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Clinical features and risk factors of primary gout

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Objective: The aim of this study was to explore the clinical features and related risk factors of primary gout in the northeastern area of Sichuan.

Methods: A total of 583 subjects with gout and a cohort of 459 control subjects without gout were matched in terms of age and sex. Clinical parameters were recorded and routine biochemistry tests were conducted for both groups. Odds ratios (ORs) and 95% confidence intervals (CIs) for associations of risk factors with primary gout were utilized along with multiple logistic regression analysis.

Results: Among all the incident gout cases, only one joint was involved in the first attack in 94.9% of cases, while attacks involved the first metatarsophalangeal joint in 68.61% of cases. 364 (62.44%) patients had predisposing factors, 88.16% of which were related to dietary factors such as beer and seafood. The most common comorbidity was hyperlipidemia (66.90%), followed by hypertension (35.68%) and hypercholesterolemia (23.33%). Incidence of tophi was significantly correlated with the course of disease and the level of serum uric acid (all $p<0.01$). In addition, multiple logistic regression analysis revealed that the occurrence of primary gout was correlated with the following factors: hyperuricemia, alcohol use, BMI, hypertriglyceridemia, diet, hypertension and smoking ($p<0.05$).

Conclusion: We were able to demonstrate that the clinical manifestations of gout were heterogeneous. Hyperuricemia, alcohol intake, obesity, hypertriglyceridemia, purine-rich diets, hypertension and smoking were the most important risk factors for primary gout. However, further prospective studies are needed to investigate the specific pathogenesis between risk factors and primary gout.

Key words: Gout; Primary; Clinical features; Risk factors

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Introduction

Gout, one of the most common forms of inflammatory arthritis, is caused by monosodium urate crystal deposition secondary to persistent hyperuricemia (HUA) [1,2]. Chronic hyperuricemia is the biochemical basis of gout. HUA may occur secondary to increased uric acid formation, decreased uric acid excretion, or a combination of both mechanisms. HUA is defined as a serum uric acid level >7.0mg/dL in males and >6.0 mg/dL in females [3]. Epidemiological data have shown a significant increase in the incidence of gout in recent decades. About 1-2% of adults in western developed countries are affected by gout [1]. In addition to the involvement of the bones and joints, gout can also involve multiple systems, such as skin and soft tissue. With progression of the disease, patients may present with acute and chronic inflammation in joints and bursa, tophi, gouty nephropathy and other clinical manifestations. HUA/gout has also been shown to be an independent risk factor for hypertension, stroke and cardiovascular disease [4,5]. Although male gender [6], alcohol intake [7], obesity [8], and purine-rich diets [9] are positively associated with the occurrence of gout, whether gout is influenced by other environmental factors is rarely reported. To this end, 583 gout patients in the northeastern area of Sichuan were incorporated into

the survey in order to analyze their clinical characteristics and risk factors for the disease. The purpose of this study is to deepen the understanding of gout, and to provide a theoretical basis for primary gout prevention for high-risk population.

Methods

Study population

A retrospective observational study was conducted from January 2007 to March 2013. A total of 583 patients with primary gouty arthritis (GA) were enrolled in this study, all of them from Affiliated Hospital of North Sichuan Medical College outpatient and inpatient department. Of these, 95.71% were male, and the mean age ± standard deviation (SD) was 48.18 ± 12.16 years. 459 healthy subjects recruited from the same outpatient medical examination setting were selected as control group (healthy control subjects, HC, 94.99% male, mean age 47.35 ± 11.28). Gout patients satisfied at least 6 of 12 criteria from the 1977 American College of Rheumatology criteria for gout. Patients with liver and kidney disease, diabetes, hypertension, prior tumors, blood disease and other related diseases were excluded. All populations were ethnic Chinese Han. This study was approved by the ethics committee of Affiliated Hospital of North Sichuan Medical College (IRB: 2007ER(AR)-003), and each subject signed the informed consent.

