Biomedical Research 2018; 29 (9): 1856-1860 *ISSN 0970-938X*
www.biomedres.info

Serum uric acid as a predictor of cerebral injury outcome.

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Abstract

Background: The relationship between serum uric acid levels and the prognosis of acute stroke and Traumatic Brain Injury (TBI) is not clear. We investigated the value of serum uric acid levels for predicting poor neurological outcomes of acute stroke and traumatic brain injury.
Methods: 140 patients with acute ischemic stroke and Traumatic Brain Injury (TBI) were admitted to hospital and levels of serum uric acid (μmol/L) were determined from venous blood within 24 h. Clinical data was analysed by logistic regression and Receiver Operating Characteristic (ROC) curves. Patients were monitored after 180-day discharge and grouped as unfavorable or favorable based on Glasgow Outcome Scale (GOS) scores.
Results: There was a significant difference in serum uric acid (285 (range 196 to 362) *vs.* 185 (range 120 to 258), p=0.0001) between unfavorable and favorable groups, respectively. Uric acid was determined to be an independent predictor for poor neurological outcomes of acute stroke and TBI. After adjusting for age and Glasgow Coma Scale (GCS) score, the Odds Ratio (OR) for uric acid was 1.005 (95% CI: 1.0002-1.0101, p=0.039). The area under the ROC curve for serum uric acid was 0.714 (95% CI: 0.632-0.787). The optimal cut-off value of serum uric acid determined by the maximum Youden index was 265 μmol/L (sensitivity 55.4%, specificity 82.1%). ROC analysis showed that the positive predictive value of serum uric acid was 88.9% while the negative one was 41.6%.
Conclusions: The observations suggest that serum uric acid levels could be used as an independent predictor of poor outcome following acute stroke or TBI.

Keywords: Acute stroke, Traumatic brain injury, Uric acid, Prognosis.

Accepted on March 5, 2018

Introduction

More than 150 years ago, Garrod observed elevated uric acid levels in the blood of patients suffering from gout [1]. More recent years have seen a renewed interest in hyperuricemia and its association with clinical disorders other than gout, including hypertension, atherosclerosis, cardiovascular disease, and chronic kidney disease [2]. In addition, studies have revealed the impact of uric acid on cellular metabolism [3-6]. For example, uric acid can act as an endogenous antioxidant and a powerful scavenger of Reactive Oxygen Species (ROS) and hydroxyl radicals (OH) [7]. Paradoxically, uric acid has also been implicated as a pro-oxidant and pro-inflammatory factor. Recently, *in vivo* studies by Kono et al. demonstrated a key role of uric acid in the inflammatory response to necrotic cells in mice. Uric acid was not only released from intracellular stores of dead cells but was generated in large amounts in association with the degradation of nucleic acids [8]. In the area of cerebral injury, considerable debate has centered on whether uric acid acts as a neuroprotective anti-oxidant or a neurotoxic pro-oxidant [9-11].

In this study, we ascertained potential correlation of serum uric acid levels in patients with acute ischemic stroke and Traumatic Brain Injury (TBI) with results from a 180 d follow-up using the Glasgow Outcome Scale (GOS). The aim of the study was to investigate the potential value of serum uric acid as a prognostic indicator of favorable vs. unfavorable outcomes of cerebral injury.

Materials and Methods

Patient characteristics

The study group consisted of 140 patients with acute ischemic stroke or Traumatic Brain Injury (TBI) admitted to the

emergency department or intensive care unit of the Second Affiliated Hospital of Wenzhou Medical University between November 2012 and December 2014. Inclusion criteria were acute stroke or TBI within 24 h with Glasgow Coma Scale (GCS) score between 3 and 15. Exclusion criteria were age younger than 18 years, pregnancy, taking allopurinol and gout or autoimmune disease. Patient characteristics including age, gender, GCS and clinical factors possibly affecting levels of serum uric acid were recorded. Levels of serum uric acid were determined from venous blood samples within 24 h of admission using an Olympus AU2700 automatic biochemical analyzer. Patient follow-up after 180 d discharge was conducted by telephone and recorded. Patients were classified based on the following GOS scores: 1 (death); 2 (vegetative state-unable to interact with environment); 3 (severe disability-unable to live independently); 4 (moderate disability-capable of independent living but unable to return to work or school); 5 (complete recovery-able to return to work or school) [12]. Patients were then grouped as favorable (high GOS score of 4-5) or unfavorable (low GOS score of 1-3).

