71)	18(64.29)				
Type 2 diabetes mellitus	Yes	24(58.54)	17(41.46)	0.010	5.308	3.953	1.196, 13.06
	No	5(26.32)	14(73.68)				
Hypertension	Yes	25(64.10)	14(35.90)	<0.001	10.91	7.59	2.13,27.04
	No	4(19.05)	17(80.95)				
Dyslipidaemia	Yes	19(52.78)	17(47.22)	0.207	0.7	1.565	0.552, 4.437
	No	10(41.67)	14(58.33)				
Stroke duration in hours	<6	4(36.36)	7(63.64)	0.203	0.759	0.549	0.142, 2.116
	>6	25(51.02)	24(48.98)				
NIHSS	<5	17(39.53)	26(60.47)	0.005	6.648	0.207	0.050,0.719
	>5	13(76.47)	4(23.53)				

p value <0.05 is considered to be significant and <0.001 is highly significant

Table 4: Association of baseline characteristics with outcome of stroke

Characteristics		Outcome N(%)		p value	Chi square value	OR	CI
		Good (n=34)	Poor (n=26)				
Age in years	<50	24(70.59)	10(29.41)	0.007	6.09	3.84	1.303,11.32
	>50	10(38.46)	16(61.54)				
Sex	Male	22(61.11)	14(38.89)	0.205	0.7119	1.57	0.553, 4.462
	Female	12(50)	12(50)				
BMI	<24.9	15(65.22)	8(34.78)	0.154	1.092	1.78	0.607, 5.195
	>25	19(51.35)	18(48.65)				
Smoking	Yes	13(40.63)	19(59.37)	0.004	7.066	0.228	0.075, 0.691
	No	21(75)	7(25)				
Type 2 diabetes mellitus	Yes	18(43.90)	23(56.10)	0.001	8.447	0.146	0.036, 0.582
	No	16(84.21)	3(15.79)				
Hypertension	Yes	18(46.15)	21(53.85)	0.014	4.932	0.267	0.081, 0.876
	No	16(76.19)	5(23.81)				
Dyslipidaemia	Yes	18(50)	18(50)	0.108	1.602	0.5	0.171, 1.459
	No	16(66.67)	8(33.33)				
Hyperuricemia	Present	9(31.03)	20(68.97)	<0.001	14.77	0.108	0.032, 0.354
	Absent	25(80.65)	6(19.35)				

p value <0.05 is considered to be significant and <0.001 is highly significant.

Table 5: Relation of NIHSS values with uric acid levels during the course of admission

Days	NIHSS scores	Hyper uricemia	
		Present	Absent
Day 0	<5 (mild)	9(31.03)	20(68.97)
	>5(moderate to severe)	25(80.65)	6(19.35)
Day 2	<5 (mild)	10(35.71)	18(64.29)
	>5(moderate to severe)	25(78.13)	7(21.87)
Day 7	<5 (mild)	12(35.29)	22(64.71)
	>5(moderate to severe)	17(77.27)	5(22.73)

(Table 1) The data of 60 patients who fulfilled the inclusion criteria and participated in the study were analysed. Mean age of the study participants were found to be 49.2±9.04 years (range 32- 64 years). The proportion of participants age less than 50 years here slightly higher compared to those more than 50 years old. Majority (60%) of the participants were male. A large proportion (46.66%) were middle class people compared to lower and upper class. 37(61.67%) of the study participants were either overweight or obese. 53.33% of the study participants had the habit of smoking. Hyperuricemia was found in 48.6% of the study participants. On admission the mean NIHSS scores were compared between both the groups and was found that the scores were higher (4.7±1.6) in patients with hyperuricemia compared to (6.5±2.8) among those with normal uric acid levels and was found to be statistically significant (p value = 0.003). NIHSS score was used to determine the outcome of the stroke patients and was found that 34(56.67%) had good outcome and 26(43.33%) had poor outcome observed on day 7.

(Table 2 & 3) 68.33%, 65% and 60% of the study participants were found to have diabetes, hypertension and dyslipidaemia respectively. Majority of the male participants 58.33%, and only 33.33%, of the female patients with stroke were found to have hyperuricemia. 59.38%, 58.54% and 64.10% with smoking diabetes and hypertension respectively were found to have hyperuricemia. There was a statistically significant association observed between hyper uricemia and gender, smoking, T2diabetes and hypertension. Mean duration of stroke in hours 5.2±2.4 hours. Duration of stroke <6hrs was noticed in 11(18.33%) and >6hrs in 49(81.67%) patients.

