Study of Serum Uric Acid Level as an Independent Risk Factor in Acute Ischemic Stroke

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ABSTRACT

BACKGROUND

Stroke entails a high socioeconomic burden due to increased mortality and morbidity. The role of serum uric acid (SUA) level as an independent risk factor for stroke has been questioned for many years. Evidence from epidemiological studies suggest that elevated SUA levels may be associated with an increased risk of stroke and cardiovascular events.

METHODS

113 patients of first ever lifetime acute ischemic stroke admitted in Karnataka Institute of Medical Sciences, Hubli Hospital, were included. Blood samples were taken and CT scans were done within 24 hrs. of onset of stroke. Serum uric acid levels were analysed in patients and were compared with risk factors like hypertension, diabetes, adverse lipid profile, smoking and alcoholism.

RESULTS

The age of subjects ranged from 25 years to 90 years. Mean age was 59.2 ± 14.5 yrs. Most of the patients were aged ≥ 65 yrs. (46%). 76 were males (67.3%) and 37 females (32.7%). Male to female ratio in this study was 2.05:1. 37.2% patients were diabetic. 56.6% patients were hypertensive. 46.9% patients had elevated SUA levels. Mean SUA levels in 113 acute ischemic stroke patients was 6.5 ± 1.4. Mean SUA levels among males 6.4 ± 1.5 and among females it was 6.6 ± 1.5. (difference not statistically significant). Mean SUA level was higher (6.83 ± 1.5 mg/dl) among hypertensives (6.83 ± 1.5) compared to non-hypertensive patients (6.21 ± 1.4) and the difference was statistically significant. Mean SUA was higher among diabetics (6.9 ± 1.5) as compared to non-diabetics (6.2 ± 1.4) and the difference was statistically significant.

CONCLUSIONS

SUA levels were significantly elevated in ischemic stroke patients within 24 hours after symptom onset. SUA levels were significantly higher among hypertensive patients as compared to normotensive patients. SUA levels were significantly higher among diabetic patients as compared to non-diabetic patients. Due to the high prevalence of high SUA in patients with acute stroke, and its accompanying increase in hypertension and diabetes mellitus, it can be considered as a risk factor for acute stroke.

KEYWORDS

Acute Ischemic Stroke, Uric acid, GCS, Hyperuricemia, Diabetes, Hypertension, Smoking

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BACKGROUND

A stroke, or cerebrovascular accident, is defined as an abrupt onset of a neurological deficit that is attributable to a focal vascular cause.[1] The incidence of cerebrovascular diseases increases with age, and the number of strokes is projected to increase as the elderly population grows, with a doubling in stroke deaths in the United States by 2030. For India, community surveys have shown a crude prevalence rate for 'hemiplegia' in the range of 200 per 100,000 persons, nearly 1.5% of all urban hospital admissions, 4.5% of all medical and around 20% of neurological cases.[2] Serum Uric Acid is an inert product of ingested and endogen nucleoproteins catabolism. It is the breakdown product of purines from DNA, RNA, ATP and cAMP. In this process hypoxanthine is converted by the enzyme xanthine oxidase to xanthine and further to uric acid. UA is the most abundant aqueous antioxidant in humans. In recent years, much attention has been paid to the role of uric acid in disease modification. 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.[3]

Overwhelming evidence suggests that hyperuricemia is linked to obesity, hypertension, reduced HDL cholesterol, hypertriglyceridemia, hyperinsulinemia and reduced insulin sensitivity, components of the metabolic syndrome. Thus, the role of uric acid in patients with stroke or other vascular disease is contentious and there is conflicting data on this subject. Some authors have suggested that elevated uric acid levels are closely associated with stroke risk factors and therefore hyperuricemia is a marker in patients at high risk for stroke. These observations have prompted interest in the potential impact of raised uric acid concentrations in the setting of acute ischemic stroke.[4]

The present study was done to estimate serum uric acid levels in patients of acute ischemic stroke and to assess its risk factor potential and also study the association between SUA and other risk factors of stroke namely hypertension, Diabetes mellitus, and adverse lipid profile.

