Gout and Hyperuricemia. 2017; 4(1): 32-36
Access publication Mar. 2017

Gout and Hyperuricemia

Associated factors in patients with refractory gout

Jing Yang[1], Jian-ling Dong[1,*], Jinmei Zou[1], Yu Zhang[1], Lan Tian[1], Min Li[1]

Objective: To analyze associated factors of patients with refractory gout.
Methods: 150 gout patients were recruited and divided into the refractory or nonrefractory gout group in this cross-sectional study. The association of refractory gout with variables was assessed using bivariate correlations. Subsequent binary logistic models with appropriate adjustments were used to find the associated factors of refractory gout patients.
Results: The prevalence of hypertension, gouty nephropathy and delayed prescription of urate-lowering therapy was higher in refractory gout group compared with controls ($p<0.05$). Patients with refractory had less awareness about gout and the goals of urate-lowering therapy, and poorer medication compliance ($p<0.05$). A multivariate unconditional logistic regression analysis showed five associated factors in patients with refractory gout, including disease duration (Odds ratio (OR)=1.31, $p<0.001$), gouty nephropathy (OR=4.64, $p=0.024$), awareness about goal of urate-lowering therapy (OR=0.20, $p=0.005$), delay in prescription of urate-lowering therapy (OR=2.97, $p=0.034$) and medication compliance (OR=4.74, $p=0.003$).
Conclusion: The study showed that gout patients with longer gout duration, gouty nephropathy, less knowledge about the goals of urate-lowering therapy, delayed use of urate-lowering therapy and poor drug compliance were more prone to develop refractory gout.

Key words: Gout; Refractory gout; Gouty nephropathy; Compliance

[1]Department of Rheumatology, Mianyang Central Hospital, 621000, Sichuan, China.

*Corresponding author:
Jian-ling Dong,
Department of Rheumatology, Mianyang Central Hospital, 621000, Sichuan, China.
Email: dong1980565@163.com

Tel: 13689687601
Fax: 0816-2243604

Submitted on Feb. 16, 2017; accepted on Apr. 5, 2017.

Introduction

Gout is an inflammatory disease caused by the deposition of urate crystals in musculoskeletal and other tissues. When serum concentrations of urate exceed approximately 6mg/dl [1], urate may precipitate in joint space leading to acute attacks of arthritis. Continued accumulation of urate lead to tophus formation, chronic inflammatory arthritis, and joint destruction [2]. The global prevalence of gout is 0.08% [3]; although diagnostic methods and treatment for gout has obviously improved in recent years, as the population ages and socioeconomic conditions improve, the social burdens of gout are expected to increase [3], posing a severe challenge to rheumatologists.

Refractory gout refers to symptomatic gout where treatment has failed to maintain a serum uric acid (SUA) level below 6 mg/dl with oral urate-lowering therapies (ULTs) and appropriate medical management [4]. Patients with refractory gout are at risk for progressive urate crystal deposition disease characterized by frequent attacks of acute gouty arthritis, gouty arthropathy, and enlarging tophi which are often associated with chronic pain, impairment of physical function and compromised quality of life [5]. Urate-lowering treatments that are currently available in China include allopurinol, febuxostat, and benzbromarone. The goal of therapy is to reduce serum urate concentrations to 6mg/dl. However, in patients with refractory gout, a serum urate level 4mg/L or lower is recommended [6].The object of the present study was to identify the associated factors in patient with refractory gout.

Methods

Participants

A cross-sectional observational study was conducted in 150 gout patients. All patients included in the study were greater than 18 years of age, fulfilled the American College of Gout 1987 criteria for the classification of gout [7], and visited the rheumatic outpatient center in Mianyang of Sichuan, China, between January 2013 and July 2014. Patients who met the following criteria were considered as having refractory gout: a baseline serum UA of 8.0 mg/dl or greater, at least three or more self-reported gout flares during the previous eighteen months, and one or more tophi or gouty arthropath. They also had contraindications for or intolerance to treatment with allopurinol or a failure to achieve a normal SUA after at least three months of treatment with the maximum medically appropriate dose of allopurinol (the only xanthine oxidase inhibitor approved during the trials).

