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Acute ischemic non-embolic stroke and serum level of uric acid

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Keywords
Ischemic Stroke, Uric Acid, Risk Factor

Abstract

Background: Impact of high level of uric acid on stroke is still controversial. We conducted this study to investigate the relationship between acute ischemic non-embolic stroke and serum levels of uric acid.

Methods: This was a case-control study on patients with acute ischemic non-embolic stroke in Rafsanjan, Iran. The control group consisted of normal persons who were similar to the case group in terms of age and gender. Serum level of uric acid in the first 24 hours of admission was measured with photometry method.

Results: In a total of 130 patients (59 mens), hyperuricemia was seen in 13.0% of subjects in the control group and 10.7% of subjects in the case group. Nine patients in case group and 7 patients in control group with hyperuricemia were women. No significant relationship was found between acute ischemic non-embolic stroke and serum level of uric acid.

Conclusion: There was no relationship between uric acid and acute ischemic non-embolic stroke.

Introduction

Stroke is one of the most common and the most fatal and debilitating neurologic disease. Numerous risk factors are involved in the development of stroke, such as hypertension, cigarette smoking, hyperlipidemia and diabetes.[1] Recent studies indicate that there may be other factors influencing the development or course of the disease like serum level of uric acid. In a study on American population with acute stroke, those with higher serum levels of uric acid were observed to be more debilitated with more recurrences and cardiovascular accidents.[2] A 3-month follow-up of stroke patients in England indicated greater mortality for those who had higher uric acid levels.[3] A study in Greece on 163 patients suffering from non-embolic ischemic stroke indicated more complications and greater risk of recurrence for those with higher uric acid levels.[4] Another study in USA showed that hyperuricemia increased the risk for both cerebral and cardiac vascular accidents.[5] One study recommended lowering uric acid levels in order to prevent these accidents.[6] A meta-analysis showed hyperuricemia may modestly increase the risks of both stroke incidence and mortality.[7] Another study in China showed hyperuricemia in females is an independent risk factor for plaque formation in the bulb of common carotid.[8] In addition, one study in Baltimore showed even high normal uric acid is associated with increased risk of

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mild cognitive dysfunction in elderly adults.[9] In contrast, some studies even indicated a neuroprotective role for uric acid which attenuates the symptoms through its antioxidant properties.[10] A Spanish study on animal models reported that administration of uric acid following stroke accompanies lower mortality and complications.[9] Another study in England indicated that higher uric acid levels in patients with stroke are associated with less intense lesions.[10] High uric acid has even been reported to be associated with better clinical conditions.[11] In summery, some studies have found that uric acid predicts the development of stroke, whereas others have failed to identify uric acid as a significant and independent risk factor after controlling for other atherosclerotic risk factors.[12-14] Considering this controversy, we conducted this study to evaluate the serum level of uric acid in patients with acute ischemic non-embolic stroke in Rafsanjan, Iran.

Materials and Methods

This was a case-control study on 130 patients with acute ischemic non-embolic stroke referring to Ali-Ibn-Abitaleb Hospital in Rafsanjan, Iran, from August 2008 to June 2009. Sampling was performed using convenience method. 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 MRI and cases of hemorrhage were excluded from the study. If necessary, CT scan or contrast materials were used for confirming diagnosis. Then, transcranial and carotid Doppler ultrasound, electrocardiography, echocardiography and a visit by a cardiologist were performed to rule out cases of embolism.

Subjects with a history of vascular disease i.e., previous stroke, angina, myocardial infarction, revascularizations, and peripheral artery disease, blood dyscrasias, active infections, neoplasia, gout, renal or liver disease, thyroid dysfunction, chronic obstructive pulmonary disease, chronic inflammatory bowel disease and excessive alcohol consumption were excluded. Stroke patients and controls with a known or possible cardiac source of emboli (atrial fibrillation, heart valve disease, patients receiving anticoagulant treatment) were also excluded. None of the participants was receiving specific lipid-lowering treatment (i.e. a statin or a fibrate). 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 initiatiation. Blood samples were taken of normal subjects who were similar to the case group in terms of age and gender.

Uric acid level was measured with photometry using the diagnostic kit for quantification of uric acid prepared by ParsAzmoon Company. Hyperuricemia was defined as a serum urate concentration > 7 mg/dl.[15] 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 ≥ 110 mg/dL at least in 2 separate analyses), 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).[11]

Data were analyzed with SPSS software version 16, using the chi-square test. The informed consent was obtained from all patients and the study protocol was approved by the Institutional Ethics Committee. This study did not have any conflict of interest and was not supported by any drug company.