METHODS

113 patients of first ever lifetime acute ischemic stroke admitted in Karnataka Institute of Medical Sciences, Hubli hospital were included. The blood samples were taken, and CT scans were done within 24 hours of onset of stroke. Blood samples were sent for biochemical analysis for serum uric acid and other relevant investigations and 2D ECHO was done. The patients were further evaluated for presence of additional risk factors like hypertension, diabetes, adverse lipid profile, smoking and alcoholism. Serum uric acid levels were analysed in patients and were compared with risk factors like hypertension, diabetes, adverse lipid profile, smoking and alcoholism.

RESULTS

A total of 113 cases of acute ischemic stroke patients were included and were analysed regarding correlation of serum uric acid with acute ischemic stroke patients and risk factors for acute ischemic stroke like diabetes mellitus, hypertension, dyslipidaemia, smoking, alcohol consumption. Among 113 patients mean age group was 59.2 ± 14.5 years with Male to female ratio of 2.05:1. Among 113 patients, 56.6% were hypertensive and 37.2% were diabetics. One patient had ischemic heart disease.

Features	Frequency	Percentage
Diabetes mellitus	42	37.2
Hypertension	64	56.6
Ischemic heart disease	1	0.9

Table 1

Among 113, 50.4% were smokers. 30.1% were alcoholics. All smokers and alcoholics were males. Among 113, 55 patients had right hemiparesis constituting 48.3% whereas 48 patients had left hemiparesis, 6 patients had quadriparesis, secondary to brainstem infarct, and 4 had ataxia.

Features	Frequency	Percentage
Ataxia	4	3.5
Right hemiparesis	55	48.7
Left hemiparesis	48	42.5
Quadriparesis	6	5.3

Table 2

Among 113 patients, 29.2% had right MCA infarct, 29.2% had left MCA infarct, 14.2% had right basal ganglia infarct, 15.1% had left basal ganglia infarct, 3.5% had cerebellar infarct, and 5.3% had pontine infarct, normal CT scan in 3.5%.

Features	Frequency	Percentage
Left BG infarct	17	15.1
Left MCA infarct	33	29.2
Right BG infarct	16	14.2
Right MCA infarct	33	29.2
Right cerebellar infarct	4	3.5
Pontine infarct	6	5.3
Normal CT	4	3.5

Table 3

There is no universally accepted definition for hyperuricemia based only on serum UA levels. We defined participants as having hyperuricemia if their serum uric acid concentration was > 7.0 mg/dL in men or >6.0 mg/ dL in women. Among 113 acute ischemic stroke patients studied, 46.9% had elevated serum uric acid. Mean serum uric acid in male ischemic stroke patients was 6.4 ± 1.5. Mean serum uric in female ischemic stroke patients is 6.6 ± 1.5. Difference was not statistically significant. Mean serum uric acid level was 6.5 ± 1.4. The difference between mean SUA levels among patients with normal lipid profile and those with dyslipidaemia was not significant. Mean SUA was higher among patients with severe brain injury as compared to those with mild to moderate brain injury. However, the difference was not statistically significant. Mean SUA levels

among smokers was 6.4 ± 1.4 and 6.6 ± 1.5. However, this difference was not statistically significant.

DISCUSSION

A stroke, or cerebrovascular accident, is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause. (1) Stroke accounted for about one third of cardiovascular deaths (5·7 million deaths) and 46·6 million Disability Adjusted Life Years (DALYs) [5] The incidence of stroke increases dramatically with advancing age, and increasing age is the most powerful risk factor for stroke. The incidence of stroke doubles each decade past 55 years of age. Half of all strokes occur in people older than 75 years. Women have higher stroke case-fatality rates as compared with men. Men age 45–75 develop ischaemic strokes at higher rates than women; thereafter, stroke rates are higher in women.[6]

In India, where ischaemic stroke accounts for 80% of all strokes, 10% to 15% of strokes occur in people younger than 40 years and are mostly related to intracranial atherosclerosis.[7] An increased risk is seen with a family history of stroke among first-degree relatives. Genetic factors have been linked with ischemic stroke, but specific genetic variants remain largely unknown.[8] Hypertension is the most significant of the risk factors increasing the relative risk for stroke an estimated three- to fourf old.[9] Diabetes mellitus obesity, hypertension, and dyslipidaemia often co-exist in patients with DM that add on to stroke risk.[10] In addition, DM increases morbidity and mortality after stroke.

