

Serum Uric Acid as an Independent Predictor of Recurrence in Ischemic Stroke Patients

Akbar Hamzei Moghaddam¹, Farhad Iranmanesh², Mohamah Ali Shafa², Reza Hamzei Moghaddam², Hadi Eslami²

¹ Neuroscience Research Center, Kerman University of Medical Sciences, Iran.

² Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran

ABSTRACT

Background and Purpose: The relationship between uric acid and stroke recurrence is ambiguous. Some studies have explored this relationship in acute ischemic stroke but had different results. We evaluated the association of admission uric acid level with risk of stroke recurrence in patients with ischemic stroke.

Methods: We studied ischemic stroke patients presenting to our hospital with Magnetic Resonance Imaging-confirmed acute ischemic stroke. Blood samples were drawn within 24 h of admission for uric acid concentration. Information on age, prior hypertension, hyperlipidemia, diabetes, ischemic heart disease, and smoking status was collected. We assessed the relationship between uric acid level and stroke recurrence at 90 days after stroke onset.

Results: Two hundred patients were studied. Twenty-seven patients suffered from a recurrence event. Hyperuricemia was found in 48 (24%) patients. Mean serum uric acid level in patients with recurrence was 6.6 ± 1.3 and in patients without recurrence was 5.2 ± 1.5 mg/dl. On multiple logistic regression analysis, the independent relationship between higher uric acid level levels and recurrence was confirmed (odds ratio, 1.29; 95% confidence interval, 1.12-1.73; $p=0.01$).

Conclusion: Elevated uric acid concentration is significantly and independently associated with increased risk of stroke recurrence in ischemic stroke patients.

Keywords: Uric acid; Stroke; Recurrence

ICNSJ 2015; 2 (3) :101-104

www.journals.sbmu.ac.ir/neuroscience

Correspondence to: Mohamah Ali Shafa, MD, Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran; Tel: +98(913)3970831; E- mail: fpp_farhad@yahoo.com

Received: July, 2015

Accepted: September, 2015

INTRODUCTION

Over the last few years, considerable progress has been made in identifying modifiable cerebrovascular risk factors. Serum uric acid (UA) has traditionally been thought of as an inert byproduct of the catabolism of ingested and endogenous nucleoproteins and purines¹. Several large studies have identified an elevated serum UA concentration as a predictor of cardiovascular events such as myocardial infarction². The relationship between serum UA and stroke is not clear. Some epidemiologic studies have reported a relationship between serum UA and poor prognosis in patients with stroke for example,

a retrospective analysis of hospitalization data of 2495 patients in Glasgow suggested that higher serum UA on admission predicted poor outcome and higher vascular event rate following ischemic stroke. Kim et al³ conducted a systematic review and meta-analysis of 16 prospective cohort studies including 238449 adults to assess the association between hyperuricemia and risk of stroke incidence and mortality. They found that hyperuricemia may modestly but statically significant increase the risk of both stroke incidence and mortality⁴. Despite these clinical and epidemiological evidence, some authorities do not consider elevated uric acid to be a

true cerebrovascular risk factor. For example, in some experimental models of acute ischemic stroke, UA levels are associated with better functional recovery because of its synergistic effect with alteplase⁵. Also, results from a recent meta-analysis suggested that serum UA level has a protective effect on neurological outcome after acute ischemic stroke⁶. Therefore the role of uric acid as a risk factor for acute stroke is controversial, so in this study we decided to evaluate the relationship between serum UA level and stroke recurrence at 90 days after stroke onset.

MATERIALS AND METHODS

A total of 200 patients, who were admitted in Shafa Hospital (Kerman, Iran) were evaluated in a cohort study. The patients were recruited from March 2013 to September 2014 with acute ischemic stroke. Blood samples for uric acid were obtained from all patients who were admitted for the first time with a clinical suspicion of stroke. Subsequently, all patients underwent brain Computed Tomography scan and brain Magnetic Resonance Imaging (MRI) (T1, T2 and DWI), then hemorrhagic strokes were excluded from the study. Stroke patients with a known or possible cardiac source of emboli (atrial fibrillation, heart valve disease, patients receiving anticoagulant treatment) were also excluded. Transcranial and carotid Doppler ultrasound, electrocardiography, transthoracic echocardiography (and if necessary transesophageal) and a visit by a cardiologist were performed to rule out cases of embolism. Patients with history of previous stroke, blood dyscrasias, active infections, neoplasm, gout, renal or liver disease, thyroid dysfunction, chronic obstructive pulmonary disease, and chronic inflammatory bowel disease and alcohol consumption were excluded. Other exclusion criteria were history of consuming medication that affects level of uric acid (corticosteroids, colchicine and allopurinol) as well as strokes that more than 24 hours passed from their onset. Uric acid level was measured with photometry using the diagnostic kit for quantification of uric acid prepared by Pars Azmoon Company. Blood samples were drawn within 24 h of admission and hyperuricemia was defined as a serum UA concentration > 7 mg/dl for men and > 5.7 for women (1). Data were collected with regards

