A STUDY OF SERUM URIC ACID LEVEL AND RISK FOR ACUTE ISCHEMIC NONEMBOLIC STROKE IN ELDERLY SUBJECTS

Medicine

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ABSTRACT

The study is conducted to determine the association between serum uric acid (SUA) and acute non embolic ischemic stroke and to assess its risk factor potential using statistical analysis.

The observational, cross-sectional, case control, retrospective was conducted in the N.R.S. Medical College and Hospital, Kolkata. Study was done from 1st February 2017 to 30th September 2018 i.e., through one and half year period.

About 200 patients (100 cases & 100 controls).

It was also found that serum uric acid was also independent risk factor for causing acute ischemic non embolic stroke. It is also suggested that further studies are required to assess whether lowering of SUA level with drugs can actually reduce the risk of ischemic stroke.

KEYWORDS

INTRODUCTION

Among all the neurological diseases of adult life, the cerebrovascular ones clearly rank the first in frequency and importance. Stroke is the second leading cause of death worldwide, causing 6.2 million deaths in 2011¹. 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 patient than in the general population². Stroke also entails a high socioeconomic burden due to increased morbidity and mortality. Ischemic strokes account for more than 80% of total stroke events³. Early identification of individual at risk could be of help in primary prevention strategies⁴. Known modifiable risk factors like hypertension, DM, Smoking obesity are well documented. Newer not well-known risk factor are like homocysteine and serum uric acid. SUA is one of the major aqueous antioxidant in the humans, and contributes as much as two – third of the plasma free radical scavenging ability. It is particularly effective in quenching hydroxyl, superoxide and peroxynitrite radicals, and may serve a protective physiological role by preventing lipid peroxidation⁵. Uric acid is considered an effective antioxidant and high SUA levels could be a compensatory mechanism to counteract oxidative stress⁶⁻⁷. It has been suggested that increased levels of SUA may be the result of the evolution of protective mechanisms in primate (including human) against oxygen radicals⁸. In animal models, local UA concentrations significantly increase in acute brain injury. For example, in rat, middle cerebral artery occlusion causes a significant increase in cerebral UA concentrations, which can persist for several days after injury⁹. Elevated SUA levels have been proposed as an independent risk factor in cardiovascular morbidity and mortality. Evidence from epidemiological studies suggests that the elevated SUA levels may predict an increased risk for cardiovascular (CV) events including stroke¹⁰⁻¹¹. Moreover, therapeutic modalities with a SUA lowering potential have been shown to reduce CV disease morbidity and mortality. Raised SUC level is a surrogate marker of metabolic Syndrome and increased SUC level is also associated with CV morbidity and mortality. Diabetes mellitus confers a twofold to four fold higher risk of the incidence of an adverse vascular event including cerebrovascular accidents¹². This increased risk has only been partially attributed to the pathologic effects of diabetes on risk factors associated with hyperinsulinemia¹². SUA has been recently associated with insulin resistance¹¹. One study¹³ indicates hyperuricemia is a useful predictor of cerebrovascular events in elderly diabetic patients independent of the remaining CV risk factors. : Though it has been recognised as an important risk factor for

confirmed whether high SUA levels have an important role in the etiopathogenesis of Cerebrovascular disease or if it is just a coincidental finding¹⁸. Studies like NHANES I have provided data to support a positive association between SUA and stroke in middle age people, after accounting for other confounding factors¹⁹. Stroke entails a high socio-economic burden due to increased morbidity and mortality.

1. The study is conducted to determine the association between serum uric acid (SUA) and acute non embolic ischemic stroke and to assess its risk factor potential using statistical analysis.

2. To study the association between serum uric acid (SUA) and other risk factors namely hypertension, Diabetes mellitus, coronary artery disease (CAD) and adverse lipid profile.

MATERIALS AND METHODS

The observational, cross-sectional, case control, retrospective was conducted in the N.R.S. Medical College and Hospital, Kolkata. Study was done from 1st February 2017 to 30th September 2018 i.e., through one and half year period.

Sample Size:

About 200 (100 cases & 100 controls).

Sample Design:

Patients admitted in N.R.S MEDICAL COLLEGE with first ever in life time acute non embolic ischemic stroke with or without CT scan evidence of infarction within 24 hrs of onset of stroke. Patients with previous history of TIA/CVA or who are on thiazide diuretics or known cases of gout or show clinical evidences of gout or with chronic renal failure or CT Scan showing of hemorrhage or SOL other than infarct or known cardiac diseases or with hematological abnormalities are excluded from study.