(Table 4) Poor outcome of the disease was mostly seen in >50 years of age as almost 61.54% of this age group presented with poor outcome. There was no significant difference in outcome measured between both the genders and BMI did not play a significant role in the outcome of stroke. Poor outcome was observed in 59.37% of the

smokers compared to 25% of the non-smokers. 56.10%, 53.855 and 50% of the study participants presenting with diabetes, hypertension and dyslipidaemia had poor outcome compared to 15.79%, 23.81% and 33.33% of those without the respective disease. Thus, there was a statistically significant association established between age, smoking, T2diabetes, hypertension and dyslipidaemia and the outcome of stroke. 68.97% of the participants with hyperuricemia presented with poor outcome compared to 19.35% of those with no hyperuricemia and the difference was statistically highly significant. 76.47% of the patients who had NIHSS score >5 presented with hyperuricemia compared to 39.53% of those whose scores were <5.

Thus, with the results obtained ad taking into consideration the odds ratio and significant association of each variable, its seen that hyperuricemia is associated with people with poor prognosis, thus indicating the raised level of serum uric acid being a poor prognostic marker in addition to these increasing age, smoking, type 2 diabetes mellitus, hypertension and dyslipidaemia were also the other risk factors associated with poor outcome of the disease.

Discussion

In our study the mean age of the study participants was 49.2±9.04 years (range 32- 64 years), with majority 60% being male. These were similar to the study done by Sylaja PN et al., who showed 58.3±14.7 years of mean age and 67.2% men[5]. In our study though the majority of the participants were male, poor outcome was observed in almost 50% of the female participants compared to 39% of the male population, the test did not give a statistically significant value. In the global stroke fact sheet by Feigin VL[1] it was stated that the prevalence of stoke was higher in female compared to male and also there were no noticeable sex difference observed in relation to stroke-related death, which were slightly deviated from our findings. These might be due to the geographical variation of lifestyle and other contributing factors leading to stroke.In our study hyperuricemia is seen commonly in males compared to females, smokers, type 2 diabetes, hypertensives, and patients with dyslipidaemia. These findings were similar to a study done by Chamorro Ángel et al. [19], showing high level of uric acid in men, hypertensives, alcohol drinkers and patients with coronary, pulmonary, or renal diseases. The study also showed that the serum uric acid level is one of the independent good outcome predictors in patients with stroke which is in contrast to our study. In our study we had observed that high levels of serum uric acid is associated with poor outcome of stroke which is similar to the studies done by Bansal et al. [20]and Kim et al. [21]. These studies showed that hyperuricemia is significantly associated with the risk of both stroke incidence and mortality, that the elevated serum uric acid plays a role in causation of ischemic stroke, especially in younger patients, thus affecting the outcome. In our study it was observed that hyperuricemia was found to be associated with higher NIHSS scores and vice versa which was similar to few studies done by Wang R et al. [22]and Liu X et al. [23].

In a study done by Weir et al. [24]. on 2500 stroke survivors, showed hyperuricemia was associated with an increased risk of stroke by 27% anticipating a worse outcome and increased chances of repeated stroke. Mapoure et al. in a recent study, also confirmed the higher serum uric acid quintile ranges (SUA 71-84 mg/L and SUA > 85 mg/L) had more poor outcomes and proportion of death[25].Therefore, concluding the results of our study and the previous literatures, it is evident that high uric acid levels or hyperuricemia are associated with an increased incidence of stroke and are a strong indicator of negative post stroke functional outcome

Conclusion

In our study the association of hyperuricemia with the patients with poor outcome was significantly higher as compared with good outcome. Hyperuricemia was also observed to be higher in men than women and was found to be associated with diabetes, hypertension and smoking. In patients with poor outcome in ischemic stroke other risk factors found to have significant association were smoking, diabetes, hypertension and dyslipidaemia. In spite of the protective physiology of uric acid, it is been evidently proved that hyperuricemia leads to poor outcome in stroke patients. Further research should be targeted on establishing a strong relationship between hyperuricemia and stroke by introduction of urate-lowering therapy, and thereby measuring the outcome to determine the exact association.

Limitation

Single centre study which might affect the external validity.

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