to patient demography, medical history, initial National Institutes of Health Stroke Scale (NIHSS) score and risk factors for stroke. The record of risk factors included the following: arterial hypertension (treated or systolic blood pressure > 160 mmHg or diastolic > 90 mmHg in repeated measures), diabetes (treated or fasting glucose ≥ 126 mg/dl at), dyslipidemia (treated or ≥ 240 mg/dl), coronary heart disease (history of angina, myocardial infarction, or congestive heart failure), smoking (> 5 cigarettes per day), alcohol intake (> 2 drinks per day)⁷. The above information was then recorded prospectively into a computerized database. The patients followed for 3 months and recurrence was defined as a new cerebrovascular event that was confirmed by brain MRI (T1, T2 and DWI).

T test were used for analysis. Also logistic regression analyses were used to determine the association between UA status and recurrence at three months. All cerebrovascular risk factors were included in the multivariate analysis because they were potential prognostic factors. The significance level was set at P<0.05 for all statistical analyses. The informed consent was obtained from all patients and the study protocol was approved by the Ethics Committee of Kerman Medical University, Kerman, Iran. This study did not have any conflict of interest and was not supported by any drug company.

RESULTS

Two hundred acute ischemic stroke patients were studied of whom 105 (53%) were female and 95 (47%) were male. Mean age of the patients was 64.8 (SD±11.5) years. Twenty-seven (13.5%) patients suffered a recurrence event (15 male and 12 female). Hyperuricemia was found in 48 (24%) patients. Mean NIHSS in hyperuricemia patients was 24.25 (SD±6.5) and in non hyperuricemia patients was 25.45 (SD±5.8). The difference was not statistically significant. Mean serum uric acid level in patients with recurrence was 6.6±1.3 and in patients without recurrence was 5.2±1.5 mg/dl. In patients with recurrence, 15 patients had hyperuricemia and in patients without recurrence, 33 patients had hyperuricemia (Table 1). There was a

Table 1. Frequency of stroke recurrence according to serum uric acid level.

Hyperuricemia	Recurrence		
	Yes	No	Total
Yes	15 (55.6%)	33 (19.1%)	48 (24%)
No	12 (44.4%)	140 (80.9%)	152 (76%)
Total	27 (100%)	173 (100%)	200 (100%)

Table 2. Frequency of stroke risk factors according to uric acid level.

Uric Acid	Risk factors									
	Hypertension		Diabetes Mellitus		Hyperlipidemia		Ischemic Heart Disease		Smoking	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Normal	71 (70.3%)	81 (81.8%)	45 (65.2%)	107 (81.7%)	65 (78.3%)	87 (74.4%)	54 (62.1%)	98 (86.7%)	42 (93.3%)	110 (71%)
Abnormal	30 (29.7%)	18 (18.2%)	24 (34.8%)	24 (18.3%)	18 (21.7%)	30 (25.6%)	33 (37.9)	15 (13.3%)	3 (6.7%)	45 (29%)
P-value	0.54		0.16		0.32		0.001		0.017	

statistically significant difference between hyperuricemia and recurrence in ischemic stroke patients. Results of the multivariate logistic regression analyses revealed that UA (odds ratio, 1.29; 95% confidence interval, 1.12-1.73; p=0.01), could remain in the model as significant risk factor. Frequency of stroke risk factors according to uric acid level is shown in Table 2.