SUA should be reduced and maintained to a level below 300 μmol/l (5mg/dl) to prevent further crystal formation and to encourage dissolution of excited crystals in patients with refractory gout. Only patients who signed an informed consent form were enrolled. The study was approved by the Ethics Committee of the Mianyang Central Hospital (IRB number: 20150101).

All refractory gout patients had initially received once-daily febuxostat (40mg), allopurinol (300mg), or benzbromarone (50mg) for three month or more. If the serum urate level could not achieve the target value of <6.0 mg/dl, the dosage of the drugs were titrated, where permitted by safety and renal function monitoring. All patients with gout flares received colchicine 0.5-1 mg/day as prophylaxis during the urate-lowering therapy. When colchicine was not tolerated, a non-steroidal anti-inflammatory drug was prescribed. Each treatment regimen was evaluated after a treatment period of 1 month by measuring serum urate.

Clinical assessments

All participants underwent a thorough structured interview including a detailed review of demographics (age, sex, height and weight, education, family history), medical history, hospital records, and physical examination including body mass index (BMI). Form of gout, disease duration, comorbidities and pharmacotherapy was obtained from medical records. Interviews were standardized in a written protocol and lasted approximately 50 minutes. These interviews were conducted by one researcher and took place in a discrete place in the waiting room on the day of a visit to the rheumatologist. The study subjects' electronic medical records were reviewed for chronic conditions such as diabetes, hypertension, cardiovascular disease, and hyperlipidemia defined by international classification of diseases (ICD)-9 codes used by physicians for administrative purposes; pharmacotherapy was obtained from medical records.

Measurements

The questionnaire was developed to include questions on the following topics: knowledge about gout, adverse effect to urate-lowering therapy, and treatment history before standard urate-lowering therapy. The statements focused on the etiology of gout (e.g. gout is caused by too much uric acid, gout flares can result from crystals forming in and around joints), urate-lowering therapy (e.g. urate-lowering therapy is the key to treating gout, medications which lower uric acid such as allopurinol or probenecid should be taken), the goal of urate-lowering therapy (serum urate should be lowered in patients with gout to achieve, at a minimum, a serum urate level 6 mg/dl; achieving and maintaining target serum urate level is critical for alleviating the clinical manifestations of gout), and time of urate-lowering therapy.

Patients designated these statements as either "True", "False", or "Not Sure". Each item was scored with 1 point given for each correct answer and 0 for incorrect or "Not Sure" responses.

For the assessment of side effects, patients were asked: "Do you experience any side effects after your treatment?" Treatment history was assessed based on answers to three questions:

1) Have you ever used urate-lowering therapy? 2) Has there been any delay with prescribing urate-lowering therapy? 3) Has urate-lowering therapy been used for more than three months? The four items were assessed using 1 for yes or 0 for no.

The items assessing overall health motivation and trust were drawn from existing measures. The knowledge and belief items were developed by the authors for this present study. A number of background items were included (e.g. age, education). Preliminary versions of the questionnaire were pre-tested using cognitive interviews with a convenience sample of 5 patients in 1:1 sessions. A brief description of each set of items follows.

The patient drug compliance was determined using the Compliance Questionnaire Rheumatology (CQR) [8]. For

our purposes, this 19-item questionnaire was adapted for gout by replacing the term "rheumatoid arthritis" with the term "gout". The possible range of this questionnaire is 0 (complete noncompliance) to 100 (perfect compliance), with a cutoff score of 80%.

Interviews were standardized in a written protocol and lasted approximately 40 min. These interviews were conducted by one researcher and took place in a discrete place in the waiting room on the day of a visit to the rheumatologist. All questionnaires were evaluated in the standard way.

Statistical analysis

All values are expressed as mean ± standard deviation (SD), median (25th-75th percentile values) or percentages as appropriate. Comparisons were performed by Student's t-test, Mann-Whitney U-test and chi-square test for normally distributed, abnormally distributed and categorical variables, respectively. Logistic regression analysis was utilized to identify the independence risk factor in refractory gout patients. Significance was set at a value of $p<0.05$. All analyses were conducted using SPSS 17.0.