Results

Of total, 45.4% of participants in both groups were men. The mean age in case group was 72.7 ± 8.6 years for women and 65.2 ± 9.2 years for men. In control group, it was 71.6 ± 7.4 years for women and 64.5 ± 8.6 years for men. The age ranged from 42 to 101 years in the two groups. In this study, 13.0% in the case group and 10.7% in the control group had hyperuricemia. No significant relationship was found between acute ischemic non-embolic stroke and high serum level of uric acid. Nine patients in case group and 7 patients in control group with hyperuricemia were women. Moreover, no significant relationship was observed between gender and hyperuricemia in patients with stroke. Moreover, no significant relationship was observed between stroke risk factors and hyperuricemia. The frequency of stroke risk factors in patients with and without hyperuricemia is shown in table 1.

Table 1. The frequency of stroke risk factors in patients with and without hyperuricemia

risk factor	Normal uric acid	Hyperuricemia
Arterial hypertension	45	4
Diabetes	33	3
Dyslipidemia	27	3
Coronary heart disease	31	4
Smoking	5	1
Alcohol intake	1	0

Discussion

Stroke is particularly important due to its high risk of recurrence.[1] Despite many years of study on this disease and identification of its major risk factors and effort aimed at controlling them, many studies are still

being conducted on its etiology and its other associated factors.[1] One such factor, which has been the subject of controversy from long ago, is the blood level of uric acid. Preliminary studies indicated the role of serum level of uric acid in patients with myocardial infarction. Those studies indicated that elevated serum levels of uric acid increased the risk of mortality in patients with myocardial infarction and cardiac failure.[16] Subsequent studies demonstrated that elevated serum level of uric acid is associated with long-term mortality due to coronary heart disease and all causes mortality. Furthermore, elevated serum levels of uric acid were shown to increase the risk of stroke and recurrent infarction in patients suffering from myocardial infarction.[17-19] The findings of these studies and the fact that thrombotic stroke and myocardial infarction are similar in many risk factors and pathophysiology, have resulted in considerable attention paid recently to the role of uric acid in patients with stroke.

Our study found no significant relationship between high serum levels of uric acid and occurrence of thrombotic stroke. This finding means that hyperuricemia is not a risk factor of ischemic stroke. A prospective follow-up study also showed that there was no significant relationship between urate and vascular events.[20] Brouns et al. study showed that decreases in uric acid during the first week after onset of stroke correlates with more severe stroke, unfavorable stroke evolution and poor long-term outcome.[15] Some studies even indicated a neuroprotective role for uric acid.[21] Chamorro et al. showed that in patients with acute ischemic stroke, there is a 12% increase in the odds of good clinical outcome for each milligram per deciliter increase of serum uric acid. Furthermore, they showed that serum uric acid inversely correlates with early neurological impairment and final infarction size on computed tomography or magnetic resonance imaging.[11] Amaro et al. showed that the increased levels of uric acid are associated with better outcome in patients with stroke treated with reperfusion therapies.[22] The effects of raising circulating uric acid concentrations, by direct administration, have also been studied in vivo in a rat model of acute ischaemic stroke, involving transient occlusion of one middle cerebral artery for 2 hours. Administration of uric acid, prior to ischemia or during the subsequent reperfusion period, caused a significant reduction in infarct volume, and led to improved behavioral outcome. These findings suggest that early elevation of uric acid, during or shortly after acute ischaemic stroke, could confer significant protection against neurological deficit.[9,23]

Cerebral infarction initiates a complex cascade of metabolic events in the surrounding tissue, and free-radical-mediated oxidative damage plays a key role in the pathogenesis of cerebral ischemia. Free radical activity is characteristically increased in patients with any one of several major vascular risk factors, and is thought to play a key role in the early development of atherosclerosis. Uric acid is the most abundant aqueous antioxidant in humans, and contributes as much as two-thirds of all free radical scavenging capacity in plasma. It is particularly effective in quenching hydroxyl, superoxide and peroxynitrite radicals, and may serve a protective physiological role by preventing lipid peroxidation. In a variety of organs and vascular beds, local uric acid concentrations are increased during acute oxidative stress and ischemia, and the increased concentrations might be a compensatory mechanism that confers protection against increased free radical activity.[10,12,13] Despite these studies, Weir et al. study showed that elevated urate level predicted a lower chance of good 90-day outcome independently of stroke severity and other prognostic factors.[3] Moreover, Chen et al. study showed that hyperuricemia was an independent risk factor of mortality from all causes, total cardiovascular disease, and ischemic stroke in the Taiwanese general population, in high-risk groups, and potentially in low-risk groups.[24] A 12.5 year follow-up of hyperuricemic people in the United States observed higher risks of ischemic stroke and myocardial infarction for these people.[5] In addition, association between uric acid and acute ischaemic/non-embolic stroke was assessed in a population-based case-control study in Greece. Findings of this study showed that elevated uric acid is associated with an increased risk for acute ischaemic/non-embolic stroke in a strictly defined population of elderly individuals independently of concurrent metabolic derangements.[4] In a cross-sectional study in USA, the relationship between serum uric acid and aggregate volume of white matter hyperintense signals observed on proton density and T2-weighted brain MR images was examined in a community sample of 177 adults. They found that that mildly elevated serum uric acid is associated with increased burden of cerebral ischemic pathology, particularly in older adults.[25] The standard prevalence of hyperuricemia on baseline is 5.4%, being 7.7% in male and 3.9% in female. The standard incidence of carotid plaque is 45.3%, being 51.7% in male and 42.7% in female. Li et al. showed that the incidence of plaque in the bulb of common carotid arteries was the highest in patients with hyperuricemia.[8] Khan and colleagues also showed that elevated serum urate is associated with increased arterial stiffness in stroke survivors, independently of other risk factors.[26] Heo et al. in their study showed