Ethical considerations

The study was carried out in accordance with the Helsinki Declaration and was approved by the ethical committee of the Second Affiliated Hospital of Wenzhou Medical University. Informed consent was waived because data used in the study had already been collected for clinical purposes. Additionally, the study in no way interfered with patient treatment and data were organized & maintained in such a way that individual patients could not be identified.

Statistical analyses

Categorical data are presented as frequency and percentage (%). Measurement data with normal or non-normal distribution are presented as mean ± SD or median M (Q 25, Q 75), respectively. Comparisons of continuous variables were performed using the Mann-Whitney U test or unpaired t-test. The chi-square test was applied to categorical variables. Independent prognosis predictors were determined by univariate and multivariate logistic regression. Odds Ratios (OR) and 95% Confidence Intervals (CI) were calculated. A Receiver Operating Characteristic (ROC) curve was plotted for predictors, and the Area Under the Curve (AUC) was used to assess the value of prognosis prediction. Stata version 12 (StataCorp, Texas, USA) and MedCalc version 11 (MedCalc Software, Mariakerke, Belgium) were used for statistical analyses and ROC curves, respectively. $p<0.05$ (two-tailed) was considered to be statistically significant.

Results

Clinical characteristics of the 140 patients are summarized in Table 1. 101 patients (72.1%) were grouped as unfavorable and exhibited older age, increased incidence of hypertension and diabetes, higher serum creatinine, higher c-reactive protein, and lower GCS scores relative to 39 patients (27.9%) grouped as favorable ($p<0.05$ for all characteristics). Moreover, there was a significant difference in serum uric acid levels ($p<0.001$) in unfavorable (285, range 196 to 362) *vs.* favorable group patients (185, range 120 to 258).

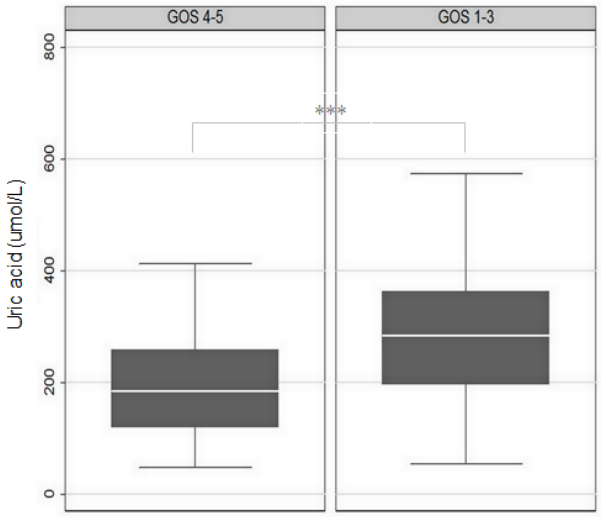

Figure 1. *Serum uric acid level (μmol/L) reflects GOS score. Box plots showing GOS scores of patients 180 d following discharge plotted against mean Serum Uric Acid (SUA) levels determined within 24 h of hospital admission. Higher SUA levels were detected among patients with the lowest GOS scores and grouped as unfavorable (see text). Lower SUA levels were seen in those patients with GOS scores of 4 and 5 that were grouped as favorable (GOS score 1, n=59; GOS score 2, n=3; GOS score 3, n=39; GOS score 4, n=6; GOS score 5, n=33). The data are expressed as mean ± Standard Deviation (SD). ***means p<0.001.*

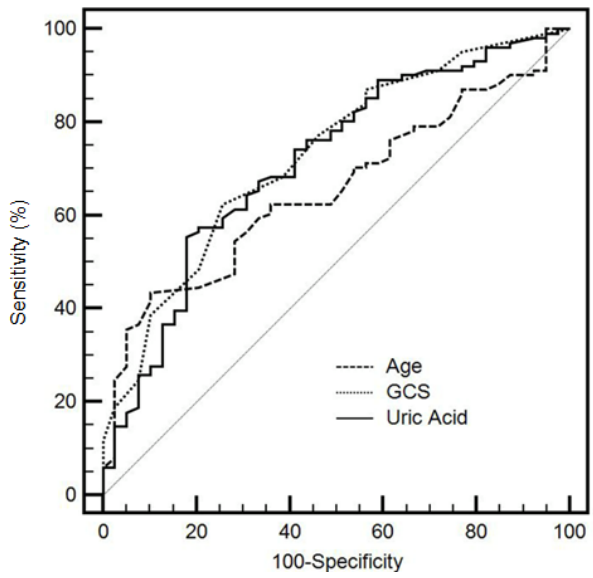

Figure 2. *ROC curves of outcome predictors Age, GCS score and serum uric acid. Receiver Operating Characteristic (ROC) curves plotted for predictors. The area under the curve was used to assess the value of prognosis prediction.*

