The Association among Hyperuricemia, Aspirin Resistance, and Ischemic Events Recurrence in Stroke Patients

Yongkang Zhang
the First Rehabilitation Hospital of Shanghai
Huihui Lv
Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine
Zhuqing Shi
state key laboratory of genetic engineering and ministry of education key laboratory of contemporary anthropology
Xu Liu
state key laboratory of genetic engineering and ministry of educational key laboratory of contemporary anthropology
Wei Liu
the First Rehabilitation Hospital of Shanghai
Qianyun Liu
Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine
Yajing Huo
Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine
Xie Long
Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine
Mingyuan Liu
Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine
Yinting Zhou
Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine
Guoqin Zhu
SPH xing ling sci. & tech. pharmaceutical co.
Haibo Wu

Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine

Yan Han (hanyan@shutcm.deu.cn)

Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine https://orcid.org/0000-0002-7654-0906

Research

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Abstract

Background: It is unclear about the relationship among hyperuricemia, aspirin resistance (AR) and recurrence of ischemic events in ischemic stroke patients. This study focuses on this topic.

Methods: In this prospective, observational, and single-center study, acute ischemic stroke (AIS) patients within 14 days of onset were recruited. Every patient took aspirin 100mg/d during the follow-up period, the aspirin reaction unit (ARU) was detected by the VerifyNow System on the 5-7th day, and serum uric acid (SUA) level was also tested. ARU≥550 is defined as AR. Patients were followed up for 3 years and record ischemic events recurrence in the clinical database we built (including transient ischemic attack, ischemic stroke recurrence, major adverse cardiovascular events, and vascular composite death).

Results: A total of 138 patients with newly ischemic stroke were recruited in this study, of which 27 were AR and 14 were hyperuricemia. A total of 119 patients completed 3-year follow up, among which 32 patients experienced at least one endpoint, 23 patients had aspirin resistance, and 12 patients had hyperuricemia. Among these 32 patients, no one had hyperuricemia. In the univariate analysis, hyperuricemia was significantly associated with no ischemic events (p=0.035); the incidence of AR was significantly associated with recurrent ischemic events (p=0.012); hyperuricemia has no association with AR (p=0.457).

Conclusions: Hyperuricemia might be a protective factor in patients with AIS, and AR has a significant association with ischemic events recurrence which is not associated with hyperuricemia.

1. Introduction

Stroke is the second most common cause of death around the world, which brings a huge financial burden [1]. Uric acid (UA), a strong antioxidant compound, is the final metabolite of purines. So far, the association between serum uric acid (SUA) level and clinical outcomes in patients with acute ischemic stroke (AIS) remains unclear. Some researchers believe that high SUA level can protect patients with AIS [2–4], but others do not agree with this opinion [5–9]. Experimental UA treatment protects neural, vascular and cardiac cells from oxidative damage in vitro [10]. Furthermore, high SUA levels in humans have been associated with neuroprotection in several neurodegenerative and neuroinflammatory diseases [11, 12].

An increasing number of clinical studies have confirmed that platelet reactivity to antiplatelet therapy varies widely among individuals and indicates that aspirin resistance (AR) may be related to an increased rate of ischemic events. Although the administration of low-dose aspirin may cause hyperuricemia [13, 14], the dispute over whether to use aspirin in ischemic stroke patients with hyperuricemia still exists. Meanwhile, the study on the relationship between high SUA level and AR is still limited. Up to date, only one study [15] has demonstrated that hyperuricemia is an independent predictor of AR. Based on the above, this study was designed to investigate the association among hyperuricemia, ischemic events recurrence and AR.

2. Materials And Methods

2.1 Study Patients

This is a prospective, observational, single-center study. From August 2012 to July 2014, AIS patients within 14 days of onset were recruited. The inclusion criteria were: (1) participants > 18 years of age and < 90 years of age; (2) newly ischemic stroke diagnosis by magnetic resonance imaging (MRI). Exclusion criteria were: (1) hemorrhagic disease, valvular heart disease, or tumors; (2) taking other antiplatelet drugs or anticoagulants; (3) patients who are allergic to aspirin; (4) patients who are pregnant or trying to conceive. All enrolled patients take aspirin 100 mg/d during the follow up period. Before inclusion in the study, patients signed informed consent forms. The study was approved by the Shanghai Changhai Hospital Ethics Committee (No. 2011 − 260).

2.2 SUA level and Platelet Function Test

Blood samples were drawn 1 h after taking aspirin on the 5-7th day. Patients whose SUA level were above 420 μmol/L were diagnosed with hyperuricemia. The aspirin reaction unit (ARU) was tested by the VerifyNow system (Accumetrics, San Diego, CA, USA). We define ARU ≥ 550 as AR.

2.3 Clinical Endpoints

The primary endpoint was the ischemic events recurrence during the 3-year follow up period (including transient ischemic attack, recurrent stroke, major adverse cardiovascular events, and vascular composite death). The safety endpoint was bleeding (including subcutaneous hemorrhage, intracranial hemorrhage and gastrointestinal hemorrhage).