Inclusion Criteria

- Patient admitted in our hospital with first-ever-in life time acute ischemic non embolic stroke with or without CT scan evidence of infarction within 24 hours of onset of stroke.

Exclusion Criteria

- Patients with previous history of TIA/CVA
- Patients who are on thiazide diuretics
- Patients who are known cases of gout or show clinical evidences of gout

Cerebrovascular events in many research studies¹⁴⁻¹⁷, it is yet to be

- Patients with chronic renal failure
- Patients who's CT scan show hemorrhage or either space occupying lesions other than infarct.
- Patients who were of known cardiac diseases with or without atrial fibrillation which could be sources of emboli or whose echocardiogram shown sources of emboli.
- Patients with hematological abnormalities like leukemia or other myeloproliferative disorders.

Statistical Analysis:

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS 24.0. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or unpaired samples. Paired t-tests were a form of blocking and had greater power than unpaired tests. A chi-squared test (χ^2 test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. Without other qualification, 'chi-squared test' often is used as short for Pearson's chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate.

RESULT AND DISCUSSION

The well recognized risk factors for stroke like age, smoking, diabetes, hypertension, metabolic syndrome explain only a part of the cases. Hence a search for other risk factors is the need of the hour. This study was conducted to study the role of serum uric acid in acute ischemic stroke and its effect on stroke outcome.

The male to female ratio was 1.32:1. The mean age of the cases was 68.61 ± 7.47 years with the range of 57 to 90 years. The mean SUA levels among males and females did not attain statistical significance (5.6885 ± 1.27 vs 5.6897 ± 1.32) p-value > 0.05

Pearce et al²¹ (1969) observed higher SUA values in males as compared to females (5.28 ± 0.66 vs. 4.47 ± 0.78 mg/dl)¹⁰. Similar results were obtained in the study by Milionis et al²³ and in the Rotterdam study²² (348 vs. 302 μ mol/L).

We found that stroke patients had a significantly higher SUA levels when compared to the controls (6.25 ± 1.30 mg/dl vs. 5.12 ± 0.99 mg/dl, $P < 0.05$) Table.19 On multiple regression analysis, correlation of SUA with ischemic stroke was found to be independent of other major risk factors for stroke (OR = 6.8749, $z = 4.4829$, 95% C.I. = 2.9594 to 15.9710, $P < 0.0001$). Table.36 these findings are in accordance with most of the data published worldwide.

Milionis et al²³. Observed that the SUA levels were significantly higher in stroke patients compared with controls (5.6 ± 1.7 mg/dl vs. 4.8 ± 1.4 mg/dl, $P < 0.001$). Srikrishna R and Suresh DR²⁴ found that serum uric acid levels were significantly higher in cases as compared to controls (6.56 ± 0.73 vs. 4.66 ± 0.47 , $P < 0.05$). In The Rotterdam study²², high serum uric acid levels were associated with the risk of stroke.

In our study we found that SUA levels increased with increasing age and this is statistically significant p-value < 0.0001.

In our study, correlation between hypertension and ischemic stroke was found to be independent on multiple logistic regression analysis (OR = 5.9815, $z = 4.9176$, 95% C.I. = 2.9323 to 12.2017, $P < 0.0001$) Table.36

It was also found that SUA levels among hypertensive patients were significantly higher as compared to normotensive patients (6.28 ± 1.29 vs. 5.21 ± 1.11 mg/dl, $P < 0.05$). Table. 31

Milionis et al²³ observed that SUA levels were higher in hypertensive subjects compared with non hypertensives (5.4 ± 1.6 mg/dl vs. 5.0 ± 1.6 mg/dl, $P = 0.04$). Lehto et al¹² also found that the prevalence of hypertension among hyperuricemic subjects was higher as compared to the patients with SUA levels in the normal range (67.3% vs. 41.2%, $P < 0.001$).

In our study we found that diabetes mellitus is a risk factor for stroke ($\chi^2 = 5.26$, OR = 3.50, 95% C.I. = 1.59-7.67, p-value = 0.021).

We found that SUA levels in patients suffering from diabetes mellitus

were significantly higher as compared to those in non diabetic subjects (6.55 ± 1.15 vs. 5.50 ± 1.2 mg/dl, $P < 0.05$).