Parameters

All patients enrolled were asked about demographic and clinical characteristics of their gout, and comorbid diseases. Demographic information included sex, birthdate, and race. Clinical features included disease duration (years), the first joint affected by gout onset, the cumulative number of joints involved (joint number), gout flare frequency, the presence of tophi (yes or no), eating habits, predisposing factors, smoking situation, alcohol intake, family history, etc. Comorbid diseases included previously physician-diagnosed hypertension, diabetes, cardiovascular diseases, cerebrovascular diseases, and renal calculus. Healthy subjects were questioned other than clinical features. The height and body weight of the two groups were measured and body mass index (BMI) was calculated. According to the 2011 Chinese Expert Consensus on Obesity, obesity was defined as a BMI ≥28kg/m^2. Blood pressure was measured three times after 15 minutes of rest in a sitting position, with the mean blood-pressure readings used in the analyses.

Laboratory findings such as serum uric acid (sUA), glucose (GLU), blood lipids, very low density lipoprotein cholesterol (VLDL-C), apolipoprotein A1 (apoA1) and apolipoprotein B100 (apoB100) were tested by Automatic Chemistry Analyzer, in which sUA was detected by colorimetric method with enzyme ratio. Blood cell count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were also determined.

Diagnosis criteria

Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or current use of antihypertensive medication. Hyperlipidemia was defined as satisfying at least one of the following: total cholesterol (TC) >6.22mmol/L, triglycerides (TG) >2.26mmol/L, low density lipoprotein cholesterol (LDL-C) ≥4.14mmol/L, or high density lipoprotein cholesterol (HDL-C) ≥1.04mmol/L. Hypertriglyceridemia alone was defined as TG >2.26mmol/L. Hypercholesterolemia alone was defined as TC >6.22mmol/L.

Statistical analysis

SPSS 16.0 was used for the statistical analysis. Measurement data were reported as mean ± SD and assessed using Student's t-test. The enumeration data were expressed as percentages and were compared with the χ^2 test. We then constructed a multivariable logistic regression using all factors with associations to analyze primary gout. The independent variables were hypertension, diabetes, body mass index, smoking, alcohol intake, dietary habits (purine-rich diets), sUA, triglyceride level and total cholesterol. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A value of $p<0.05$ was defined as significant.

Results

The clinical characteristics of patients with primary gout

There were 583 cases of incident gout in the study population. The age of gout onset was 16-72 years old, with an average age of 53.00 ± 14.20 years. The average disease duration was 6.45 ± 7.30 years. Nearly all gout patients had one joint involvement at some point; we analyzed the involvement pattern of these joints. More than half of the patients had first metatarsophalangeal (MTP1) involvement, while 17.32% had ankle joint, 5.15% had knee joint,

3.60% had hand joint, and 5.32% had heel, the dorsum of foot and other parts. When patients presented with severe joint pain, 62.43% had predisposing factors, 88.16% reported alcohol intake and high purine diet intake, 11.84% reported fatigue, chills and other non-dietary factors before their gout flare. Patients with primary gout also have a variety of complications. The most common comorbidity was hyperlipidemia (66.90%), followed by hypertension (35.68%) and hypercholesterolemia (23.33%). Furthermore, the study found that 12.17% of gout patients had concurrent tophus and 18.01% had diabetes. However, tophus occurs more frequently between 3 to 8 years after the gout disease, and the course of the disease was significantly extended in these patients (11.90 ± 8.00 vs 6.15 ± 7.40 years, p<0.001). The average sUA was 565.00 ± 134.40 μmol/L, which was significantly higher that of patients without tophi (456.00 ± 105.20 μmol/L, p=0.001).

There were differences between gout patients and healthy controls

There was no significant difference between gout patients and controls in age and sex. White blood cells (WBC), neutrophils (GR), monocytes (Mo), globulin (GLOB), sUA, BMI, GLU, TG, VLDL and apoB100 were significantly higher in the GA group (Table 1). In contrast, the proportions of HDL was significantly lower in the GA group (1.16 ± 0.41 vs 1.36 ± 0.31 mmol/L, p=0.026) compared with the HC group. As expected, we found that serum inflammatory markers for infectious arthritis like ESR and CRP were several times higher than the normal value in gout patients (Reference value: CRP 0-9mg/L, ESR 0-21mm/h).

