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CLINICAL STUDY

Is serum uric acid a predictive factor for stroke in men with hypertriglyceridemia?

Lai YJ[1], Hsu CY[2,3,4,5,6,7,8,9,10]

Department of Neurology, China Medical University Hospital, Taichung, Taiwan. **4211@mail.pch.org.tw**

ABSTRACT

OBJECTIVE: This study investigated the association between serum uric acid (sUA) and stroke risk in men with hypertriglyceridemia.

METHODS: Between 2002 and 2012, male patients with pure hypertriglyceridemia and a triglyceride (TG) level ≥ 150 mg/dL were enrolled. Eligible patients were categorized into two groups according to their sUA levels (≥ and < 8 mg/dL). Clinical characteristics and comorbidities that are risk factors for stroke were recorded and compared between the groups.

RESULTS: A total of 265 male patients (95 with sUA ≥ 8 mg/dL and 170 with sUA < 8 mg/dL) were enrolled. The incidence of ischemic type of stroke was significantly higher in patients with sUA ≥ 8 mg/dL (p = 0.038), particularly in the age range of 45–65 years. Multivariate Cox proportional analyses confirmed that age (p = 0.003) and UA (p = 0.019) were major predictive factors for stroke free (ischemic type of stroke) survival.

CONCLUSION: Among men with hypertriglyceridemia, the incidence rate of ischemic type of stroke significantly increased with sUA levels ≥ 8 mg/dL, particularly in men aged 45 to 65 years. Hyperuricemia is considered a potential predictive factor for ischemic type of stroke and may indicate the need for preventive management in patients with hypertriglyceridemia *(Tab. 3, Fig. 1, Ref. 28)*. Text in PDF *www.elis.sk.*

KEY WORDS: hypertriglyceridemia, hyperuricemia, stroke.

Introduction

Stroke is a major global cause of death and disability (1), and thus is a worldwide health issue. Stroke is attributed to ameliorable risk factors (2), hypertension, diabetes, hyperlipidemia, alcohol consumption, smoking, cardiac-related issues and ratio of apolipoprotein B to A1 were found to be strongly associated with an increased risk of ischemic stroke (3, 4).

Triglyceride (TG) is an ester that is transported by lipoproteins such as chylomicrons and very low density lipoproteins. According to guidelines published by the American Heart Association, the TG level is considered to be high when it is over 1.7 mmol/L (150 mg/dL). Hypertriglyceridemia is one of the components of the metabolic syndrome. A national health and nutrition examination survey showed that one third of respondents had hypertriglyceridemia, and that the prevalence of this disease is increasing. A high TG level has been associated with a high risk of cardiovascular disease (CVD), acute pancreatitis, and myocardial infarction (5, 6).

Several studies have attempted to identify an association between serum uric acid (sUA) and CVD (7–12). Increased levels of sUA may predict cardiovascular events in a population with a relatively high risk of stroke (8). Increased level of sUA was associated with stroke risk in diabetes patients (7) and was an independent predictor of ischemic stroke in patients who do not take diuretic medication (9). Some studies have reported disappearance of this association after adjustment for various confounding factors (13, 14). However, two meta-analyses have found a significant association among hyperuricemia, stroke incidence, and mortality after adjustment for known cardiovascular risk factors (10, 11). Thus, an association among sUA, hypertriglyceridemia, and stroke may exist. This study investigated the possible association between sUA and stroke risk in men with hypertriglyceridemia.

Methods

Between 2002 and 2012, male patients with pure hypertriglyceridemia and a TG level ≥ 150 mg/dL (without previous TG level ≥ 150 mg/dL for at least a one-year tracking time) were enrolled in this study. Because sex differences between sUA and several diseases have been described in previous studies (15, 16), only male patients were recruited. Patients were excluded if they had a medical history of stroke (a), total follow-up period of less than

[1]Department of Neurology, China Medical University Hospital, Taichung, Taiwan, [2]Department of Family Medicine, Puli Christian Hospital, Puli, Taiwan, [3]Department of Medical Education and Research, Puli Christian Hospital, Puli, Taiwan, [4]Department of Optometry, Central Taiwan University of Science and Technology, Taichung, Taiwan, [5]Center for General Education, National Taichung University of Science and Technology, Taichung, Taiwan, [6]The General Education Center, Chaoyang University of Technology, Taichung, Taiwan, [7]Department of General Education, National Chin-Yi University of Technology, Taichung, Taiwan, [8]Center for General Education, Feng Chia University, Taichung, Taiwan, [9]Center for General Education, National Chi Nan University, Puli, Taiwan, and [10]Rural Generalist Program Japan

Address for correspondence: C-Y Hsu, Tie-Shan Road 1, Puli, Nantou 545, Taiwan.
Phone: 886.492912151, Fax: 886.492916901

1 year (b), showed a high average cholesterol level (≥ 200 mg/dL) (c), and were under hemodialysis within one year before or after the date when participants satisfied the criteria (d). This was to eliminate the effect of high serum cholesterol, and to ensure that the effect of pure hypertriglyceridemia is observed. In addition, we excluded patients with hemodialysis. This is because for those on dialysis, sUA is a factor that reflects a patient's nutritional status, while low sUA level is associated with high mortality (17, 18).

