Evaluation of serum uric acid in acute ischaemic stroke

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ABSTRACT

Background: The role of serum uric acid as a risk factor for acute ischaemic stroke is controversial and there is little information about it. Present study was done to estimate serum uric acid levels in patients of acute ischaemic stroke and to assess its risk factor potential.

Methods: It was a prospective case control study carried out in the department of Medicine at Sri Guru Ramdas Institute of Medical Sciences and Research, Vallah, Sri Amritsar, Punjab, India from January 2015 to July 2016. 50 cases of acute ischaemic stroke were enrolled and were compared with same number of age and sex matched healthy controls. Serum uric acid levels were measured in cases (within 24 hours of stroke evolution). Glasgow coma scale (GCS) score was calculated for cases at time of admission. The results were statistically analysed.

Results: Mean serum uric acid level in cases was 6.15±1.91mg/dl whereas it was 5.1±1.4 mg/dl in controls. The difference of serum uric acid levels between cases and controls was statistically significant (p = 0.0054). Patients with poor GCS had higher mean serum uric acid levels as compared to patients with mild or moderate GCS score which was statistically significant(p = 0.0426).

Conclusions: Serum uric acid can be used as a marker for increased risk of stroke. Furthermore, serum uric acid can also be used for risk stratification after stroke.

Keywords: GCS, Stroke, Serum uric acid

INTRODUCTION

A stroke or cerebrovascular accident is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause. Stroke is the third common cause of death in the world after coronary heart disease and cancer especially in the elderly. The mortality rate of stroke in the acute phase is as high as 20% and it remains higher for several years after the acute event in stroke patients than in the general population. Cerebral ischemia initiates a complex cascade of metabolic events, generating nitric oxide and free oxygen radicals. These free radicals and reactive oxygen species (ROS) mediate a great part of injuries appearing after a transitory ischemic attack or during permanent ischemia, modifying macromolecules especially DNA, initiating apoptosis and necrosis.

Serum uric acid being one of the major aqueous antioxidant in human beings should have a protective role in stroke patients. Several large studies have provided conflicting results regarding the clinical significance of elevated serum uric acid levels in cerebrovascular diseases. Many studies including the National Health And Nutrition Examination Survey (NHANES) study concluded that uric acid is an independent risk factor for development of cardiovascular and cerebrovascular diseases. By contrast a prospective hospital-based study involving 881 patients found that higher level of serum urate predicted better outcomes following stroke, suggesting that serum urate may be beneficial and protect against poor outcomes. In addition an experimental study showed that uric acid administered early after thromboembolic stroke is neuroprotective in the rat brain.
and it extends the benefits of recombinant tissue plasminogen activator (rtPA).\(^6\)

Therefore the role of uric acid as a risk factor for acute ischaemic stroke is controversial. Amidst this controversy and lack of Indian data, it was decided to carry out the present study with the aim of studying serum uric acid levels in patients of acute ischaemic stroke and to determine its risk factor potential.

**METHODS**

The present case control study was undertaken in the department of Medicine at Sri Guru Ramdas Institute of Medical Sciences and Research, Vallah, Sri Amritsar, Punjab, India. The study was conducted after approval from Institutional Thesis and Ethical Committee. 100 Subjects were included in the study after informed consent. This case control study included two groups with 50 subjects in each group.

**Group A**

Consisted of 50 patients reporting to emergency department within 24 hours of onset of symptoms of stroke as per inclusion and exclusion criteria.

**Group B**

Consisted of age and sex matched 50 normal healthy individuals from same population reporting to out-patient department with minor complaints.

**Inclusion criteria**

Patients admitted in our hospital with symptoms suggestive of acute stroke within 24 hours of onset of ischemic stroke for the first time in life as evidenced by MRI Scan.

**Exclusion criteria**

Patients with evidence of hemorrhage or other space occupying lesions other than ischemic infarct in MRI scan, previous history of cerebrovascular accidents, history of intake of thiazide diuretics, complaints of gouty arthritis or clinical evidence of gout, chronic renal failure, hematological abnormalities like leukemia or other myeloproliferative disorder.

A detailed history and thorough clinical examination was carried out in each patient. Apart from routine investigation, estimation of serum uric acid was carried out in patients reporting to emergency department within 24 hours of onset of symptoms of acute ischemic stroke. The severity of stroke was assessed as per Glasgow Coma Scale (GCS).