Results

Clinical characteristics

Refractory gout patients, when compared to non-refractory counterparts, were older (57.43 ± 15.73 vs 52.00 ± 16.16 years, t=-2.06, p=0.041), had longer disease duration (11.66 ± 9.18 vs 3.84 ± 0.42 years, t=-7.29, p<0.001), and were more likely to have hypertension (20.00 vs 13.33%, p=0.001). They also had higher incidence of gouty nephropathy (17.33 vs 2.67%, p<0.001). There was no significant difference between the patient group and controls in terms of sex, degree of education, family history and BMI. Of the 150 patients, 30% refractory patients were noncompliant with treatment compared to controls; there were also more patients that delayed the use of urate-lowering therapy (26.67 vs 14.00%, p<0.001). There were no significant differences between refractory and non-refractory gout patients in terms of awareness about causes of the disease, persistence of urate-lowering, therapy, how to choose urate-lowering therapy, the time of urate-lowering therapy, and history treatment including whether or not use blood uric acid drugs, whether or not persistence of urate-lowering therapy, and whether or not have adverse effect to urate-lowering therapy (Table 1).

Multivariable analysis

A logistic regression model including the 7 suspicious risk factors including age, disease duration, hypertension, gouty nephropathy, awareness about goal of urate-low-

Table 1. Clinical characteristics of patients with refractory gout and controls.

Factor	Refractory (n=65)	Control (n=85)	p
Male, n (%)	63 (42.00)	81 (54.00)	0.698
Age (mean ± SD)	57.43 ± 15.73	52.00 ± 16.16	0.041
Education degree, n (%)			
< High school and college	28 (18.67)	40 (26.67)	0.741
≥ High school and college	37 (24.67)	45 (28.00)	
BMI (kg/m^2, mean ± SD)	24.69 ± 3.22	25.09 ± 3.88	0.538
Disease duration, years	11.66 ± 9.18	3.84 ± 0.42	<0.001
Family history of gout, n (%)			
Yes	23 (15.33)	39 (26.00)	0.242
No	42 (28.00)	46 (30.67)	
Comorbidities, n (%)			
Diabetes	7 (4.67)	9 (6.00)	1.000
Hypertension	30 (20.00)	20 (13.33)	0.001
Cardiovascular disease	3 (2.00)	4 (2.67)	1.000
Hyperlipidemia	16 (10.67)	20 (13.33)	0.849
Number of affected joints			
≥ 3	14 (9.33)	11 (7.33)	0.188
< 3	51 (34.00)	74 (49.33)	
Gouty nephropathy, n (%)	26 (17.33)	4 (2.67)	<0.001
Patients with knowledge regarding:			
The etiology of gout, n (%)	44 (29.33)	46 (30.67)	0.130
Urate-lowering therapy, n (%)	23 (15.33)	25 (16.67)	0.482
Goal of urate-lowering therapy, n (%)	13 (8.67)	31 (20.67)	0.031
Time of urate-lowering therapy, n (%)	15 (10.00)	18 (12.00)	0.843
Treatment history			
Use of urate-lowering therapy Yes, n (%)	20 (13.33)	36 (24.00)	0.174
Delay of prescribing of urate-lowering therapy Yes, n (%)	40 (26.67)	21 (14.00)	<0.001
Persistence of urate-lowering therapy Yes, n (%)	12 (8.00)	9 (6.00)	0.235
Adverse effect to urate-lowering therapy Yes, n (%)	4 (2.67)	1 (0.67)	0.167
Poor drug compliance, n (%)	45 (30.00)	21 (14.00)	<0.001

SD: standard deviation.

Table 2. Logistic regression analysis of risk factors in patients with refractory gout.

