Clinical Features of Familial Gout and Effects of Probable Genetic Association Between Gout and Its Related Disorders

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We examined whether the age at onset, gender, arthritic manifestations, and tophus formation in familial gout are different from those in nonfamilial gout, and we also examined the contributory effect of genetic association to the concurrence of hypertriglyceridemia, hypercholesterolemia, type 2 diabetes mellitus (DM), hypertension, obesity, and renal insufficiency with gout in Taiwan. A total of 21,373 gout patients' data from Ho-Ping Gout database were analyzed in this study retrospectively. The clinical and laboratory data were compared between familial and nonfamilial gout. Mean age at onset of gout in familial subjects was significantly 7.5 years lower than that of nonfamilial subjects (40.9 ± 13.4 *v* 48.4 ± 14.2 years, *P* = .0001), while gender, arthritic severity, and tophus formation were not significantly different between these 2 groups. Familial gout had lower serum triglyceride (TG), total cholesterol (TC), and percentage of hypertension than nonfamilial gout (182.4 ± 125.3 *v* 195.9 ± 135.8 mg/dL, *P* = .0001; 207.5 ± 42.5 *v* 210.4 ± 48.8 mg/dL, *P* = .0003; and 19.57% *v* 22.56%, *P* < .0001, respectively). Their serum creatinine, body mass index (BMI), and percentage of type 2 DM were not significantly different. Our results demonstrate that familial gout is associated with precocious onset. Furthermore, the contributory effect of genetic association to the concurrence of hyperlipidemia and hypertension with gout is less than that of environmental factors, while the effect of genetic association to the concurrence of obesity, type 2 DM, and renal insufficiency with gout is equivalent to that of environmental factors.

GOUT IS A metabolic disorder manifested as arthritis that is attributed to deposition of monosodium urate monohydrate crystals secondary to hyperuricemia.[1] Gout is recognized as a familial disorder since antiquity[1] and this group of gout patients with a family history is called familial gout. According to the case reports of familial gout in Caucasian[2-7] and Japanese subjects,[8,9] familial gout patients and their family members tend to have precocious onset of hyperuricemia[2-9] and consequent precipitation of urate in their joints inducing gouty arthritis early in their life. Apart from the feature of precocious onset in familial gout, it has not been well elucidated whether their arthritis is more severe than those of nonfamilial gout and whether familial gout is more predisposed to tophus formation. A study comparing these clinical features between familial and nonfamilial gout is needed to answer these questions.

Although it is well known that gout is a disease of male preponderance,[1] familial gout has been observed in both genders.[2-9] Except for some rare x-linked transmitted type, familial gout should predominantly be a polygenic disease,[1] and both male and female family members could have the same probability of inheriting the gene for gout. Therefore, in familial gouty patients, the proportion of female subjects should be equal to that of male ones. However, the impact of female hormone that is uricosuric in action cannot be neglected, because it has been well known that estradiol can lower serum urate (UA) in females.[10,11] Nevertheless, under the impact of heredity, whether male preponderance still exists in familial gout or not is in question, and there has been no study involving a large number of gouty families to examine this.

In addition to the articular involvements, gout is also associated with many metabolic disorders, including obesity, hypertension, and hypertriglyceridemia.[1] Although it has not been firmly established whether type 2 diabetes mellitus (DM) or hypercholesterolemia is associated with gout,[1] our previous work on 4,000 Taiwanese gouty patients has shown that gout in Taiwan has a higher prevalence of type 2 DM and serum total cholesterol (TC) levels than the age-matched general population.[12] The etiology of the association between gout and these metabolic disorders may be multiple. Many environmental factors are usually considered to be most responsible for their association,[1] while genetic factors have rarely been paid attention to. There were only 3 studies considering the genetic association between gout and its related disorders, and these studies were all focusing on hypertriglyceridemia[13-15] with no study on other metabolic disorders related to gout. The investigators found a higher frequency of apoprotein CIII S2 allele[13,14] and apolipoprotein e4 allele[15] in gouty subjects and thus suggested that the association between gout and hypertriglyceridemia was due to genetic linkage.[13,14] However, they neglected the fact that their subjects encompassed all gouty patients, and thus most of the subjects were nonfamilial gouty patients who did not carry the defective gene(s) for gout. Studies on subjects mostly not carrying the defective genes for gout cannot reveal the genetic association between gout and hypertriglyceridemia. Whether there is a genetic association between them is still unknown. However, the contributory effect of genetic association, if any, to their concurrence can be examined in a study comparing serum triglyceride (TG) be-