The results of all the investigations performed on patients of group A was compared and statistically analysed with Group B who served as control.

**RESULTS**

The comparison of the baseline characteristics between the cases and controls represent the mean age, kidney function parameters and lipid profile of all patients (Table 1). The mean age of cases (65.30±12.11) was comparable to controls (61.44±12.84). Both the groups were comparable for male female ratio (1.5 for cases vs 1.27 for controls). The kidney function parameters of the cases i.e. blood urea (40.96±7.57 mg/dl) and serum creatinine (1.10±0.25 mg/dl) was also found to be comparable to controls, 36.26±9.48 mg/dl and 0.91±0.16 mg/dl, respectively (Table1).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (Mean± SD)</th>
<th>Cases (Mean± SD)</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.44±12.84</td>
<td>65.30±12.11</td>
<td>NS</td>
</tr>
<tr>
<td>B.Urea (mg/dl)</td>
<td>36.26±9.48</td>
<td>40.96±7.57</td>
<td>NS</td>
</tr>
<tr>
<td>S.Creat (mg/dl)</td>
<td>0.91±0.16</td>
<td>1.10±0.25</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>178.42±53.76</td>
<td>166.16±51.47</td>
<td>NS</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>165.32±97.90</td>
<td>151.00±72.38</td>
<td>NS</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>42.24±10.74</td>
<td>36.66±10.37</td>
<td>NS</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>110.50±38.29</td>
<td>100.58±36.58</td>
<td>NS</td>
</tr>
<tr>
<td>VLDL (mg/dl)</td>
<td>32.74±19.56</td>
<td>29.88±14.48</td>
<td>NS</td>
</tr>
</tbody>
</table>

The mean serum uric acid level was significantly higher in cases (6.15±1.91) as compared to controls (5.1±1.4) (\(p = 0.0054\)) (Table 2). In the present study severity of stroke among cases was assessed by GCS score. Out of 50 patients; 22 patients (44%) had severe GCS score, 17 patients (34%) had moderate GCS score and 11 patients (22%) had mild GCS score. Mean serum uric acid in acute stroke patients who had severe GCS score (6.77±2.43 mg/dl) was higher than that those who had mild/moderate GCS score (5.67±1.21 mg/dl) and the difference was statistically significant (\(p = 0.042\)) (Table 3).
The serum uric acid levels were compared based on the physiological/etiological factors among the cases, viz. male and female, diabetic and non-diabetic, hypertensive and non-hypertensive. In our study, amongst cases 60% of the patients were between 60 to 79 years with 17 males (56%) and 13 females (65%). No significant difference was found on comparison among male and female physiology, diabetic and non-diabetic etiology, whereas the serum uric acid was significantly higher among hypertensives in comparison to non-hypertensives (Table 4). The serum uric acid was further compared between normal and deranged lipid profile among cases viz., cholesterol, TG, HDL and LDL. No significant difference in serum uric acid was found among these comparisons (Table 5).

Table 2: Comparison of serum uric acid levels between cases and controls.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (Mean±SD)</th>
<th>Cases (Mean±SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUA (mg/dl)</td>
<td>5.1±1.4</td>
<td>6.15±1.91</td>
<td>0.0054</td>
</tr>
</tbody>
</table>

DISCUSSION

A stroke or cerebrovascular accident is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause. Stroke is an important cause of morbidity and long term disability; upto 40% survivors are not expected to recover their independence with self-care and 25% unable to walk independently. Cerebral ischemia initiates a complex cascade of metabolic events, generating nitric oxide and free oxygen radicals. Those free radicals and reactive oxygen species (ROS) mediate a great part of injuries appearing after a transitory ischemic attack or during permanent ischemia, modifying macromolecules especially DNA, initiating apoptosis and necrosis. Serum uric acid being one of the major aqueous antioxidant in human beings should have a protective role in stroke patients.

But only few studies have shown higher levels of serum uric acid being neuroprotective in patients with stroke.

Therefore the role of uric acid as a risk factor for acute ischemic stroke is controversial. Hence the present study was conducted to determine risk factor potential of serum uric acid levels in patients with acute ischemic stroke. Amidst this controversy and lack of Indian data, it was decided to carry out the present study with the aim of studying uric acid levels in patients of acute ischemic stroke. In our study we determined the role of serum uric acid in acute stroke patients and its prognostic significance on stroke outcome.