Figure 1 indicates that favorable group (GOS scores of 4 and 5) had lower serum uric acid level compared to the unfavorable group (GOS scores of 1 to 3). The box plot demonstrated that

there was a significant difference (285 (196, 362) *vs.* 185 (120,258), p<0.001) between two groups. Spearman correlation analysis indicated that the level of serum uric acid was correlated with GCS (r=-0.1614, p=0.0453) and GOS (r=-0.3789, p=0.0001) scores.

Univariate and multivariate logistic regression identified age, GCS score and serum uric acid as independent predictors of poor outcome (Table 2). The adjusted odds ratios for the predictors were 1.038, 95% CI: 1.007-1.070 (age); 0.746, 95% CI: 0.640-0.870 (GCS score); and 1.005, 95% CI: 1.000-1.010 (serum uric acid).

ROC curves are shown in Figure 2. The AUC of serum uric acid for predicting an unfavorable outcome (GOS score 1 to 3) was 0.714, 95% CI: 0.632 to 0.787. The AUC of GCS score for predicting an unfavorable outcome was 0.729, 95% CI: 0.647 to 0.800. The AUC of age for predicting an unfavorable outcome was 0.654, 95% CI: 0.567 to 0.733. The AUC of serum uric acid was not statistically significant with regard to age and GCS (p=0.399 and p=0.820, respectively) (Table 3). The optimal cut-off value of uric acid determined by the maximum Youden index was 265 μmol/L (sensitivity 55.4%, specificity 82.1%).

Table 1. *Clinical characteristics of unfavorable and favorable patient groups.*

Characteristic	Unfavorable (n=101) (GOS score 1-3)	Favorable (n=39) (GOS score 4-5)	p value
Gender (n, %)			
Male	68 (67.3)	25 (64.1)	0.718[a]
Female	33 (32.7)	14 (35.9)	
Age (mean ± SD)	64.2 ± 18.3	55.4 ± 15.6	0.010[b]
GCS score	8 (6, 10)	11 (8, 14)	<0.001[c]
Diagnosis			
Acute ischemic stroke, n (%)	33 (32.7)	2 (5.1)	<0.0011[a]
Intracerebral hemorrhage, n (%)	47 (46.5)	19 (48.7)	
Traumatic brain injury, n (%)	21 (20.8)	18 (46.2)	
Hypertension, n (%)	62 (61.4)	12 (30.8)	0.001[a]
Diabetes at baseline, n (%)	19 (18.8)	1 (2.56)	0.014[a]
Platelet count, × 10^9/L	182 ± 64	193.1± 62.4	0.357[b]
White cell count, × 10^9/L	12.9 ± 5.5	12.1 ± 4.2	0.421[b]
Hemoglobin, g/dl	126.1 ± 24.3	123.4 ± 23.3	0.562[b]
SUA[a], mmol/L	285 (196, 362)	185 (120,258)	<0.001[a]
Serum creatinine, mmol/L	94.6 (70.1,111.7)	65.3 (52.6,84.9)	<0.001[c]
Glutamic-pyruvic transaminase, U/L	42.5 ± 119.8	36.6 ± 47.1	0.766[b]
Total bilirubin, μmol/L	19± 9.2	21 ± 11.3	0.283[b]
Albumin	41.7 ± 74.4	34.9 ± 4.7	0.567[b]
C-reactive protein	16.1 (7.5, 64.4)	5 (3, 25)	<0.001[c]

GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Scale. [a]SUA: Serum Uric Acid; [a]chi-square test; [b]t-test; [c]Mann-Whitney U test.

Table 2. *Logistic regression analysis for independent predictors.*

Predictors	Univariate logistic regression		Multivariate logistic regression	
	Crude OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Age (y)	1.0280 (1.0069-1.0496)	<0.001	1.0383 (1.0075-1.0702)	0.015
GCS	0.7829 (0.6973-0.8789)	<0.001	0.7459 (0.6395-0.8700)	<0.001
SUA[a] (μmol/L)	1.0072 (1.0032-1.0111)	<0.001	1.0052 (1.0003-1.0102)	0.039

GCS: Glasgow Coma Scale; [a]SUA: Serum Uric Acid; OR: Odds Ratio; CI: Confidence Interval.

Table 3. Receiver operating characteristic curve analyses for predictors.