2.4 Statistical Analysis

Continuous variables in the study data were expressed as mean ± standard deviation, and classification variables were expressed as percentages. Baseline clinical features were compared stratified by outcome and the ARU value. Continuous variables were analyzed using Student *t* test or Wilcoxon Mann-Whitney *U* test. Classification variables were analyzed using Pearson χ^2 test and Fisher exact test. All *p* values less than 0.05 ware considered statistical significance. All statistical analyses were performed using SPSS for Mac version 25(SPSS Inc., Chicago, IL, USA).

3. Results

A total of 138 patients were enrolled in the study, of which 10 (7.25%) were lost to follow-up, 6 (4.35%) had experienced safety endpoint (4 intracranial hemorrhages, 1 gastrointestinal hemorrhage, 1 subcutaneous hemorrhage), 3 (2.17%) switched to other antiplatelet drugs or anticoagulants instead of aspirin. A total of 119 patients completed the 3-year follow-up, of which 65 (54.62%) were males and 54 (45.38%) were females. 23 (19.33%) were AR and 12 (10.08%) were hyperuricemia.

In 119 patients, 32 (26.89%) have experienced endpoint events, none of these 32 patients were had hyperuricemia. The numbers of patients with AR ($p = 0.0117$) and stroke history ($p = 0.0119$) in the endpoint events group were significantly higher than those in the no-endpoint events group, but no patients with hyperuricemia experienced endpoint events ($p = 0.0346$). Besides, there were no significant differences in sex, age, height, weight, BMI, complications and laboratory tests between two groups (Table 1).

Table 1
Characteristics of Study Population

Variable	Patients with endpoints (N = 32)	Patients without endpoints (N = 87)	*p* value
Aspirin resistance, n (%)	11(34.4)	12(13.8)	0.012*
Male, n (%)	17(53.1)	48(55.2)	0.842
Age, years, mean ± SD	66.66 ± 10.44	62.78 ± 12.60	0.123
Height, cm, mean ± SD	163.77 ± 8.98	165.85 ± 6.62	0.358
Weight, kg, mean ± SD	66.34 ± 13.71	65.61 ± 10.62	0.760
BMI, kg/m^2, mean ± SD	24.70 ± 4.61	23.74 ± 2.89	0.281
Hypertension, n (%)	24(75.0)	61(70.1)	0.601
Diabetes, n (%)	17(53.1)	30(34.5)	0.065
Dyslipidemia, n (%)	13(40.6)	43(49.4)	0.394
Cholesterol, mmol/L, mean ± SD	4.43 ± 1.00	4.81 ± 1.29	0.135
TG, mmol/L, mean ± SD	1.53 ± 0.85	1.88 ± 1.66	0.150
HDL, mmol/L, mean ± SD	1.11 ± 0.28	1.21 ± 0.33	0.088
LDL, mmol/L, mean ± SD	2.37 ± 0.76	2.54 ± 0.87	0.326
BPC, 10^9/L, mean ± SD	201.90 ± 60.85	215.42 ± 59.02	0.281
Heart disease history, n (%)	1(3.1)	6(6.9)	0.673
Stroke history, n (%)	14(43.8)	18(20.7)	0.012*
Hyperuricemia, n (%)	0(0)	12(13.8)	0.035*

SD, standard deviation; BMI, body mass index; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; BPC, blood platelet count, Significant differences are marked by *$p < 0.05$.

According to ARU values detected by the VerifyNow system, the patients were divided into aspirin-resistant group and aspirin-sensitive group. Between these 2 groups, hyperuricemia was not significantly

associated with AR ($p = 0.457$) (Table 2).

Table 2
Characteristics of Patients with Aspirin-Resistant and Aspirin-Sensitive

Variables	Aspirin-resistant (N = 23)	Aspirin-sensitive (N = 96)	p value
Male, n (%)	18(78.3)	47(49.0)	0.011*
Age, years, mean ± SD	66.83 ± 10.86	63.10 ± 12.37	0.188
Height, cm, mean ± SD	167.57 ± 7.78	164.80 ± 7.16	0.060
Weight, kg, mean ± SD	64.94 ± 12.61	66.02 ± 11.25	0.689
BMI, kg/m^2, mean ± SD	23.02 ± 3.46	24.23 ± 3.42	0.129
Hypertension, n (%)	18(78.3)	67(69.8)	0.419
Diabetes, n (%)	7(30.4)	40(41.7)	0.322
Dyslipidemia, n (%)	13(56.5)	43(44.8)	0.311
Cholesterol, mmol/L, mean ± SD	4.76 ± 1.05	4.67 ± 1.27	0.545
TG, mmol/L, mean ± SD	1.45 ± 0.66	1.88 ± 1.63	0.235
HDL, mmol/L, mean ± SD	1.26 ± 0.33	1.17 ± 0.32	0.133
LDL, mmol/L, mean ± SD	2.58 ± 0.79	2.47 ± 0.85	0.601
BPC, 10^9/L, mean ± SD	195.09 ± 59.26	215.94 ± 59.21	0.133
Heart disease history, n (%)	2(8.7)	5(5.2)	0.619
Stroke history, n (%)	1(4.3)	31(32.3)	0.007*
Hyperuricemia, n (%)	1(4.3)	11(11.5)	0.457

SD, standard deviation; ARU, aspirin reaction unit; BMI, body mass index; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; BPC, blood platelet count, Significant differences are marked by *$p < 0.05$.