CONCLUSION

In this cohort study of 200 ischemic stroke patients, serum uric acid was significantly associated with risk of stroke recurrence. On the other hand, serum UA measured within the first 24 hours after hospital admission for acute ischemic stroke is an independent marker of recurrence and can predict future cerebrovascular events. This relationship holds true even after correction for the presence of established cerebrovascular risk factors such as hypertension, diabetes mellitus, and hyperlipidemia and smoking.

The association between serum uric acid and ischemic stroke is in accordance with previous studies⁸⁻¹¹. Similarly to our study Weir et al found that, independently of other prognostic factors, higher serum UA levels predicted poor outcome and higher vascular event rates³. Newman et al in another study found, elevated UA concentration is significantly and independently associated with increased risk of recurrent stroke in diabetic stroke patients¹². To assess the hypothesis that UA is associated with stroke outcomes, a prospective follow-up study was performed in a cohort of Asian patients with ischemic stroke by Seet et al. Vascular outcome was defined as a composite of recurrent stroke, myocardial infarction or vascular death during the study period. A U-shaped relationship between UA quartiles and poor functional outcomes was demonstrated¹³. Also, many studies have found elevated serum UA indicative of a poor prognosis in vascular event¹⁴. Wu et al evaluated the relationship between uric acid levels and outcomes (modified Rankin scale [mRS] > 2, all-cause death, vascular events, stroke recurrent) at 14 days, 90 days, and 1 year after stroke onset. They found lower serum uric acid levels independently

predicted poor functional outcomes (mRS >2) at 1 year after ischemic stroke onset. Also, lower serum uric acid levels were independently correlated with vascular events in the first year in ischemic stroke patients¹⁵. Higgins et al performed a randomized, double-blind, placebo-controlled study, examining the effect of 1-year treatment with allopurinol (300 mg daily), on change in carotid intima-media thickness (CIMT (progression. Allopurinol reduced CIMT progression at 1 year compared with placebo in patients with recent ischemic stroke and TIA¹⁶.

Quite opposite to our findings and above-mentioned studied, it has been claimed that treatment with uric acid in combination with thrombolysis would be of benefit to patients suffering from acute stroke¹⁷. Wang et al in a systematic review and meta-analysis showed serum uric acid level has a protective effect on neurological outcome after acute ischemic stroke. High uric acid level at the onset is a biomarker of better prognosis in patients with acute ischemic stroke⁶. Li et al in another meta-analysis suggested UA as a type of neuroprotective agents for the ischemic stroke¹.

It is a matter of controversy whether serum uric acid is an independent predictor of mortality; morbidity and recurrence in patients with ischemic stroke Apart from the interactions between uric acid and other risk factors, there are several plausible mechanisms whereby uric acid may directly affect atherogenesis or the clinical course of cerebrovascular disease. It has been suggested that serum uric acid may have harmful effects on platelet function and cause endothelial dysfunction^{18,19}. Stimulation of the inflammatory pathway by UA is another mechanism²⁰. Also, Uric acid may stimulate vascular smooth cell proliferation, and reduce vascular nitric oxide production. The action of xanthine oxidase leads to generation of superoxide anions This could mean that xantine oxidase activity is the key risk factor, with uric acid just an epiphenomenon²¹. Our study has some limitations. The main limitation was the short-term follow-up period after stroke. Another limitation was lack of evaluation of association between serum UA and motility and morbidity.

CONCLUSION

In conclusion, according to our findings, elevated UA concentration is significantly and independently associated with increased risk of stroke recurrence in ischemic stroke patients. However, if identified as an etiological agent in the pathogenesis of vascular disease, hyperuricemia could be targeted therapeutically in the same way that we now routinely treat other cerebrovascular risk factors such as hypertension.

ACKNOWLEDGMENTS

Authors thank the Neurology Research Center of Kerman for supporting this project. This research was funded by Kerman University of Medical Sciences.

CONFLICT OF INTEREST

None declared.