	AUC	SE	95% CI
Age (y)	0.654	0.0474	0.569 to 0.733
GCS	0.729	0.0466	0.647 to 0.800
SUA[a] (μmol/L)	0.714	0.0491	0.632 to 0.787

GCS: Glasgow Coma Scale; [a]SUA: Serum Uric Acid; AUC: Area Under the ROC Curve; SE: Standard Error; CI; Confidence Interval.

Discussion

In recent years, incidents of acute stroke and TBI have increased resulting in high rates of disability and mortality [13,14]. Many studies have shown a relationship between elevated serum uric acid and vascular events [15,16] and it is thought that elevated serum uric acid levels can increase morbidity and mortality due to cerebral infarction [17-20]. Recently, Chen et al. confirmed that high serum uric acid is a risk factor for poor prognosis of ICH [21]. Tayag et al. studied cerebral uric acid following experimental TBI in rats, reporting that cortical uric acid levels were not affected 1 hour post-TBI but were elevated ten-fold at 24 and 48 h [22]. Histological evidence of neurodegeneration was found not only in the cortex but also in the anteroventral thalamus. These observations suggest that, as in stroke, uric acid measurements may be a convenient and sensitive method for measuring peroxidative damage in TBI [22]. To understand the role of SUA in brain damage, we performed a retrospective case-control study and discovered that serum uric acid is an accurate predictor of poor prognosis in patients with acute stroke and TBI. As anticipated, we found that age and GCS were also independent predictors of poor outcome. Multivariate analysis did not identify hypertension, diabetes mellitus, C-reactive protein or serum creatinine as independent outcome predictors.

Uric acid function differs in intracellular and extracellular milieus [23]. Although it is a potent extracellular anti-oxidant, uric acid exerts pro-oxidative effects inside the cell [24] and this is mediated by a NADPH oxidase-dependent pathway. Plasma uric acid is a circulating marker of oxidative damage for various pathological conditions including ischemic liver injury, ischemic-reperfusion injury, hyperlipidemia, chronic heart failure, atherosclerosis, and diabetes [25-29].

The results of the current study indicate that serum uric acid levels can indicate poor outcomes in cases of acute stroke and TBI. However, this was a retrospective, single center study of a small number of Chinese patients. The conclusions will need to be confirmed by further multi-center investigations of larger sample size and more extensive categorization among patients.

Conclusions

Serum uric acid levels measured at an early stage may be useful as an independent predictor of poor outcome following acute stroke and TBI.

Competing Interests

The authors declare no competing interests.

Acknowledgements

This work was supported by the Suzhou Municipal Science and Technology Project (Grant No.SYS201616) and the Natural Science Foundation of Jiangsu Province of China (Grant No. BK20170369).

References

1. Garrod AB. Observations on certain pathological conditions of the blood and urine, in gout, rheumatism, and Brights disease. Med Chirurg Trans 1848; 31: 83-97.
2. Kuwabara M. Hyperuricemia, Cardiovascular disease, and hypertension. Pulse (Basel) 2016; 3: 242-252.
3. Cirillo P, Sato W, Reungjui S, Heinig M, Gersch M, Sautin Y, Nakagawa T, Johnson RJ. Uric acid, the metabolic syndrome, and renal disease. J Am Soci Nephrol 2006; 17: 165-168.
4. Sheu WH, Tseng YH. Uric acid: an additional component of metabolic syndrome? J Chinese Med Assoc JCMA 2006; 69: 99-100.
5. Nakagawa T, Hu H, Zharikov S, Tuttle KR, Short RA, Glushakova O, Ouyang X, Feig DI, Block ER, Herrera-Acosta J, Patel JM, Johnson RJ. A causal role for uric acid in fructose-induced metabolic syndrome. Am J Physiol Renal Physiol 2006; 290: 625-631.
6. Cantor JR, Abu-Remaileh M, Kanarek N, Freinkman E, Gao X, Louissaint A, Jr., Lewis CA, Sabatini DM. Physiologic medium rewires cellular metabolism and reveals uric acid as an endogenous inhibitor of UMP synthase. Cell 2017; 169: 258-272.
7. Sautin YY, Nakagawa T, Zharikov S, Johnson RJ. Adverse effects of the classic antioxidant uric acid in adipocytes: NADPH oxidase-mediated oxidative/nitrosative stress. Am J Physiol Cell Physiol 2007; 293: 584-596.
8. Kanellis J, Johnson RJ. Editorial comment-elevated uric acid and ischemic stroke: accumulating evidence that it is injurious and not neuroprotective. Stroke 2003; 34: 1956-1957.
9. Cutler RG. Urate and ascorbate: their possible roles as antioxidants in determining longevity of mammalian species. Arc Gerontol Geriatr 1984; 3: 321-348.