Our findings are in accordance with the findings of Longo-Mbenza et al²⁵ who observed significantly higher frequency of hyperuricemia among diabetic patients.

In our study we found that obesity is a risk factor for stroke ($\chi^2 = 8.139$ OR = 3.531, 95% C.I. = 1.426-8.742, p-value = 0.0043).

Per Harnesen et al²⁶. also found that obesity is a risk factor for stroke (OR = 2.23, 95% C.I. = 1.83 - 2.72). Also, Milionis et al²³ who found significantly higher levels of SUA among overweight patients (BMI > 25) as compared to non-obese patients (5.4 ± 1.6 vs. 4.9 ± 1.5 mg/dl, $P = 0.004$). In this study it was observed that mean SUA level is higher among obese patients than non-obese patients (6.07 ± 1.03 vs. 5.6 ± 1.30 , p value significant).

Similarly, Strasak et al²⁷. also observed a positive correlation between SUA and smoking ($r = 0.11$, $P < 0.001$). Mozos et al²⁸ also found that SUA levels were significantly higher in smokers as compared to nonsmokers (5.7 ± 1.3 vs. 5.0 ± 1.1 mg/dl, $P < 0.05$).

In this study it was observed that dyslipidemia is a risk factor for stroke ($\chi^2 = 6.25$, OR = 3.857, 95% C.I. = 1.76-8.421, p-value 0.0124).

In our study, we found a significant positive correlation between SUA levels and serum triglyceride level. Serum uric acid level increased with increasing serum triglyceride level $P < 0.0001$.

Lehto et al(12). Concluded that SUA was significantly associated with HDL cholesterol ($r = -0.25$, $P < 0.01$) and triglyceride levels ($r = 0.14$, $P < 0.01$). Bansal et al²⁹. Found a significant correlation between SUA and triglyceride ($P < 0.05$). Our findings correlate with the above mentioned studies.

In this study it was observed that coronary artery disease (CAD) is a risk factor for stroke ($\chi^2 = 12.25$, OR = 8.070, 95% C.I. = 3.206-20.317, p-value = 0.004). Table.29. In this study it was observed that mean SUA level is higher among patients with CAD than patient without CAD (6.68 ± 1.08 vs. 5.46 ± 1.29 , p value < 0.05).

In this study it was observed that smoking is a risk factor for stroke ($\chi^2 = 5.472$ OR = 2.785, 95% C.I. = 1.504-5.459). In this study it was observed that mean SUA level in smokers was significantly higher as compared to nonsmokers (6.11 ± 1.18 vs. 5.49 ± 1.28 mg/dl, $P = 0.05$).

In our study, out of 100 patients, 17 patients died and remaining 83 patients were discharged from the hospital. The mean SUA levels were significantly higher in the patients who succumbed as compared to the patients who were alive at discharge (7.01 ± 1.23 vs. 6.08 ± 1.26 mg/dl, $P < 0.05$). Mozos et al²⁸ found that the patients who died had a significantly higher SUA values as compared to those who were discharged home (9.5 ± 3 mg/dl vs. 6.9 ± 4 mg/dl, $P = 0.003$). Behera Bk et al. also found that the patients who died had a significantly higher SUA values as compared to those who were discharged home (7.26 ± 0.78 mg/dl vs. 6.16 ± 1.68 mg/dl, $P = 0.014$)³⁰. Tushar B et al also found that mean SUA levels were significantly higher in the patients who succumbed as compared to the patients who were alive at discharge (8.60 ± 2.16 vs. 6.16 ± 1.68 mg/dl, $P < 0.05$).³¹

Only one study that was done by Chammoro et al³² found that higher levels of SUA at admission were associated with better outcome after stroke.

The findings of our study are in accordance with all but one study mentioned above. From the above discussion, it is evident that SUA levels are associated with increased risk for stroke as well as with poor short term and long term prognosis after stroke.

SUA is one of the major aqueous antioxidant in the human beings and constitutes as much as two third of the plasma free radical scavenging ability. It is therefore prudent to expect that SUA should have a protective role in stroke. But as discussed above only one study³² has found that higher SUA level may be neuroprotective in patients with stroke. An explanation to this comes from the study which showed that SUA can work as a pro-oxidant under certain circumstances, particularly if the levels of other antioxidants (like ascorbate) are low

³³. Various studies have also showed that uric acid can result in endothelial dysfunction which can lead to vascular diseases ³⁴. SUA can also promote LDL cholesterol in vitro ³⁵. Thus our study concludes that SUA can be used as a marker for increased risk of stroke. Furthermore, SUA can also be used for risk stratification after stroke.