Both the groups (cases and controls) were comparable for baseline characteristics representing the mean age, sex distribution, kidney function parameters and lipid profile. Amongst cases of acute ischemic stroke mean serum uric acid level was 6.15±1.91 mg/dl and 38% (male 30%, female 50%) of them were hyperuricemic. Amongst control group mean serum uric acid level was 5.1±1.4 mg/dl and 22% (male 14%, female 32%) of them had hyperuricemia. The prevalence of hyperuricemia among the patients, attending Nobel Medical College was
28.33% (male 30.06%, female 26.61%). Another large study in Bangkok population showed that prevalence of hyperuricemia is 24.4%. According to these studies prevalence of hyperuricemia is significantly higher in patients with acute stroke than normal population. These findings are consistent with our study as patients with hyperuricemia were more in stroke patients as compared to control group.

Age is the most common non-modifiable risk factor for the development of stroke. In our study, 60% of the patients are between 60 to 79 years with 17 males (56%) and 13 females (65%). Milionis et al in their study of 163 patients above 70 years for association of serum uric acid and stroke found that serum uric acid is associated with an increased risk for acute ischemic/nonembolic stroke in elderly patients independently of concurrent metabolic derangements. In the German dataset, a maximum male preponderance was found for patients aged between 55 and 64 years (proportion of male patients 0.67 (95% CI: 0.66-0.67), whereas patients older than 84 years revealed a strong overbalance of females (0.27 (0.26-0.28)). These results are analogous to the findings in this study with majority of patients belonging to age group between 60-79 years with male preponderance.

In our study amongst cases the mean serum uric acid levels were higher among males than females but this difference did not attain statistical significance. Pearce et al observed higher serum uric acid values in males as compared to females (5.28±0.66 versus 4.47±0.78 mg/dl). Mbenza LB et al found significantly higher serum uric acid level in males (6.6±7 versus 5.8±6 mg/dl, P < 0.01). Similar results were obtained in the study by Milionis et al and in the Rotterdam study (348 versus 302 μmol/L). Framingham heart study also showed higher serum uric acid in males.

Hypertension is the most common modifiable risk factor for stroke. Elevated serum uric acid level is an independent predictor of hypertension in 25% of patients with new onset untreated primary hypertension. Experimentally induced hyperuricaemia has been shown to precipitate hypertension in rats via a renal mechanism related to the inhibition of nitric oxide, the activation of the renin-angiotensin system and the subsequent development of renal arteriolosclerosis. Milionis et al observed that serum uric acid levels were higher in hypertensive subjects compared with nonhypertensives (5.4 ± 1.6 mg/dl versus 5.0 ± 1.6 mg/dl, p = 0.04). Lehto et al also found that the prevalence of hypertension among hyperuricemic subjects was higher as compared to the patients with serum uric acid levels in the normal range (67.3% versus 41.2%, P < 0.001). Similar observation was noted in our study with significantly higher serum uric acid levels among hypertensive patients as compared to normotensive patients (6.4±1.9 versus 5.1±1.3 mg/dl, p = 0.023).

Diabetes mellitus is one of the major risk factors for stroke independent of other cardiovascular risk factors. Lehto S et al in their study involving 1017 persons with NIDDM concluded that hyperuricemia is a strong predictor of stroke events in middle aged persons with NIDDM, independently of other cardiovascular risk factors. Mbenza B et al observed significantly higher frequency of hyperuricemia among diabetic patients. In our study serum uric acid levels in patients suffering from diabetes mellitus were higher as compared to those in non-diabetic subject but the levels were not statistically significant.

Several prospective studies have shown that higher levels of total cholesterol increase the risk of ischemic stroke. Amerenco P et al conducted a meta-analysis of 90000 patients and found that administration of statins reduces the risk of stroke among patients with coronary artery disease and that this risk reduction is primarily related to the extent to which LDL-C levels are lowered. In some studies relating metabolic syndrome and serum uric acid; increased serum uric acid levels correlated with low HDL-C levels. In our study mean serum uric acid level was found to be lower in patients who had elevated serum cholesterol (>200 mg/dl), triglycerides (>150 mg/dl) and LDL (>120 mg/dl) than those with normal lipid profile but the difference was not statistically significant. Also in our study mean serum uric acid level was found to be lower in patients who had elevated HDL levels (>40 mg/dl) but the difference was not significant.

