Original article

Prognostic Importance of Serum Uric Acid in Acute Ischaemic Stroke

Subhra Aditya[1], S Ghosh[2], J Banerjee[3], SP Saha[4],S Sengupta[5], SB Ganguly[6]

[1]Assistant Professor, Department of Medicine.Institute of Post Graduate Medical Education &Research, Kolkata, West Bengal, India.

[2]Assistant Professor, Department of Medicine, R.G. Kar Medical& Hospital,Kolkata, West Bengal,India.

[3]Assistant Professor. Department of Physiology.R.G. Kar Medical College & Hospital,Kolkata, West Bengal, India.

[4]Professor. Department of Neuromedicine, R.G. Kar Medical College & Hospital. Kolkata, West Bengal.

[5]Assistant Professor, Department of Medicine, R.G. Kar Medical & Hospital,Kolkata, West Bengal, India.

[6] Professor, Department of Medicine, R.G. Kar Medical & Hospital,Kolkata, West Bengal, India.

Corresponding author: Subhra Aditya[1]

Abstract

Introduction : Role of uric acid as a prognostic marker of atherosclerotic vascular diseases has remained a debatable issue. Since information on this aspect from south Asian population is rather scanty, we have evaluated prognostic significance of serum uric acid in acute ischaemic stroke, in an urban hospital of eastern India.

Methods : In this prospective observational study, 193 ischaemic stroke patients were evaluated. CT scan was done and other investigations including serum uric acid were measured at admission. Neurological assessment was done by Mathew score both at admission and at discharge. Outcome was categorized as good (Mathew score > 75) or poor (Mathew score </= 75) and analyzed by multiple logistic regression for evaluation of prognostic significance of uric acid.

Results : The age of patients (female: male =1:1.3) ranged from 40 years to 86 years (mean = 62.37±10.81). Higher uric acid level was associated with good clinical outcome (OR = 2.20, 95% CI = 1.55 to 3.13, p<0.0001).Other factors found to be predictors of good outcome are higher Mathew Score at admission (OR =1.10, 95% CI = 1.06 to 1.14, p<0.0001) and female sex (OR = 4.90, 95% CI = 1.44 to 16.63, p = 0.01). Factors associated with poor outcome were large infarct size (OR = 0.10, 95% CI = 0.02 to 0.63, p = 0.01), higher serum urea value (OR = 0.95, CI = 0.90 to 0.99, p = 0.02) and presence of atrial fibrillation (OR = 0.06, CI = 0.01 to 0.56, p = 0.01).

Conclusion: Higher serum uric acid level was associated with good clinical outcome in acute ischaemic stroke.

Key words: uric acid, stroke, prognosis, atherosclerosis, antioxidant

Introduction

Among all the neurologic diseases of adult life, the cerebrovascular ones clearly rank first in frequency and importance. At least 50% of neurologic disorders in a general hospital are of this type.(1) In addition to high mortality, the disease carries an enormous socioeconomic burden of stroke survivors. Thus, there is a continuous search for finding out a simple biochemical prognostic marker for this devastating disease.Being a natural antioxidant, uric acid has long been debated as an atherosclerotic risk factor. Several epidemiological studies have suggested the association between serum uric acid level and risk of coronary and cerebrovascular diseases.(2, 3, 4) But it is still unclear whether high serum uric acid is protective or harmful or simply acts as a passive marker of increased atherosclerotic risk. In the perspective of ischaemic stroke, some studies have

found that higher uric acid level may be harmful, [2, 5, 6] whereas others got evidence of beneficial effect.[7, 8] Although lots of research have been carried out across the globe on this controversial yet interesting issue, such information from south Asian population is rather scanty. On this background, we studied prognostic significance of serum uric acid in acute ischaemic stroke patients from eastern India during their hospital stay.

Methods

This prospective observational study was conducted in the Department of Medicine, R. G. Kar Medical College and Hospital, Kolkata, India, during November 2005 to August 2009 among the admitted patients fulfilling the following criteria.

Inclusion Criteria:

1. Cases of ischemic stroke (confirmed by CT of scan brain) presenting within 72 hours of onset of symptom.

Exclusion Criteria:

1. Age bellow 40 years..
2. Other co-morbid conditions such as – acute myocardial infarction, hepatic encephalopathy, septicemia, chronic renal failure and gout.
3. Patients receiving drugs which may alter the level of uric acid (like thiazide, allopurinol) and iron or any antioxidant
4. Patients with prior history of stroke and strokes secondary to trauma, neoplasm, vasculitis and infection.
5. Patients who received thrombolytic agent, diuretic or any other investigational drug during their hospital stay.