Further long term prospective studies are needed to establish the role of SUA in ischemic stroke. Also, trial of SUA lowering drugs in stroke patients as well as in those at increased risk of stroke can be worth considering.

SUMMARY AND CONCLUSION

1) This study shows that elevated SUA is strongly associated with an increased risk for the development of acute ischemic non embolic stroke in this study population.

2) The association between elevated SUA and ischemic stroke may need to be considered especially when treating elderly diabetic, hypertensive patients and the population with coronary artery disease.

3) Elevated SUA can be considered as one of the risk factor for acute ischemic non – embolic stroke.

4) Lowering SUA level can be considered as one of the preventive modalities for stroke incidence while treating high risk population compared with control population.

5) It is also associated with decreased survival rate among ischemic non embolic stroke patients.

REFERENCES

- Harrison's principles of internal medicine 19th edition vol 2 page 2559
- Harklia VD, Apostolos H, Haralambosk the Role of Uric Acid in stroke. The issue remains unresolved. *The Neurologist*.2008; 14: 238-242
- Bonita R. Epidemiology of stroke. *Lancet* 1992; 339: 342-4
- Buckley BM. Healthy ageing: ageing safely. *Eur Heart J* 2001; (suppl 3): N6-10
- Squadrito GL, Cueto R Splenser AE, Valavanidis A, Zhang H, Uppu RM. Et al. Reaction of uric acid with peroxynitrite and implications for the mechanism of neuroprotection by uric acid. *Arch Biochem Biophys* 2000; 376: 333-337
- Millionis HJ, Elisaf MS, Management of hypertension and dyslipidemia in patients presenting with hyperuricemia: case histories. *Curr Med Res Opin* 2000; 16: 164-170
- Sevanian A, Davies KJ, Hochstein P. Serum urate as an antioxidant for ascorbic acid. *Am J Clin Nutr* 1991; 54: 1129-34
- Millionis HJ, Elisaf MS, Management of hypertension and dyslipidemia in patients presenting with hyperuricemia: case histories. *Curr Med Res Opin* 2000; 16: 164-70
- Kanemitsu H, Trmura A, Kirino T, Karasawa S, Sano K, Iwamoto T, Yoshiura M, Iriyama K, Xanthine and uric acid levels in rat brain following focal ischemia. *J Neurochem* 1988; 51: 1882-5
- Daskalopoulou SS, Athyros VG, Elisaf M, Mikhailidis DP. Uric acid levels and vascular disease. *Curr Med Res Opin* 2004; 20: 951-4.
- Fang J, Alderman MH. Serum uric acid and cardiovascular mortality. The NHANES I epidemiologic follow-up study, 1971-1992. *JAMA* 2000; 283: 2404-10.
- Lehto S, Niskanen L, Ronnema T, Laasko M. Serum uric acid is a strong predictor of stroke in patients with non-insulin dependent diabetes mellitus. *Stroke* 1998; 29: 635-9
- Rathmann W, Funkhouser E, Dyer AR, Roseman JM. Relations of hyperuricemia with the various components of the insulin resistance syndrome in young black and white adults: The CARDIA study [Coronary Artery Risk Development in Young Adults]. *Ann Epidemiol* 1998; 8: 250-261.
- Diabetes Metab Res Rev. 2006 Jan – Feb; 22(1): 79-82: Elevated serum uric acid levels independently predicts prognosis of stroke in diabetic patients - Newman E, Rahman F, Les KR Conclusion: Increased SUA levels is significantly and independently associated with high risk of adverse vascular events in diabetic stroke patients.
- Journal of Internal Medicine* 2005; 258: 435-441: Serum uric acid levels and risk for acute ischaemic nonembolic stroke in the aged – H Milonis, K. Kalatzi, J. Goudvenos, K. Saferidis Conclusion: Elevated SUA is associated with an increased risk for acute ischaemic / nonembolic stroke in individuals aged more than 70 independent of other risk factors.
- Int J Cardiol*, 2005 Mar 18; 99(2): 269-75: Risk factors for acute ischemic non – embolic stroke in elderly patients – Milonis HJ, Liberopoulos E, Goudvenos J. Conclusion: SUA and Diabetes mellitus are important risk factors for ischemic stroke
- Stroke* 2003; 34: 1956-1957: Editorial comment – Elevated Uric Acid and Ischemic Stroke: Accumulating Evidence That it is Injurious and Not Neuroprotective – John Kanellis and Richard J. Johnson Conclusion: High SUA during an acute episode of stroke is harmful, more so if the level of vitamin-c is low,
- Waring WS. Uric acid: an important antioxidant in acute ischaemic stroke. *QJ Med* 2002; 95: 691-3.
- Fang J, Alderman MH. Serum uric acid and cardiovascular mortality. The NHANES I epidemiologic follow – up study, 1971-1992. *JAMA* 2000; 283: 2404-10.
- Berry C, Hamilton CA, Brosnan MJ, Magill FG, Berg GA, McMurray JJ, Dominiczak AF. Investigation into the sources of superoxide in human blood vessels: angiotensin II increases superoxide production in human inter- nal mammary arteries. *Circulation*. 2000; 101(18): 2206-2212.
- Pearce J, Aziz H. Uric acid and plasma lipids in cerebrovascular disease. I. Prevalence of hyperuricaemia. *Br Med J*. 1969; 4(5675): 78-80.
- Bos MJ, Koudstaal PJ, Hofman A, Witteman JC, Breteler MM. Uric acid is a risk factor for myocardial infarction and stroke: the Rotterdam study. *Stroke*. 2006; 37(6): 1503-1507.
- Millionis HJ, Kalantzi KJ, Goudvenos JA, Seferiadis K, Mikhailidis DP, Elisaf MS. Serum uric acid levels and risk for acute ischaemic non-embolic stroke in elderly subjects. *J Intern Med*. 2005; 258(5): 435-441.
- Shrikrishna R, Suresh DR. Biochemical study of anti- oxidant profile in acute ischemic stroke. *British Journal of Medical Practitioners* 2009; 2(1) 35-37.
- Longo-Mbenza B, Luila EL, Mbete P, Vita EK. Is hyper- uricemia a risk factor of stroke and coronary heart disease among Africans? *Int J Cardiol*. 1999; 71(1): 17-22.
- Harmen P, Lappas G, Rosengren A, Wilhelmsen L. Long-term risk factors for stroke: twenty-eight years of follow-up of 7457 middle-aged men in Goteborg, Sweden. *Stroke*. 2006; 37(7): 1663-1667.
- Strasak A, Ruttman E, Brant L, Kelleher C, Klenk J, Concini H, Diem G, et al. Serum uric acid and risk of cardiovascular mortality: a prospective long-term study of 83,683 Austrian men. *Clin Chem*. 2008; 54(2): 273-284.
- Mozos I, Chiulana C, Goruna C, Costea S. Serum uric acid in stroke. *Annals of West*