	β	S.E	P	OR	95% CI
Age	-0.002	0.02	0.921	1.00	0.97-1.03
Disease duration	0.27	0.07	<0.001	1.31	1.15-1.50
Hypertension	-0.26	0.50	0.610	0.77	0.29-2.08
Gouty nephropathy	1.54	0.68	0.024	4.64	1.22-17.65
Goal of urate-lowering therapy (Patients with gout about knowledge awareness)	-1.61	0.57	0.005	0.20	0.07-0.61
Delayed using of urate-lowering therapy (History of treatment information)	1.09	0.51	0.034	2.97	1.09-8.11
Poor drug compliance (History of treatment information)	1.56	0.52	0.003	4.74	1.70-13.16

S.E.: standard error; OR: odds ratio; CI: confidence interval.

ering therapy, delayed use of urate-lowering therapy, and poor drug compliance, which were chosen by single factor analysis, was utilized in order to evaluate which factors were independently associated with the presence of refractory gout. Variables that retained significance were disease duration (Odds ratio (OR)=1.31, p<0.001), and Gouty nephropathy OR=4.64, p=0.024), awareness about goal of urate-lowering therapy (OR=0.20, p=0.005) delayed use of urate-lowering therapy (OR=2.97, p=0.034), and poor drug compliance (OR=4.74, p=0.003; Table 2).

Discussion

Despite advanced understanding of the molecular bases of hyperuricemia and gouty inflammation and the extensive experience of many providers, substantial quality of care gaps exist in gout management [6]. Fels and Sundy have point out some reasons to explain refractory disease, such as delayed or insufficient dosing of urate lowering therapy and poor patient compliance or intolerance to medication [9]. Simone et al. [10] believe that particular factors related to gout pathophysiology and/or particular metabolic mechanisms may have played an essential role, resulting in a difficult to treat attack, despite adequate therapy. In our study, we similarly found that delayed prescription of uric acid lowering therapy and poor drug compliance were associated with refractory gout.

The study shows that delay of prescribing urate-lowering therapy was connected with patients with refractory gout. One study reported that, with currently prescribed doses of available oral ULTs, tophus resolution commonly requires many months to years of treatment [11]. Another study of 734 patients with untreated gout [12] reported that the frequency of gout attacks increased by 49% without treatment; in 10 and 20 years the incidence of gout stones were as high as 47% and 47% respectively. If patients with refractory gout were prescribed urate lowering therapy as soon as possible, the incidence would be reduced.

Gout is among the chronic diseases with the lowest treatment adherence rate [13]. A total of 1331 gout patients (17% of the study population) were adherent to allopurinol therapy, while 36% and 47% had partial and poor adherence, respectively [14]. We used the Compliance Questionnaire Rheumatology (CQR) to estimate drug compliance. This compliance-measuring tool was developed and validated against a Medication Event Monitoring System (MEMS device) in patients with inflammatory rheumatic diseases, with high sensitivity and specificity (98 and 67%, respectively). In our study, the proportion of compliant patients with refractory gout was lower than that of patients with rheumatoid arthritis (RA, 67%) or patients with various rheumatic disorders (52%) [8]; The reasons for noncompliance seem to be inappropriate prophylactic colchicine use, poor diagnosis and treatment knowledge about gout disease from the physician, and patients' fear of adverse drug reaction [15].

The disease duration in patients with refractory gout was longer than in controls; foreign reports for the average duration of refractory gout development are close to about 12 years or so [16]. Disease course is a risk factor for refractory gout because long course of continuous high uric acid may lead to recurrent gout arthritis and tophi formation, gouty nephropathy, and other complications. Tophi, mainly found in articular, periarticular, bursal, bone, auricular, and cutaneous tissues, are a pathognomonic feature of gout. Tophi contribute to gouty joint destruction and deformity and may undergo acute or chronic ulceration, erode adjacent bone, cause pressure effects on surrounding tissues and organs, interfere with joint function or become infected.

The prevalence of gouty nephropathy, a risk factor for refractory gout, in refractory gout patients in this study was 17.3%; this makes the management of refractory gout especially challenging. Because some gout therapies have a greater rate of adverse drug interactions in these patients, NSAIDs for the most part are contraindicated in patients with impaired kidney function. The choice of

urate-lowering agents is limited in patients with chronic kidney disease (CKD) and creatinine clearance less than 50 mL/min. Most uricosuric agents are largely ineffective. Patients with CKD are at greater risk of allopurinol hypersensitivity syndrome, even at very low doses [17]. Recent reports indicate that hyperuricemia itself may contribute to the pathogenesis of certain gout-related comorbidities, including kidney disease [18]. Hyperuricemia is also a primary risk factor for the development of gout [19]. Thus, the key is early control of uric acid levels in patients with gout.