No precise cut-off value of sUA was recommended for initial urate-lowering therapy (ULT) in managing asymptomatic hyperuricemia, and gout attack in hyperuricemic individuals with sUA levels between 7 and 8 mg/dL was low (19). We used 8 mg/dL as the cut-off point. Eligible patients were categorized into two groups according to their sUA levels (≥ and < 8 mg/dL). Clinical characteristics (age at diagnosis and race/ethnicity), and comorbidities that are risk factors for stroke (hypertension, diabetes, obesity, and atrial fibrillation; 20) were recorded and compared between the groups. No age restrictions were imposed. To identify age differences in patients based on sUA levels and stroke in men with hypertriglyceridemia, we divided patients into three age groups: < 45, 45–65, and > 65 years.

Study outcomes were stroke events of either ischemic or hemorrhagic types, in which there was at least one hospital discharge diagnosis for stroke, or at least two outpatient clinical diagnoses with detailed neuronal examinations documented in medical records with computed tomography/ magnetic resonance imaging confirmed.

Chi-square and independent t tests were used to compare the patients' characteristics, comorbidities, and events of stroke in the follow-up period. Stroke free survival rate was evaluated by plotting Kaplan–Meier curves. Univariable and multivariable Cox regression analyses were used to assess the hazard ratio of each possible confounding factor and its impact on stroke risk and to identify the prognostic factors of stroke events. A p value < 0.05 was considered significant.

Tab. 1. The differences between high and low levels of uric acid in men with pure hypertriglyceridemia.

	sUA ≥ 8mg/dL N = 95	sUA < 8mg/dL N = 170	p
Age at diagnosis	46.9±13.7	48.8±13.0	0.252
Mean follow time (year)	10.8±4.4	11.3±3.7	0.308
Mean triglyceride	365.0±192.0	358.4±239.7	0.819
Mean uric acid	9.1±1.0	6.4±1.1	< 0.001
Race			
Aborigines	20 (21.1%)	28 (16.5%)	0.353
Non-aborigines	75 (78.9%)	142 (83.5%)	
Comorbidities			
Hypertension	41 (43.2%)	81 (47.7%)	0.427
Diabetes	21 (22.1%)	59 (34.7%)	0.040
Obesity	17 (17.9%)	25 (14.7%)	0.582
Atrial fibrillation	2 (2.1%)	2 (1.2%)	0.552
Stroke	14 (14.8%)	15 (8.8%)	0.139
Ischemic	11 (11.6%)	8 (4.7%)	0.038
Hemorrhagic	3 (3.2%)	7 (4.1%)	0.694

Tab. 2. The incidence of ischemic type of stroke by different age groups.

Age	Uric acid level	Number of patients	Number of ischemic strokes	p
<45	≥ 8	45	3 (6.7%)	0.153
	< 8	66	1 (1.5%)	
45–65	≥ 8	41	6 (14.6%)	0.004
	< 8	76	1 (1.3%)	
>65	≥ 8	9	2 (22.2%)	0.960
	< 8	28	6 (21.4%)	

Results

A total of 265 male patients (95 with sUA levels ≥ 8 mg/dL and 170 with sUA levels < 8 mg/dL) were enrolled. The mean age was 46.9 years for patients with sUA levels ≥ 8 mg/dL and 48.8 years for those with sUA < 8 mg/dL (p = 0.252). The mean follow-up period was 10.8 years for patients with sUA levels ≥ 8 mg/dL and 11.3 years for those with sUA levels < 8 mg/dL (p = 0.308). Baseline characteristics between the groups were not significantly different except for diabetes (Tab. 1). The incidence of ischemic type of stroke was significantly higher in patients with sUA levels ≥ 8 mg/dL (11.6 % vs 4.7 %; p = 0.038). However, no difference in hemorrhagic type of stroke was found between the groups (Tab. 1).

To examine the effect of sUA on ischemic type of stroke in different age groups, we divided the patients into three age groups: < 45, 45–65, and > 65 years. In the age group of 45–65 years, the incidence of ischemic type of stroke was significantly higher in patients with sUA levels ≥ 8 mg/dL than in those with sUA levels < 8 mg/dL (14.6 % vs 1.3 %; p = 0.004) (Tab. 2).

The 10-year stroke free (ischemic type of stroke) survival rate was 91.2 % for the patients with sUA levels ≥ 8 mg/dL and 96.8 % for those with sUA levels < 8 mg/dL. Kaplan–Meier curves showed a significant difference (p = 0.034) (Fig. 1). The results of the univariate Cox proportional analyses showed that age and sUA were significantly associated with stroke free (ischemic type of stroke) survival. The findings of multivariate Cox proportional analyses confirmed that age and sUA were significant predictive factors for stroke free (ischemic type of stroke) survival (p = 0.003 for age and 0.019 for sUA) (Tab. 3).