- University of Timisoara, Series of Chemistry 16 (2) (2007) 227 – 236.
- Bansal BC, Gupta RR, Bansal MR, Prakash C. Serum lipids and uric acid relationship in ischemic thrombotic cerebrovascular disease. *Stroke*. 1975; 6(3): 304-307.
- Behera BK et al. *Int J Res Med Sci*. 2017 Jun; 5(6): 2353-2357.
- Tushar B, Palil ASP, Kiran MS, et al. Serum Uric Acid Levels in Acute Ischemic Stroke : A study of 100 patients. *J Neurol Res* 2011; 1 (5)-193-200
- Chamorro A, Obach V, Cervera A, Revilla M, Deulofeu R, Aponte JH. Prognostic significance of uric acid serum concentration in patients with acute ischemic stroke. *Stroke*. 2002; 33(4): 1048-1052.
- Abuja PM. Ascorbate prevents prooxidant effects of urate in oxidation of human low density lipoprotein. *FEBS Lett* 1999; 446: 305 – 308
- Waring WS, Webb DJ, Maxwell SRJ. Effect of local hyperuricaemia on endothelial function in the human forearm vascular bed. *Br J Clin Pharmacol* 2000; 49: 511P.
- Bagnati M, Perugini C, Cau C, Bordone R, Albano E, Bellomo G. When and why a water-soluble antioxidant becomes pro-oxidant during copper-induced low-density lipoprotein oxidation: a study using uric acid. *Bio-chem J*. 1999; 340 (Pt 1): 143-152.