We found that mean serum uric acid levels was significantly higher among cases than controls (6.15±1.91mg/dl, 5.1±1.4 mg/dl, P <0.05). These findings are concordant with most of the data published worldwide. Milionis et al observed that the serum uric acid levels were significantly higher in stroke patients compared with controls (5.6±1.7 mg/dl versus 4.8±1.4 mg/dl, P < 0.001). Srikrishna R et al found that serum uric acid levels were significantly higher in cases as compared to controls (6.56±0.73 versus 4.66±0.47, P < 0.05). In The Rotterdam study, high serum uric acid levels were associated with the risk of stroke.

In present study the severity of stroke was assessed by Glasgow Coma Scale (GCS). Mean serum uric acid in acute stroke patients who had severe GCS score (6.77±2.43 mg/dl) was higher than that those who had mild/moderate GCS score (5.67±1.21mg/dl) and the difference was statistically significant (p = 0.0426). Kim et al in their systematic review and meta-analysis of 16 prospective cohort studies including 238449 adults 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. Weir et al noted that higher serum urate value was significantly associated with bad outcome (OR = 0.78 per additional 0.1 mmol/L95% C.I. = 0.67 -
Pink et al also found that the patients who died had a significantly higher serum uric acid values as compared to those who were discharged home (9.5±3 mg/dl versus 6.9±4 mg/dl, P = 0.003).  

Serum uric acid is one of the major aqueous antioxidant in human beings. It is therefore prudent to expect that serum uric acid should have a protective role in stroke but review of literature suggests otherwise. There are only few studies that have concluded higher levels of serum uric acid being neuroprotective in patients with stroke. 

An explanation to this comes from the study which concluded that serum uric acid can work as pro-oxidant under certain circumstances, particularly if the levels of other antioxidants like ascorbic acid are low.  

Various studies have shown that uric acid can result in endothelial dysfunction which can lead to vascular disease. Another putative mechanism involves the role of xanthine oxidase; higher serum uric acid levels might reflect an increased activity of xanthine oxidase. The action of xanthine oxidase leads to generation of superoxide anions and the reactive oxygen species in human vasculature. Also, allopurinol, a xanthine oxidase inhibitor, was found to reduce inflammatory markers in stroke survivors. 

According to Hayden et al serum uric acid acts like an antioxidant in the early stages of atherosclerotic process, being one of the most powerful determinant of plasma antioxidant capacity. Later, in the evolution of atherosclerotic process when serum uric acid reaches 4 - 6mg/dl it becomes pro-oxidant. The antioxidant pro-oxidant urate shuttle relies on its surrounding environment. 

It follows that medications with a serum uric acid lowering capacity might be considered in these subjects. Xanthine oxidase inhibitors (i.e. allopurinol) or a variety of uricosuric agents, including probenecid and sulfipyrazone can lower elevated serum uric acid levels but it is unknown whether these agents reversibly impact cardio vascular outcomes. The latter may hold true for agents used in the treatment of hypertension (i.e. losartan, an angiotensin II receptor antagonist) and dyslipidaemia (atorvastatin, fenofibrate), which have been shown to produce a small but significant fall in serum uric acid levels. The findings of the recently published LIFE study (losartan intervention for endpoint reduction in hypertension study) in patients with hypertension and left ventricular hypertrophy suggest the possibility that a decrease in serum uric acid induced by losartan treatment attenuates cardiovascular risk, including stroke. The same was also evident in the GREACE (Greek atorvastatin and coronary heart disease evaluation) study in CHD patients receiving targeted lipid-lowering treatment with atorvastatin.

Taken together, serum uric acid levels could be of value in identifying subjects at risk for an ischemic stroke and judiciously selecting drugs (alone or in combination), which would produce a hypouricaemic effect. Further long term prospective studies are needed to establish the role of serum uric acid in ischemic stroke. Also, trial of serum uric acid lowering drugs in stroke patients as well as in those at increased risk of stroke can be worth considering. 

CONCLUSION 

Serum uric acid can be used as a marker for increased risk of stroke. Furthermore, serum uric acid can also be used for risk stratification after stroke. Further long term prospective studies are needed to establish the role of serum uric acid in ischemic stroke. Also, trial of serum uric acid lowering drugs in stroke patients as well as in those at increased risk of stroke can be worth considering.

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REFERENCES 