We studied 193 patients with ischemic stroke of various severities. Detailed history taking and clinical examination was undertaken for every patient at admission. In-hospital events and therapies administered were prospectively noted. Neurological impairment was assessed clinically with Mathew Stroke Scale [9] (Normal examination = 100, death =0) both on admission and on discharge. Routine blood tests, ECG and baseline CT scan were done in all patients on hospital arrival.

Blood was drawn on admission for all the biochemical parameters we considered for statistical analysis to avoid change in serum uric acid level due to subsequent administration of drug or intravenous fluid. We did not consider serum lipid profile in our analysis, because correct testing of this required at least 8 hours fasting. Beside these, other biochemical testing and imaging study were done as per requirement of individual patient. The duration of study in individual patient was determined by either in-hospital mortality or discharge from hospital.

CT scan was done with Siemens Souratom DR scanner. Contrast was not given routinely. On CT scan, lesions less than 5mm in size or confined to two or less contiguous slices were considered as small, infarcts involving at least one complete arterial territory were considered as large and all others were taken as medium size infarcts.[10]

The following confounding and predictive factors were considered in analysis: Age, sex, stroke severity on admission, diabetes, atrial fibrillation, tobacco and alcohol intake, hypertension, ischaemic heart disease, random blood sugar at admission, hemoglobin percent, serum urea, creatinine, sodium, potassium and size of lesion as small medium and large infarct.

Statistical analysis

Outcome of stroke patients was measured at discharge by Mathew Stroke Scale. Outcome was

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

dichotomized as poor (Mathew score >/= 75) and good (Mathew score < 75). The effect of uric acid in stroke outcome in presence of other confounding factor was assessed by logistic regression with the help of Medcalc 11 statistical software. The level of statistical significance was set at $p < 0.05$.

Results

We studied 193 patients with a slight male preponderance (Female: Male =1:1.3), age range was from 40 years to 86 years (mean = 62.37±10.81). Among established risk factors, we found hypertension (54.92%) as most common, next came diabetes (26.42%), tobacco intake (24.35%), and ischaemic heart disease (21.24%). 10.36% patients were alcoholic and atrial fibrillation was found at admission in 8.29% of patients. In 30 patients (15.54%), the size of infarct were large, involving whole arterial territory, but most of our patients (60.63%) had medium size infarctions.

A good outcome at hospital discharge (Mathew Score >75) was seen in 103 patients (53.37%) and poor outcome in 90 (46.63%) patients. The multivariate logistic analysis of factors obtained on admission revealed higher serum uric acid level is associated with good clinical outcome (OR = 2.20, 95% CI = 1.55 to 3.13, p<0.0001).

Other factors found to be predictors of good outcome (shown in table 1) are higher Mathew Score at admission (OR =1.10, 95% CI = 1.06 to 1.14, p<0.0001) and female sex (OR = 4.90, 95% CI = 1.44 to 16.63, p = 0.01).

Table 1 Predictors of good outcome

Variables	OR	95% CI	p value
Higher uric acid level	2.20	1.55 to 3.13	<0.0001
Higher Mathew Score	1.10	1.06 to 1.14	<0.0001
Female sex	4.90	1.44 to 16.63	=0.01

Factors associated with poor outcome (shown in table 2) were large infarct size (OR = 0.10, 95% CI = 0.02 to 0.63, p = 0.01), higher serum urea level (OR = 0.95, CI = 0.90 to 0.99, p = 0.02) and presence of atrial fibrillation (OR = 0.06, CI = 0.01 to 0.56, p = 0.01).