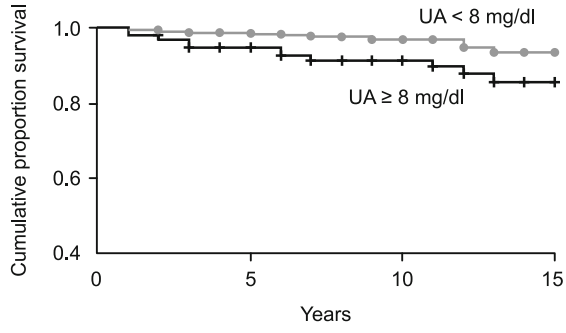

Fig. 1. The stroke free (ischemic type of stroke) survival rate between sUA ≥ 8 and < 8 mg/dl by Kaplan-Meier method.

Tab. 3. The uni- and multivariate Cox analyses for stroke free (ischemic type of stroke) survival.

Covariates	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Age	1.054	1.019–1.090	0.002	1.055	1.018–1.093	0.003
Hypertension	1.067	0.434–2.627	0.887	1.000	0.386–2.588	0.999
Diabetes	2.285	0.928–5.625	0.072	2.109	0.781–5.693	0.141
Atrial fibrillation	4.994	0.660–37.816	0.119	1.915	0.206–17.765	0.568
Obesity	1.441	0.478–4.344	0.516	1.506	0.456–4.966	0.502
Uric acid	2.573	1.035–6.397	0.042	3.120	1.203–8.092	0.019

Discussion

The atherogenic effect of lipoproteins on patients with hypertriglyceridemia has been previously confirmed (21). In the present study, we examined the relationship between sUA and stroke in men with hypertriglyceridemia. We found that the incidence rate of ischemic type of stroke increased significantly in patients with sUA ≥ 8 mg/dL, particularly in men aged 45 to 65 years. In addition, we found that age and sUA were significant predictive factors for ischemic type of stroke.

The role of sUA in humans has been previously discussed. It is associated with increased numbers of indicators of inflammation such as interleukin-6, interleukin-18, C-reactive protein, and tumor necrosis factor-alpha (22). In addition to inflammation status, sUA is associated with carotid intima-media thickness, which might lead to atherosclerosis (23). Atherogenesis and thrombogenesis are believed to play a major role in the development of coronary artery disease, and most strokes are caused by occlusion of the bloodstream (24). A high sUA level is considered to increase the stroke rate through atherogenesis. In addition, sUA impairs endothelial function by reducing nitric oxide synthase. Thus, hyperuricemia can be a risk factor for endothelial dysfunction (25, 26). Atherogenesis or endothelial dysfunction through the sUA effect increases the incidence of stroke. Our study demonstrated that a high sUA level is a significant predictive factor for ischemic type of stroke.

Age is an irreversible risk factor for ischemic stroke (3). Although Wen et al. found that the mean sUA level in men decreased slightly as age increased (27), Singh and Yu demonstrated that age is a significant factor for incidence of stroke in old patients who take allopurinol (28). Various risk factors including age, family history, hypertension, diabetes, hyperlipidemia, alcohol consumption, smoking, and cardiac-related issues (atrial fibrillation), are associated with an increased risk of ischemic stroke (3). Our study was limited to male patients, and except for age, we did not find any associations between comorbidities and ischemic stroke. One possible explanation is that identification of these factors relies on the coding from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). There may be a proportion of patients under treatment for certain diseases in local clinics who have not informed doctors at our hospital. Another explanation is that this was a population-based retrospective study with a distinct population component (nearly 19 % of patients were aborigines) and life habits. Thus, the effect scale of each factor to ischemic stroke might be different from that in the general population.

This retrospective study identified an association between sUA and stroke risk in men with hypertriglyceridemia. However, this study has several limitations. Firstly, because sUA is not a routine item in a physical examination, some patients have their first sUA checked only after a gout attack. This may have produced a bias in selecting participants; thus, the lack of sUA data resulting from this may have also limited our study. Secondly, because it was a retrospective study, data related to the life-styles of participants, such as the amount of cigarette smoking and alcohol consumption, were not available in our study based solely on reviews of patient medical records. Thus, we were unable to consider these factors. Thirdly, patients may have been under ULT after the diagnosis of gout. We did not record the fact whether participants were taking medication with ULT, which may have also influenced the results. Fourthly, this study was based on a database from a single hospital, and our study participants mainly reside in a rural area of central Taiwan. The lifestyle preferences and ethnic makeup of these participants may have influenced the results. Nevertheless, despite these limitations, ours is the first study to evaluate the association between sUA and stroke risk in a specific population of men with hypertriglyceridemia.

Conclusion

Among men with hypertriglyceridemia, the incidence rate of ischemic type of stroke significantly increased with sUA levels ≥ 8 mg/dL, particularly in the age group of 45–65 years. Hyperuricemia is considered a potential predictive factor for ischemic type of stroke and may require preventive management in patients with hypertriglyceridemia.

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