that an increased level of uric acid may be a risk factor for the presence of silent brain infarction and serum uric acid level might be a good serum marker of underlying silent brain infarction or future stroke, especially in women.[27] Kim et al. conducted a meta-analysis of prospective cohort studies to determine the association between hyperuricemia and the risk of stroke. He reported that subgroup analyses of studies adjusted for known risk factors such as age, hypertension, diabetes mellitus, and cholesterol still show that hyperuricemia was significantly associated with both stroke incidence and mortality.[7]

In this study we did not find any significant relation between hyperuricemia and age and stroke risk factors but Kodama et al. and Wu et al. showed that uric acid level is positively associated with the development of type 2 diabetes.[28,29] Guan and colleagues found that male patients with type 2 diabetic and stroke had significantly higher mean levels of serum uric acid than simple diabetic patients, but such patients in both genders all had lower HDL cholestrol levels.[30] It was shown that high urate levels were independent predictors of long-term risk of acute coronary syndrome in women who had stroke, but not in men.[31] Ouppatham et al. demonstrated a strong association of hypertension and uric acid.[32] The mechanism of cerebral injury in the context of high uric acid is still unknown. Some studies indicate that acute stroke is associated with changes in the level of tissue antioxidants, which may be the mechanism of action for uric acid.[2] Furthermore, recent experimental studies have shown that hyperuricemia is associated with endothelial dysfunction, elevated circulating levels of systemic inflammatory mediators (such as monocyte chemoattractant protein 1, NF-κB, interleukin-1β, interleukin-6 and tumor necrosis factor α) and vascular smooth muscle proliferation.[7] Other studies indicated that uric acid may exert its impact through intensification of hypertension, or chronic renal injury and the ensuing hypertension.[2] In this study, we exclude subjects with a history of vascular disease (previous stroke, angina, myocardial infarction, revascularizations and peripheral artery disease) and this selection may be affected our findings, because according to the published studies, hyperuricemia is more frequent in these patients and with this selection, we excluded some persons with hyperuricemia.

In conclusion, the role of uric acid in stroke is still controversial in many studies[12,14,33] and it appears that further studies are required to yield more reliable findings.