4. Discussion

Ischemic stroke leads to increase of intracranial free radicals and peroxynitrite, which causes brain cell death [16]. SUA is a natural antioxidant that exists in body, and concentration is approximately 10 times higher than other endogenous antioxidants [17]. SUA can scavenge oxygen free radicals and prevent lipid peroxidation effects [18]. However, until now, one is still not sure whether hyperuricemia is a protective factor or risk factor in AIS patients.

Some studies [5, 6] found the association between high SUA level and mortality of myocardial infarction, stroke, and cardiovascular disease, although it is unclear whether SUA elevation was a cause or a result [7]. Karagiannis A et al [8] showed that elevated SUA level was an independent predictor of early death after acute stroke. Kim SY et al [9] demonstrated that hyperuricemia might slightly increase mortality and the incidence of stroke.

On the contrary, some studies showed high SUA level might have neuroprotective effects in patients with AIS [11, 12], and both exogenous and endogenous UA are presented as neuroprotective roles [19, 20]. Some researchers [21] attribute it to the strong antioxidant capacity of urate. More and more studies [2–4] demonstrate that high SUA level usually predict a better outcome. A meta-analysis included 8131 AIS patients for less than a 1-year follow up found that high SUA level had a protective effect on neurological prognosis after ischemic stroke [22]. Besides, in 2014, a phase 2b/3 clinical trial (URICO-ICTUS) with 420 AIS patients completed a 90-day follow up period showed that patients with UA therapy had a better prognosis than the placebo group [23]. All these studies have demonstrated the protective effects of high UA level on AIS patients. Furthermore, our study concluded that hyperuricemia was still a protective factor for AIS in a long-term follow up. The powerful antioxidant capacity of UA may be the reason for the benefit of patients with ischemic stroke.

Aspirin is the most common antiplatelet agent recommended in guidelines. However, more and more clinical physicians observed resistance in antiplatelet therapy [24, 25]. Our study found that the incidence of AR was high in Chinese populations(19.33%), which was significantly associated with ischemic events recurrence even during the 3-year follow up. Another study has also demonstrated that AR is associated with an increased risk of severe stroke and large infarct volume in patients [25]. Only one study explored the effects of hyperuricemia on AR [15], it demonstrated that high SUA levels could be used as independent predictors of AR. But our study did not find any relationship between AR and hyperuricemia. Meanwhile, we also found that patients with stroke history were more likely to experience recurrent ischemic events, which were mostly due to more risk factors and poor cerebrovascular conditions. We did not find more recurrence occurred in diabetes patients and need to enlarge the sample size.

The use of daily low-dose aspirin (100 mg/day) reduces UA excretion in urine and increases the SUA level [13, 14]. However, there are no guidelines to suggest whether to discontinue aspirin in AIS patients with hyperuricemia. Some studies have shown that [14] usage of lowering-uric-acid drugs instead of discontinuing aspirin will be more beneficial for patients with ischemic stroke. Our study investigated the relationship among hyperuricemia, recurrent ischemic events, and AR. Hyperuricemia can reduce the incidence of ischemic events with increased risk of AR. Therefore, we believe that AIS patients who had hyperuricemia may not need to discontinue aspirin.

5. Conclusion

Hyperuricemia might have clinical benefits for AIS patients and will not affect sensitivity to aspirin. Therefore, in clinical practice, for AIS patients combined with hyperuricemia, the addition of lowering-uric-acid drugs to aspirin might be a better treatment.

6. Abbreviations

AR: aspirin resistance; AIS: acute ischemic stroke; SUA: serum uric acid; UA: uric acid; ARU: aspirin reaction unit; SD: standard deviation; BMI, body mass index; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; BPC, blood platelet count.

7. Declarations

7.1 Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Changhai Hospital and was conducted by following the regulation of China GCP. Every patient signed the informed consent form before inclusion in this study.

7.2 Conflict of Interest

None.

7.3 Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

7.4 Competing interests

The authors declared no competing interests.

7.5 Funding

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7.6 Authors' contributions

YKZ and HHL drafted the manuscript; ZQS, WL, QYL, YJH, Xie L, YTZ and GQZ helped to collect the data; Xiu L performed the statistically analysis; YH participated the design of the study and explanation of the data; MYL, HBW participated the design of the study. All authors read and approved the final manuscript.

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