Logistic regression analysis related risk factors of primary gout

We subsequently conducted logistic regression analyses using questionnaire data obtained from patients with primary gout. Hyperuricemia, alcohol intake, BMI, hypertriglyceridemia, dietary habits (purine-rich diets), hypertension and smoking were all found to be independent risk factors of gout in the multivariable regression model (Table 2). The significant relationship between sUA levels and gout incidence was more evident in the study population (OR=8.29, 95% CI=4.50-15.25). Similarly, alcohol intake, BMI, and high triglycerides played important roles in the pathogenesis of gout (all p<0.001).

Table 1. Comparison of clinical and laboratory parameters of the GA and HC group.

	GA group (n=583)	HC group (n=459)	p
Age, year*	48.18 ± 12.16	47.35 ± 11.28	0.259
Sex, male/female	558/25	436/23	0.687
Disease duration, year*	6.45 ± 7.30	-	-
Tophi, n (%)	71 (12.17)	-	-
BMI, kg/m^2*	25.99 ± 3.32	23.18 ± 4.47	<0.001
sUA, μmol/L*	509.00 ± 132.61	308.00 ± 56.34	<0.001
GLU, mmol/L,*	6.27 ± 1.82	5.18 ± 0.49	<0.001
WBC×10^9/L*	6.89 ± 2.41	4.78 ± 1.55	<0.001
GR×10^9/L*	4.75 ± 2.25	3.48 ± 0.88	<0.001
LY×10^9/L*	1.79 ± 0.73	2.13 ± 0.65	0.150
Mo×10^9/L*	0.69 ± 0.27	0.49 ± 0.19	<0.001
TG, mmol/L*	2.34 ± 1.60	1.15 ± 0.67	<0.001
GLOB, g/L*	29.96 ± 5.22	26.63 ± 4.31	<0.001
TC, mmol/L*	4.88 ± 0.98	4.45 ± 0.44	0.081
HDL, mmol/L*	1.16 ± 0.41	1.36 ± 0.31	0.026
LDL, mmol/L*	2.62 ± 0.87	2.65 ± 0.55	0.520
VLDL, mmol/L*	1.13 ± 0.69	0.53 ± 0.22	<0.001
apoA1, mmol/L*	1.30 ± 0.35	1.24 ± 0.20	0.111
apoB100, mmol/L*	0.93 ± 0.26	0.78 ± 0.14	0.015
ESR, mm/h*	30.26 ± 25.39	-	
CRP, mg/L*	18.36 ± 26.21	-	

t test or χ^2 test, p<0.05 was defined as statistically significant.
GA: primary gouty arthritis, HC: healthy control, BMI: body mass index is calculated by the equation BMI=weight(kg)/height(m)^2, sUA: blood uric acid, GLU: blood glucose, WBC: white blood cells, GR: neutrophils, LY: lymphocytes, Mo: monocytes, TG: triglycerides, TC: total cholesterol, HDL: high density lipoprotein, LDL: low density lipoprotein, VLDL: very low density lipoprotein, apoA1: lipid carrier proteinA1, apoB100: lipid carrier protein B100, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, *: the values show as mean ± standard deviation (SD).

Table 2. Multiple logistic regression analysis in primary gout.

Variable	Partial regression coefficient	Standard error	χ^2	p value	Odds ratio	95 % CI
Hypertension	1.02	0.35	8.25	0.004	2.76	1.38-5.52
Diabetes	-0.51	0.51	0.98	0.322	0.60	0.22-1.64
BMI	1.58	0.31	25.42	<0.001	4.84	2.62-8.94
Smoking	0.80	0.31	6.55	0.001	2.22	1.21-4.09
Alcohol intake	1.68	0.33	26.32	<0.001	5.34	2.82-10.13
Purine-rich diets	1.04	0.31	11.05	<0.001	2.81	1.53-5.18
sUA	2.11	0.31	46.17	<0.001	8.29	4.50-15.25
TG	1.52	0.38	16.05	<0.001	4.59	2.18-9.67
TC	-0.17	0.46	0.14	0.710	0.84	0.34-2.09
Constant	-4.28	0.52	67.12	<0.001	0.01	-

CI: confidence interval, BMI: body mass index, sUA: blood uric acid, TG: triglycerides, TC: total cholesterol.