REFERENCES

- Li R, Huang C, Chen J, Guo Y, Tan S. The role of uric acid as a potential neuroprotectant in acute ischemic stroke: a review of literature. *Neurol Sci*. 2015;36(7):1097-103.
- Storhaug HM, Norvik JV, Eriksen BO, Løchen ML, Zykova S, et al. Uric acid is a risk factor for ischemic stroke and all-cause mortality in the general population: a gender specific analysis from The Tromsø Study. *BMC Cardiovasc Disord*. 2013;11;13:115.
- Weir CJ, Muir SW, Walters MR, Lees KR. Serum Urate as an independent predictor of poor outcome and future vascular events after acute ischemic stroke. *Stroke*. 2003;34(8):1951-1956
- Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and risk of stroke: a systematic review and meta-analysis. *Arthritis Rheum*. 2009 Jul 5;61(7):885-92.
- Llull L, Laredo C, Renú A, Pérez B, Vila E, Obach V, et al. Uric Acid Therapy Improves Clinical Outcome in Women With Acute Ischemic Stroke. *Stroke*. 2015 Aug;46(8):2162-7.
- Wang Z, Lin Y, Liu Y, Chen Y, Wang B, Li C, et al. Serum Uric Acid Levels and Outcomes After Acute Ischemic Stroke. *Mol Neurobiol*. 2015 Mar 7.
- Iranmanesh F, Sheykhosslami NZ, Gadari F, Ahmady J. Acute ischemic non-embolic stroke and serum level of uric acid. *Iran J Neurol*. 2012;11(1):1-5.
- Holme I, Aastveit AH, Hammar N, Jungner I, Walldius G. Uric acid and risk of myocardial infarction, stroke and congestive heart failure in 417734 men and women in the Apolipoprotein Mortality RISK study (AMORIS). *J Intern Med* 2009;266(6):558-570.
- Huang J, Hu D, Wang Y, Zhang D, Qu Y. Dose-response relationship of serum uric acid levels with risk of stroke mortality. *Atherosclerosis*. 2014;234(1):1-3.
- Mayer FJ, Mannhalter C, Minar E, Schillinger M, Chavakis T, Siegert G, et al. The impact of uric acid on long-term mortality in patients with asymptomatic carotid atherosclerotic disease. *J Stroke Cerebrovasc Dis*. 2015;24(2):354-61.
- Mehrpour M, Khuzan M, Najimi N, Motamed MR, Fereshtehnejad SM. Serum uric acid level in acute stroke patients. *Med J Islam Repub Iran*. 2012;26(2):66-72.
- Newman EJ, Rahman FS, Lees KR, Weir CJ, Walters MR. Elevated serum urate concentration independently predicts poor outcome following stroke in patients with diabetes. *Diabetes Metab Res Rev*. 2006; 22(1):79-82.
- Seet RC, Kasiman K, Gruber J, Tang SY, Wong MC, Chang HM, et al. Is uric acid protective or deleterious in acute ischemic stroke? A prospective cohort study. *Atherosclerosis*. 2010; 209(1):215-9.
- Khalil MI, Islam MJ, Ullah MA, Khan RK, Munira S, Haque MA, et al. Association of serum uric acid with ischemic stroke. *Mymensingh Med J*. 2013; 22(2):325-30.
- Wu H, Jia Q, Liu G, Liu L, Pu Y, Zhao X, et al. Decreased uric acid levels correlate with poor outcomes in acute ischemic stroke patients, but not in cerebral hemorrhage patients. *J Stroke Cerebrovasc Dis*. 2014 Mar;23(3):469-75.
- Higgins P, Walters MR, Murray HM, McArthur K, McConnachie A, Lees KR. Allopurinol reduces brachial and central blood pressure and carotid intima-media thickness progression after ischaemic stroke and transient ischaemic attack: a randomised controlled trial. *Heart*. 2014 ;100(14):1085-92.
- Amaro S, Urrea X, Gomez-Choco M, Obach V, Cervera A, Vargas M, et al. Uric acid levels are relevant in patients with stroke treated with thrombolysis. *Stroke*. 2011;13:S28–S32.
- Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. *J Am Soc Nephrol*. 2005;13:3553–3562.
- Chamorro A, Amaro S, Castellanos M, Segura T, Arenillas J, Martí-Fàbregas J, et al. Safety and efficacy of uric acid in patients with acute stroke (URICO-ICTUS): a randomised, double-blind phase 2b/3 trial. *Lancet Neurol*. 2014;13(5):453-60.
- Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T, et al. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. *Hypertension*. 2003 Jun;41(6):1287-93.
- Berry C, Hamilton CA, Brosnan MJ, Magill FG, Berg GA, McMurray JJ, et al. Investigation into the sources of superoxide in human blood vessels: Angiotensin II increases superoxide production in human internal mammary arteries. *Circulation*. 2000;9;101(18):2206-12.