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tween familial and nonfamilial gouty patients. If the effect of genetic association is great enough, serum TG in familial gout should be higher than that in nonfamilial gout, because patients carrying the defective gene(s) for gout should have a greater probability of carrying the defective gene(s) for hypertriglyceridemia at the same time. Also, this method can be applied to other metabolic disorders associated with gout to determine the effect of genetic association. However, such a study is still lacking.

In addition to the above metabolic disorders, renal insufficiency is also a disorder that is frequently associated with gout,[1] and we have found the prevalence of renal insufficiency in Taiwanese gout to be over 20%.[12] It has not been firmly established whether urate deposition in the kidneys could mainly contribute to the declined renal function in gout.[1] Other factors, such as coexistent hypertension, lead exposure, aging, and some unknown factors may also be responsible.[1] These unknown factors consist of both environmental and genetic ones, while it is unclear which one is more contributory than the other. As far as genetic factors are concerned, 3 entities of familial nephropathy have been identified, including juvenile nephronophthisis, polycystic kidney disease type 1, and familial juvenile hyperuricemic nephropathy.[16] All 3 entities are inherited in autosomal-dominant form, and their candidate genes have been mapped to be on chromosome 2p13, 16p13, and 16p12, respectively.[17] These defective genes can cause the concurrence of both renal insufficiency and hyperuricemia precociously. However, these 3 entities of autosomal-dominant familial nephropathy are very rare, and some other hyperuricemia-associated entities of familial nephropathy with polygenic inheritance, which might account for the most part of renal dysfunction in gout, could be present. These candidate genes could also contribute to the concurrence of renal insufficiency and gout, while they have never been studied. If the contributory effect of these genes is great enough, they can result in worse renal function in familial gout than that in nonfamilial gout. Nevertheless, such a study comparing renal function between familial and nonfamilial gout is still lacking.

To determine whether the age at onset, gender, arthritic manifestations, and tophus formation in familial gout are different from those in nonfamilial gout and to determine the contributory effect of genetic association to the concurrence of hypertriglyceridemia, hypercholesterolemia, type 2 DM, hypertension, obesity, and renal insufficiency with gout, we performed a retrospective cross-sectional study to answer these questions. We compared the clinical and laboratory data between patients with and without a family history of gout from our database containing more than 21,000 Taiwanese cases.

SUBJECTS AND METHODS

Ho-Ping Gout Database

The Ho-Ping Gout Database contains the clinical and laboratory data of all gouty patients newly visiting the Clinic of Gout at Taipei Municipal Ho-Ping Hospital. This database was set up in January 1983 by Dr Ching-Lang Chen for the purpose of studying clinical aspects of gout. All new cases diagnosed as gout according to the Wallace criteria[18] at our clinic were routinely interviewed and physically examined by our rheumatologists who completed a questionnaire about their birth date, gender, age at onset, attack sites, associated disorders, medications, family history of gout, amount of alcohol consumption, and cigarette smoking. After the interview, all patients' body weight and height were measured by a nurse. All patients' serum samples were then collected the next morning for biochemical tests after an overnight fast. If the patients were taking antihyperuricemic, diuretics, or lipid-lowering medications, they were instructed to receive the biochemical tests after 1 month of discontinuing these medications. All of the above results were keyed into a computer database for future analysis. After the second visit, every patient was followed up at our clinic every 3 months.