Table 2 Predictors of poor outcome

Variables	OR	95% CI	p value
Large infarct size	0.10	0.02 to 0.63	= 0.01
Higher urea level	0.95	0.90 to 0.99	= 0.02
Atrial fibrillation	0.0637	0.01 to 0.56	=0.01

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

Discussion:

With the advancement of modern medicine and socioeconomic change, human disease epidemiology is also changing. The major causes of death and disability have shifted from infectious disease and malnutrition to cardiovascular diseases. After ischaemic heart disease and all cancers, stroke is the third most common cause of death worldwide. Three quarter of them occur in developing countries. (11) Beside high mortality, it is the most important cause of severe disability in adult and each year millions of stroke survivors have to adapt to life with restrictions in activities of daily living. As the longevity of the population increases, the overall frequency of stroke also increases. What actually dictates the functional recovery in the setting of stroke is still an area of debate. Sometimes, even patients with most severe stroke experience a remarkably good functional recovery. Knowledge of factors influencing good functional outcome is essential for more individualized treatment, counseling of patients and relatives, and eventually also in formulation of new therapeutic strategy.

Knowledge regarding the pathophysiology of atherosclerosis and about the infarcted brain tissue is increasing day by day. In focal cerebral ischaemia, tissue death occurs via necrotic as well as apoptotic pathway. Ischaemia produces necrosis by starving neurons of glucose, which in turn results in failure of mitochondria to produce ATP. Ischemia also promotes the conversion of xanthine dehydrogenase (XDH) to xanthine oxidase (XO), as the likely result of increased intracellular calcium, and activation of proteases. (12,13) Though XDH activity does not produce reactive oxygen species, the XO reaction is a major source of free radicals during ischemia and reperfusion injury.(14) Free radicals are produced by membrane lipid degradation and mitochondrial dysfunction. Free radicals cause catalytic destruction of membranes and are likely to damage other vital functions of cell. Cells then swell, a process called cellular or cytotoxic edema. Lesser degree of ischemia, as seen within the ischemic penumbra, favors apoptotic cellular death which causes cells to die days to weeks later.

Assuming the importance of oxidative stress in patients with brain ischemia, antioxidant property of uric acid (15) is recently being evaluated in ischemic stroke. Uric acid is the final breakdown product of purine metabolism in human. The absolute plasma concentration of uric acid is almost 10-fold higher than other antioxidants, such as vitamin C and vitamin E.(16) Moreover, uric acid has much higher antioxidant capacity.(17) Urate also mediates radical oxidations, (18) so it might have role to play in oxidative stress related conditions. (18,19) Many experimental studies showed that uric acid can have a neuroprotective effect. Yu et al found uric acid as protector of neurons against excitotoxic and metabolic insult in cell culture and against focal ischaemic brain injury.(8) In their study, uric acid protected cultured rat hippocampal neurons against cell death induced by glutamate, and treated neurons suppressed oxyradical accumulation, stabilized calcium homeostasis, and preserved mitochondrial functions. Romans et al reported that urate exerts additive neuroprotection to the benefits of recombinant tissue plasminogen activator in a rat model of thromboembolic stroke. (20) Clinical studies are also coming up with similar conclusions. Chamorro et al concluded that there is a 12% increase in the odds of good clinical outcome for each milligram per deciliter increase of serum uric acid in ischemic stroke patients. (7) Scott et al found uric acid to protect against secondary damage after spinal cord

injury by reducing tissue damage, nitrotyrosine formation, lipid peroxidation, and neutrophil invasion. [21]

Our study gives further support to this protective notion of uric acid in acute ischaemic stroke. Along with elevated uric acid, lesser degree of neurological impairment at admission and female sex were associated with good clinical outcome.In clinical practice, neuroprotection is largely unsuccessful so far. [22] With the emerging evidence it is clear that urate is a potential candidate for further research in this perspective. In a recent work, Chamorro et al demonstrated beneficial effect of administering uric acid in brain ischaemia. [23] Detection as well as alteration of serum uric acid level by therapeutic measures is rather easy and possible in even a compromised health care system. Being a disabling disease, stroke has got a substantial social cost. So, treatment that has even a moderate overall benefit may prove to be important.So we feel further studies are required to come to a definite conclusion regarding prognostic significance of serum urate in ischaemic stroke. Thus a substantial improvement in outcome of such a devastating disease might be provided by rather a simple and inexpensive measure.