Discussion

Within this Chinese cohort of gout patients, we described the typical clinical features. MTP1 involvement is pathognomonic of gouty arthritis. Approximately 68.61% of first gout attacks occurred at the MTP1, which was the most attacked joint. Ankle and knee involvement were also among the most commonly affected joints in patients with gout, which was in accordance with the findings of Masseoud et al. [10]. Of note, patients with gout onset at atypical sites, such as in knuckles or heel, needed more vigilance from practitioners so as not to miss diagnosis or misdiagnose. Yu et al. reported that tophus formation was used as a marker for gout severity [11]. Our research showed that only a few patients developed subcutaneous tophus, and the time from first gouty attack to visible tophi was between three to eight years. Unfortunately, we did not have any data about the predisposing factors of tophi. However, we speculated that the formation of tophi might have been due to longer disease duration and higher sUA levels.

The culprit for the onset of gout is hyperuricemia. To our knowledge, many studies have highlighted the close association between uric acid and metabolic syndrome [12,13]. The growing prevalence of obesity and metabolic syndrome may be related to the increasing prevalence of gouty arthritis in recent decades [14]. Correspondingly, we found that patients with gout had higher blood glucose and triglyceride levels than control subjects. This may be related to uric acid's role in regulating hepatic lipogenesis through the generation of mitochondrial oxidative stress [15]. Uric acid, an endogenous inhibitor of 5' adenosine monophosphate-activated protein kinase (AMPK) activity in human hepatocytes, can further inhibit β-fatty acid oxidation and stimulate triglyceride accumulation [16], and also promote gluconeogenesis [17], thus maintaining high glucose levels in the blood. According to a meta-analysis of 11 cohort studies, blood uric acid level was associated with an increased risk of diabetes [18]. These results indicate that uric acid may play an important role in the development of obesity and diabetes. We can speculate that high serum uric acid levels may underlie the metabolic syndrome pandemic. However, our logistic regression analysis indicated that there is no significant association between diabetes with incident gout. This may be due to the small study population. Therefore, larger study populations and longer prospective trials are needed to verify these findings.

Hyperuricemia is associated with increased risk of cardiovascular disease (CVD) morbidity and mortality [19,20], especially hypertension. The mechanisms regarding how hyperuricemia contributes to CVD is still not understood. Several studies have found that high uric acid levels could reduce nitric oxide bioavailability, elevate blood pressure, and induce oxidative stress in adipocytes, leading to insulin resistance and platelet adhesion [21,22]. Epidemiological studies have also reported that sUA induce endothelial dysfunction and stimulate vascular smooth cell proliferation [23,24], which may contribute to the initial manifestation of chronic vascular inflammation. Increased serum uric acid levels promote the generation of vasoconstrictive substances, eventually leading to growth and rupture of atherosclerotic plaques, potentially contributing to the progression of atherosclerotic changes. In summary, these data strongly confirm that hyperuricemia as an independent risk factor, and show a positive dose-response relationship between serum uric acid levels and the incidence of coronary heart disease (CHD). In our study, we found dyslipidemia in the GA group is consistent with the typical characteristics of atherogenic lipid profile; the TG, TC, LDL were significantly higher than that of healthy subjects, and HDL was significantly reduced. Interestingly, we also found that hypertension was an independent risk factor for gout.

There are multiple causes for the rising serum acid level and prevalence of primary gout including purine-rich diets, smoking, alcohol consumption and environmental factors. However, we found that more than 1/3 of patients (37.56%) with gouty arthritis were not affected by the above factors. These patients may be affected by genetic components and even more factors secondary to the effects of environmental and genetic interaction. Certainly, all of these components need further research.

Nowadays, gout has become a major health concern worldwide. The findings from our study are therefore clinically significant. This study also demonstrates that asymptomatic hyperuricemia possibly has much broader implications than simply a risk factor for gout. As it turns out, uric acid is not an inert molecule but rather a deleterious factor that is tremendously harmful to the human body. The key risk factors for primary gout are hyperuricemia, alcohol intake, obesity, hypertriglyceridemia, purine-rich diets, hypertension and smoking. We advise that people with high risk factors should be given reasonable dietary guidance to change their living habits and even living environment to prevent gout.

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Conflict of interest

None.

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