Achieving and maintaining serum urate level to a target is critical for alleviating the clinical manifestations of gout. This study shows that 8.67% patients with refractory gout know the importance and goals of urate-lowering therapy. We can speculate that patients with gout in China don't take into great consideration urate-lowering therapy. The present situation may be connected with the lack of uniform treatment guidelines, doctors' lack of knowledge about urate-lowering therapy [20], insufficient disease education, and patient's emphasis on gout.

In conclusion, in order to reduce the prevalence of refractory gout we propose that adequate management of refractory gout flares requires the below steps: (a) emphasis on early detection and treatment of gouty nephropathy and tophi, (b) paying close attention to health education regarding the timing of urate-lowering therapy and continued use to treat to target, (c) improve treatment compliance in gout patients. (d) If regular urate-lowering therapy fails, we should carefully analyze failure causes, and found effective urate lowering options to prevent or reverse gout progression.

References

1. Fiddis RW, Vlachos N, Calvert PD. Studies of urate crystallisation in relation to gout. Ann Rheum Dis. 1983; 42 Suppl 1: 12-5.
2. Roddy E, Choi HK. Epidemiology of gout. Rheum Dis Clin North Am. 2014; 40: 155-75.
3. Smith E, Hoy D, Cross M, et al. The global burden of gout: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis. 2014; 73: 1470-6.
4. Becker MA, Schumacher HR, Benjamin KL, et al. Quality of life and disability in patients with treatment-failure gout. J Rheumatol. 2009; 36: 1041-8.
5. Khanna PP, Nuki G, Bardin T, et al. Tophi and frequent gout flares are associated with impairments to quality of life, productivity, and increased healthcare resource use: Results from a cross-sectional survey. Health Qual Life Outcomes. 2012; 10: 117.
6. Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken). 2012; 64: 1447-61.
7. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yu TF. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum. 1977; 20: 895-900.
8. Hromadkova L, Soukup T, Cermakova E, Vlcek J. Drug compliance in patients with systemic scleroderma. Clin Rheumatol. 2012; 31: 1577-83.
9. Fels E, Sundy JS. Refractory gout: what is it and what to do about it? Curr Opin Rheumatol. 2008; 20: 198-202.
10. Fargetti S, Goldenstein-Schainberg C, Silva Abreu A, Fuller R. Refractory gout attack. Case Rep Med. 2012; 2012: 657694.
11. Li-Yu J, Clayburne G, Sieck M, et al. Treatment of chronic gout. Can we determine when urate stores are depleted enough to prevent attacks of gout? J Rheumatol. 2001; 28: 577-80.
12. Gutman AB. The past four decades of progress in the knowledge of gout, with an assessment of the present status. Arthritis Rheum. 1973; 16: 431-45.
13. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. Pharmacotherapy. 2008; 28: 437-43.
14. Zandman-Goddard G, Amital H, Shamrayevsky N, Raz R, Shalev V, Chodick G. Rates of adherence and persistence with allopurinol therapy among gout patients in Israel. Rheumatology (Oxford). 2013; 52: 1126-31.
15. Perez-Ruiz F. Treating to target: a strategy to cure gout. Rheumatology (Oxford). 2009; 48 Suppl 2: ii9-ii14.
16. Becker MA, Baraf HS, Yood RA, et al. Long-term safety of pegloticase in chronic gout refractory to conventional treatment. Ann Rheum Dis. 2013; 72: 1469-74.
17. Hung SI, Chung WH, Liou L, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci U S A. 2005; 102: 4134-9.
18. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum. 2011; 63: 3136-41.
19. Heinig M, Johnson RJ. Role of uric acid in hypertension, renal disease, and metabolic syndrome. Cleve Clin J Med. 2006; 73: 1059-64.
20. Doherty M, Jansen TL, Nuki G, et al. Gout: why is this curable disease so seldom cured? Ann Rheum Dis. 2012; 71: 1765-70.