References

1. Ropper AH, Brown RH. Adams and Victor's principles of neurology. 8th Edn. USA. Mc Grow-Hill Companies, Inc. 2005; p – 660
2. Lehto S, Niskanen L, Ronnemaa T, Laakso M. Serum uric acid is a strong predictor of stroke in patients with non-insulin-dependent Diabetes Mellitus. *Ann epiodemiol.* 1996; 6: 331-340.
3. Verdecchia P, Schillaci G, Reboldi GP, Santeusanio F, Porcellati C, Brunetti P. Relation between serum uric acid and risk of cardiovascular disease in essential hypertension: The PIUMA study stroke. 1991; 22:1548 – 1553.
4. Freedman DS, Willamson DF, Gunter EW, Byers T. Relation of serum uric acid to mortality and ischaemic heart disease. *Am J Epidemiol* . 1995; 141, 637 – 644.
5. Mazza A, Pessina AC, Pavei A, Scarpa R, Kikhonoff V, Casiglia E. Predictor of stroke mortality in elderly people from the general population. The Cardiovascular Study in the Elderly. Eur J Epidemiol. 2001; 17: 1097 -1104.
6. Fang J, Alderman MH. Serum Uric Acid and Cardiovascular mortality: The NHANES I epidemiologic follow up study, 1971 to 1992: National Health and Nutrition Examination Survey. JAMA. 2000; 283: 2404 – 2410.
7. Chamorro A, Obach V, Cevera A, Revilla M, Deulofeu R, Aponte JH. Prognostic significance of uric acid serum concentration in patients with acute ischaemic stroke. *Stroke* 2002; 33: 1048 -1052.
8. Yu ZF, Bruce-keller AJ, Goodman Y, Mattson MP. Uric acid protects neurons against focal ischaemic brain injury in vivo. *J Neurosci Res*. 1998: 53; 613 -625.
9. Mathew NT, Meyer JS, Rivera JM, Charney JZ, Hartman A. Double-blind evaluation of glycerol therapy in acute cerebral infarction. *Lancet.* 1972; 2: 1327–1329.

10. Candelise L, Landi G, Orazio EN, Boccardi E. Prognostic significance of hyperglycaemia in acute stroke. Arch Neurol 1985;42:661-3.
11. Murrey CJL, Lopez AD. Mortality by cause for eight regions of world: Global burden of disease study. *Lancet* 1997;349:1269-76.
12. Uemura Y, Miller JM, Matson WR, Beal MF. Neurochemical analysis of focal ischemia in rats. *Stroke.* 1991; 22: 1548–1553.
13. Engerson TD, McKelvey G, Rhyne DB, Boggio EB, Synder SJ, Jones HP. Conversion of xanthine dehydrogenase to oxidase in ischemic rat tissues. *J Clin Invest.* 1987; 79: 1564–1570.
14. McCord JM. Oxygen-derived free radicals in postischemic tissue injury. *N Engl J Med.* 1985; 312: 159–163.
15. Matsushita S, Ibuki F, Aoki A. Chemical reactivity of the nucleic acid bases. I. Antioxidative ability of the nucleic acid and their related substances on the oxidation of unsaturated fatty acid. Arch Biochem Biophys. 1963; 102: 446 -451.
16. Becker BF. Towards the physiological function of uric acid. Free Radicals Biol Med. 1993; 14: 615 – 631.
17. Buettner GR. The pecking order of free radicals and antioxidants: lipid peroxidation, α-tocopherol, and ascorbate. *Arch Biochem Biophys.* 1993; 300: 535–543.
18. Proctor P. Electron - Transfer Factors in psychosis and dyskinesia. Physiol Chem Phys. 1972; 4: 349 -360.
19. Proctor PH. Free radical and Human Diseases. In: CRC Handbook of Free Radicals and Antioxidants in Biomedicine. Vol. 1. Boca Raton. Fla : CRC Press, Inc: 1989; 209 – 221.
20. Romanos E, Planas AM, Amaro S, Chamorro A. Uric acid reduces brain damage and improves the benefits of rt-PA in a rat model of thromboembolic stroke. Journal of Cerebral Flow and Metabolism. 2007; 27: 14 – 20.
21. Scott GS, Cuzzocrea S, Genovese T, Koprowski H, Hooper DC. Uric acid protects against secondary damages after spinal cord injury. Proc Natl Acad Sci USA. 2005; 102: 3483 – 3488.
22. Cheng YD, Al-khoury L, Zivin JA. Neuroprotection for ishǽmic stroke: Two decades of success and failure. Neuro Report 1. 2004; 1: 36 – 45.
23. Chamorro A, Planas AM, Muner DS, Deulofeu R. Uric acid administration for neuroprotection in patients with acute brain ishǽmia. Med Hypothesis. 2004; 62: 173 – 176.