Protocol

To show the effect of all possible genes for gout, not only those of autosomal dominant or recessive inheritance, we did not analyze gouty families including many affected members in this study, but we broke these families into affected singles with positive family history. If 1 or more of a gouty patient's third-degree or closer relatives was also affected by gout and the diagnosis had been confirmed by a rheumatologist, he (or she) was defined as familial gout. On the contrary, if none of a gouty patient's third-degree or closer relatives was affected by gout, he (or she) was defined as nonfamilial gout.

In this study, experiments were organized into 2 series. Familial gout was defined as the dependent variable in both series, while different sets of independent variables were defined in each series. Independent variables that would not be affected by age were analyzed in the first series, while those that would be affected by age were analyzed in the second series. Cases in the databank from January 1983 to December 1998 were selected in this study. Because this is a retrospective study and some data could be missing for various reasons, the valid number for each variable was also given in the results.

First Series

To determine whether age at onset, gender, arthritic manifestations, and tophus formation in familial gout are different from those in nonfamilial gout in the first series, age at onset, first attack at the first metatarsal phalangeal (MTP) joint, joint count, and tophus were selected as independent variables. Because female subjects were mostly postmenopausal[19,20] and older in age, their proportion could be increased by age. To prevent the confounding effect of age, gender was analyzed in the second series.

Second Series

To determine the contributory effect of genetic association to the concurrence of hypertriglyceridemia, hypercholesterolemia, type 2 DM, hypertension, obesity, and renal insufficiency with gout in the second series, serum TC, TG, and creatinine concentrations, body mass index (BMI), hypertension, and type 2 DM were selected as independent variables. The background data of serum UA and alcohol consumption were also included in the list of independent variables. To prevent the confounding effect of age on the prevalence of diseases and their biochemical results, only nonfamilial gouty subjects with similar ages to familial gouty subjects were included in the second series. Because familial gout patients were younger in age and fewer in case number than nonfamilial gout subjects, we calculated the mean age of familial gout first and adjusted the mean age of nonfamilial gout subjects to approach that of familial gout subjects. We selected those nonfamilial subjects whose ages were within 1 standard deviation from the mean age of familial gout subjects. After calculation, nonfamilial gouty subjects within the range of 30 to 60 years were selected.

Table 1. Comparison of Clinical Features Between Familial and Nonfamilial Gout by Student's *t* Test

Clinical Characteristics	Dependent Variable		*P* Value
	Familial Gout	Nonfamilial Gout	
Age at first visit (yr)	45.8 ± 13.9 (n = 4,471)	52.9 ± 14.2 (n = 16,902)	.0001
Age at onset (yr)	40.9 ± 13.4 (n = 4,390)	48.4 ± 14.2 (n = 16,647)	.0001
Joint count (joints)	2.5 ± 1.5 (n = 4,456)	2.5 ± 1.4 (n = 16,856)	.8490

NOTE. Values are means ± SD.

Study Variables

Study variables were defined and the definition of some variables deserves more explanation. A patient could only be said to have hypertension if he (or she) had a history of hypertension and was receiving regular medical control or if his (or her) resting blood pressure was over 150/90 mm Hg twice during 2 separate measurements[21] in our clinic. A patient could only be said to have type 2 DM if he (or she) had a history of type 2 DM and was receiving regular medical control or if his (or her) fasting serum glucose concentration exceeded 140 mg/dL on 2 separate measurements[22] in our clinic. The variable BMI was defined as the result of body weight (in kilograms) divided by height (in meters) square.[23]

Laboratory Tests

Sera extracted from blood samples were stored at -70°C and analyzed within 24 hours. Serum UA, TC, TG, and creatinine concentrations were measured by an autoanalyzer (Biotechnica model ARCO PC, Rome, Italy) at Taipei Municipal Ho-Ping Hospital.

Statistical Analysis

In both series, data of variables were analyzed by Student's *t* test or χ^2 test to determine whether there was any differences between familial and nonfamilial gout. Because of the large case numbers in this study, we considered differences significant at $P < .01$.