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References

1. Victor M, Ropper AH. *Adam's and Victor's principles of neurology*, Ed. 8th. McGraw-Hill Company, New York 2005:958-80.
2. Kanellis J, Johonson RJ. *Elevated uric acid and ischemic stroke*. Stroke. 2003; 34:1956-7.
3. Weir C J, Muir S W, Walters MR, et al. *Serum Urate as an Independent Predictor of Poor Outcome and Future Vascular Events after Acute stroke*. Stroke. 2003; 34:1951.
4. Milionis HJ, Kalantzi KJ, Goudevenos JA, et al. *Serum uric acid levels and risk for acute ischaemic non-embolic stroke in elderly subjects.* J Intern Med. 2005; 258:435-41.
5. Hozawa A, Folsom AR, Ibrahim H, et al. *Serum uric acid and risk of ischemic stroke: the ARIC Study*. Atherosclerosis. 2006; 187:401-7.
6. Muir S, Harrow C, Dawson J, et al. *Allopurinol use yields potentially beneficial effects on inflammatory indices in those with recent ischemic stroke; a randomised, double blind placebo controlled trial*. Stroke. 2008; 39:3303–7.
7. Kim SY, Guevara JP, Kim KM, et al. *Hyperuricemia and risk of stroke: A systematic review and meta-analysis.* Arthritis Rheum. 2009; 61:885–92.
8. Li Y, Zhao D, Liu J, et al. *The association between hyperuricemia and prevalence of carotid plaque.* Zhonghua Nei Ke Za Zhi. 2008; 47:906-9.
9. Romanos E, Planas AM, Amaro S, et al. *Uric acid reduces brain damage and improves the benefits of rt-PA in a rat model of thromboembolic stroke*. J Cereb Blood Flow Metab. 2007; 27:14-20.
10. Waring WS. *Uric acid: an important antioxidant in acute ischemic stroke.* QJM. 2002; 95:691-3.
11. Chamorro Á, Obach V, Cervera Á, et al. *Prognostic Significance of Uric Acid Serum Concentration in Patients With Acute Ischemic stroke*. Stroke. 2002; 33:1048.
12. Dimitroula HV, Hatzitolios AI, Karvounis HI. *The role of uric acid in stroke: the issue remains unresolved*. Neurologist. 2008; 14:238-42.
13. Proctor PH. *Uric Acid: Neuroprotective or Neurotoxic?* Stroke. 2008; 39:e88.
14. Dawson J, Quinn T, Lees K, et al. *The Continued Yin and Yang of Uric Acid.* Stroke. 2008; 39:e9.
15. Brouns R, Wauters A, Van De, Vijver G, et al. *Decrease in uric acid in acute ischemic stroke correlates with stroke severity, evolution and outcome.* Clin Chem Lab Med. 2010; 48:383-90.
16. Alderman M, Redfern JS. *Serum uric acid-a cardiovasular risk factor?* Ther Umsch. 2004; 61:547-5.
17. Puddu PE, Lanti M, Menotti A, et al. *Serum uric acid for short-term prediction of cardiovascular disease incidence in the Gubbio population Study.* Acta Cardiol. 2001; 56:243-51.
18. Conen D, Wietlisbach V, Bovet P, et al. *Prevalence of hyperuricemia and relation of serum uric acid with cardiovascular risk factors in a developing country*. BMC Public Health. 2004; 4:9.
19. Chien KL, Hsu HC, Sung FC, et al. *Hyperuricemia as a risk factor on cardiovascular events in Taiwan: The Chin-Shan Community Cardiovascular Cohort Study*. Atherosclerosis. 2005; 183:147-55.
20. Seet RC, Kasiman K, Gruber J, et al. *Is uric acid protective or deleterious in acute ischemic stroke? A prospective cohort study*. Atherosclerosis. 2010; 209:215-9.
21. Chamorro A, Planas AM, Muner DS, et al. *Uric acid administration for neuroprotection in patients with acute brain ischemia*. Med Hypotheses. 2004; 62:173-6.
22. Amaro S, Urra X, Gómez-Choco M, et al. *Uric acid levels are relevant in patients with stroke treated with thrombolysis.* Stroke. 2011; 42:S28-32.
23. Amaro S, Planas AM, Chamorro A. *Uric acid administration in patients with acute stroke: a novel approach to neuroprotection.* Expert Rev Neurother. 2008; 8:259-70.

24. Chen JH, Chuang SY, Chen HJ, et al. *Serum uric acid level as an independent risk factor for all-cause, cardiovascular, and ischemic stroke mortality: A Chinese cohort study.* Arthritis Rheum. 2009; 61:225–32.
25. Schretlen DJ, Inscore AB, Vannorsdall TD, et al. *Serum uric acid and brain ischemia in normal elderly adults.* Neurology. 2007; 69:1418-23.
26. Khan F, George J, Wong K, et al. *The association between serum urate levels and arterial stiffness/endothelial function in stroke survivors*. Atherosclerosis. 2008; 200:374-9.
27. Heo SH, Lee SH. *High levels of serum uric acid are associated with silent brain infarction.* J Neurol Sci. 2010; 297:6-10.
28. Kodama S, Saito K, Yachi Y, et al. *Association between serum uric acid and development of type 2 diabetes.* Diabetes Care. 2009; 32:1737-42.
29. Wu D, Liu H, Li SH. *Association of elevated uric acid with metabolic disorders and analysis of the risk factors of hyperuricemia in type 2 diabetes mellitus.* Nan Fang Yi Ke Da Xue Bao. 2011; 31:544-7.
30. Guan MP, Xue YM, Shen J, et al. *Serum uric acid in type 2 diabetic patients complicated by stroke.* Di Yi Jun Yi Da Xue Bao. 2002; 22:70-1.
31. Koton S, Howard SC, Warlow CP, et al. *Serum urate predicts long-term risk of acute coronary events in women after a transient ischaemic attack and stroke.* Cerebrovasc Dis. 2008; 26:517-24.
32. Ouppatham S, Bancha S, Choovichian P. *The relationship of hyperuricemia and blood pressure in the Thai army population.* Acta Cardiol. 2001; 56:243-51.
33. Edwards NL. *The role of hyperuricemia in vascular disorders.* Curr Opin Rheumatol. 2009; 21:132.