10. Kono H, Chen CJ, Ontiveros F, Rock KL. Uric acid promotes an acute inflammatory response to sterile cell death in mice. J Clin Investig 2010; 120: 1939-1949.
11. Proctor PH. Uric acid: neuroprotective or neurotoxic? Stroke 2008; 39: 88.
12. Lingsma HF, Roozenbeek B, Steyerberg EW, Murray GD, Maas AI. Early prognosis in traumatic brain injury: from prophecies to predictions. Lancet Neurol 2010; 9: 543-554.
13. Liao CC, Chou YC, Yeh CC, Hu CJ, Chiu WT, Chen TL. Stroke risk and outcomes in patients with traumatic brain injury: 2 nationwide studies. Mayo Clin Proc 2014; 89: 163-172.
14. Xiong Y, Mahmood A, Chopp M. Emerging treatments for traumatic brain injury. Exp Opin Emerg Drugs 2009; 14: 67-84.
15. Yang TY, Fang CY, Chen JS, Po HL, Chou LP, Chiang CY, Ueng KC. Association of serum uric acid with cardiovascular disease in taiwanese patients with primary hypertension. Acta Cardiologica Sinica 2015; 31: 42-51.
16. Iliesiu A, Campeanu A, Dusceac D. Serum uric acid and cardiovascular disease. Maedica 2010; 5: 186-192.
17. Weir CJ, Muir SW, Walters MR, Lees KR. Serum urate as an independent predictor of poor outcome and future vascular events after acute stroke. Stroke 2003; 34: 1951-1956.
18. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. JAMA 2000; 283: 2404-2410.
19. Hozawa A, Folsom AR, Ibrahim H, Nieto FJ, Rosamond WD, Shahar E. Serum uric acid and risk of ischemic stroke: the ARIC Study. Atherosclerosis 2006; 187: 401-407.
20. 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. Stroke 1998; 29: 635-639.
21. Chen H, Li F, Wang X, Kong Y, Wang Y. Retrospective analysis of the predictive effect of routine biochemical results on the prognosis of intracerebral hemorrhage. Acta Neurochirurgica Suppl 2011; 111: 403-406.
22. Tayag EC, Nair SN, Wahhab S, Katsetos CD, Lighthall JW, Lehmann JC. Cerebral uric acid increases following experimental traumatic brain injury in rat. Brain Res 1996; 733: 287-291.
23. Johnson RJ, Rivard C, Nakagawa T, Sautin YY, Sanchez-Lozada LG. Uric acid: more to learn, more experiments to do. Am J Hypertens 2009; 22: 952-953.
24. Schorn C, Janko C, Munoz L, Schulze C, Strysio M, Schett G, Herrmann M. Sodium and potassium urate crystals differ in their inflammatory potential. Autoimmunity 2009; 42: 314-316.
25. Lyngdoh T, Marques-Vidal P, Paccaud F, Preisig M, Waeber G, Bochud M, Vollenweider P. Elevated serum uric acid is associated with high circulating inflammatory cytokines in the population-based Colaus study. PloS One 2011; 6: 19901.
26. Ruggiero C, Cherubini A, Ble A, Bos AJ, Maggio M, Dixit VD, Lauretani F, Bandinelli S, Senin U, Ferrucci L. Uric acid and inflammatory markers. Eur Heart J 2006; 27: 1174-1181.
27. Leyva F, Anker SD, Godsland IF, Teixeira M, Hellewell PG, Kox WJ, Poole-Wilson PA, Coats AJ. Uric acid in chronic heart failure: a marker of chronic inflammation. Eur Heart J 1998; 19: 1814-1822.
28. Olexa P, Olexova M, Gonsorcik J, Tkac I, Kiselova J, Olejnikova M. Uric acid-a marker for systemic inflammatory response in patients with congestive heart failure? Wiener Klinische Wochenschrift 2002; 114: 211-215.
29. Ruggiero C, Cherubini A, Miller E, 3rd, Maggio M, Najjar SS, Lauretani F, Bandinelli S, Senin U, Ferrucci L. Usefulness of uric acid to predict changes in C-reactive protein and interleukin-6 in 3-year period in Italians aged 21 to 98 years. Am J Cardiol 2007; 100: 115-121.

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