Dyslipidaemia, Obstructive sleep apnea (OSA),Aortic-arch atheromatosis, Elevated haematocrit, haemoglobin concentration, increased blood viscosity, Elevation of plasma fibrinogen, Antiphospholipid (APL) antibodies, Elevated von Willebrand factor, Elevated levels of fasting total homocysteine, high-dose oestrogen oral contraceptives are all associated with increased risk for stroke.

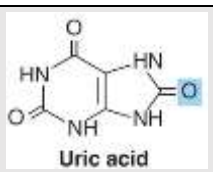

Figure 1. Molecular structure of Uric Acid

Uric acid is the final breakdown product of purine degradation in humans. It is weak diprotic acid with pKa values of 5.75 and 10.3. Urates, the ionized forms of uric acid, predominate in plasma, extracellular fluid, and synovial fluid, with ~98% existing as monosodium urate at pH 7.4.[11] Although purine nucleotides are synthesized and degraded in all tissues, urate is produced only in tissues that contain xanthine oxidase, primarily the liver and small intestine. The kidneys clear urate from the plasma and maintain physiologic balance by utilizing specific organic anion transporters (OATs). In adulthood, concentrations rise steadily over time and vary with height, body weight, blood pressure, renal function, and alcohol intake.[11]

SUA also possesses oxidative properties by mediating the production of radicals that have pro-oxidant effect on low density lipoprotein cholesterol.[12] SUA also reduces the bioavailability of NO by increasing arginase activity, reduces endothelial NO synthase phosphorylation, and increases intracellular superoxide formation.[13] In addition, uric acid caused a decrease in adiponectin production, an insulin sensitizer and anti-inflammatory agent. The oxidative stress and inflammation in adipocytes has been recognized as the mechanism underlying insulin resistance and atherosclerosis Kim et al. revealed in a systematic review involving of 16 cohort studies involving over 238,000 subjects that hyperuricaemia was significantly associated with a higher risk for stroke incidence (adjusted RR = 1.47, P <0.05) and stroke mortality (adjusted RR = 1.26, P < 0.05) compared with normouricaemia.[14]

In the Apo Lipoprotein Mortality Risk (AMORIS) study, elevated SUA was shown to be associated with a higher risk for haemorrhagic and ischemic stroke.[15] in a study on American population by Kanellis J et al with acute stroke, those with higher serum levels of uric acid were observed to be more debilitated with more recurrences and cardiovascular accidents.[15] A 3- month follow-up of stroke patients by Weir C J et al in England indicated greater mortality for those who had higher uric acid levels.[16]

A study in Greece on 163 patients by Millinois et al suffering from non-embolic ischemic stroke indicated more complications and greater risk of recurrence for those with higher uric acid levels. Findings of this study showed that elevated uric acid is associated with an increased risk for acute ischemic/non-embolic stroke in a strictly defined population of elderly individuals independently of concurrent metabolic derangements.[17] Another study in USA, ARIC study, showed that hyperuricemia increased the risk for both cerebral and cardiac vascular accidents. A 12.5-year follow-up of hyperuricaemic people in the United States observed higher risks of ischemic stroke and myocardial infarction for these people.[18] In this study, we observe greater incidence of acute stroke in patients with high SUA, and increased risk when associated systemic comorbidities like hypertension and Diabetes Mellitus.

CONCLUSIONS

Serum uric acid levels were significantly elevated in patients with acute ischemic stroke. Serum uric acid levels were significantly higher among hypertensive patients as compared to normotensive patients. Serum uric acid levels were significantly higher among diabetic patients as compared to non-diabetic patients. Due to the high prevalence of hyperuricemia in patients with acute stroke, and its accompanying increase in hypertension and diabetes mellitus, it can be considered as a risk factor for acute stroke. So, screening for hyperuricemia in patients with DM and Hypertension and treating and lowering of serum uric acid level can be considered as one of the preventing modalities for stroke while treating high risk population.

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