RESULTS

First Series

Mean age at onset of familial gout was 7.5 years earlier than that of nonfamilial gout (Table 1). Except for age at onset, arthritic manifestations and percentage of tophus formation were not significantly different between familial and nonfamilial gout (Tables 1 and 2).

Table 2. Comparison of Clinical Features Between Familial and Nonfamilial Gout by χ^2 Test

Clinical Features		Dependent Variable		P (χ^2)
		Familial Gout (%)	Nonfamilial Gout (%)	
First MTP arthritis at onset	Yes	1,988 (44.62)	7,735 (45.91)	.131
	No	2,467 (55.38)	9,115 (54.09)	
Tophus	Present	379 (8.55)	1,457 (8.71)	.764
	Absent	4,054 (91.45)	15,277 (91.29)	

NOTE. Values are the case numbers and their percentage in each dependent variable.

Abbreviation: MTP, metatarsal phalangeal.

Second Series

After age adjustment, although mean ages of familial and nonfamilial gout were still significantly different, their difference was only 0.8 year (Table 3). Gender proportion was not significantly different between the 2 groups (Table 3). The background data of drinking habit and serum UA between the 2 groups were significantly different. The percentage of drinking habit in familial gout was 4.85% lower than that in nonfamilial gout (Table 4), while mean serum UA in familial gout was only 0.09 mg/dL higher than that in nonfamilial gout (Table 3).

Mean serum TG and TC concentrations in familial gout were significantly 13.5 and 2.9 mg/dL lower than that in nonfamilial gout, respectively (Table 3). The percentage of hypertension in familial gout was significantly 2.99% lower than that in nonfamilial gout (Table 4). Mean serum creatinine concentration, BMI, and percentage of type 2 DM were not significantly different between these 2 groups (Tables 3 and 4).

DISCUSSION

Among the clinical features of familial gout, our results demonstrate that familial gout is associated with precocious onset. We found that mean age at onset of familial gout was significantly 7.5 years lower than that of nonfamilial gout. However, our results also show that arthritic pattern, severity, and tophus formation were not significantly different between familial and nonfamilial gout, which indicates that familial gout is not more predisposed to severe arthritis or tophus formation than nonfamilial gout. The factor that predisposes gouty familial members to the precocious onset of urate precipitation in joints is their precocious onset of hyperuricemia.

Moreover, male preponderance still exists in familial gout, and this study cannot show a higher proportion of female subjects in familial gout, which may be due to the low penetrance of defective genes in female subjects by the protective action of female sex hormones. This means that even female subjects who inherited the defective genes for gout would not suffer from gout precociously before menopause, because the effect of estradiol to lower the serum UA level could be greater than that of defective genes to elevate the serum UA level. After menopause, however, the effect of defective genes would become more and more prominent with the ultimate development of hyperuricemia and/or gout.

As far as the genetic aspect of gout-related disorders is concerned, contrary to the expectation of previous reports,[13,14] our results show that the concurrence of hypertriglyceridemia and hypercholesterolemia with gout is not mainly caused by the

Table 3. Comparison of Laboratory Abnormalities in Familial and Nonfamilial Gout by Student's *t* Test

Clinical and Laboratory Data	Dependent Variable		*P* Value
	Familial Gout	Nonfamilial Gout	
Age at first visit (yr)	45.8 ± 13.9 (n = 4,471)	46.6 ± 8.7 (n = 10,525)	.0003
UA (mg/dL)	10.18 ± 1.63 (n = 4,455)	10.09 ± 1.60 (n = 10,434)	.0012
TG (mg/dL)	182.4 ± 125.3 (n = 4,270)	195.9 ± 135.8 (n = 10,149)	.0001
TC (mg/dL)	207.5 ± 42.5 (n = 4,424)	210.4 ± 48.8 (n = 10,397)	.0003
BMI (kg/m^2)	25.8 ± 3.7 (n = 4,455)	25.9 ± 3.4 (n = 10,469)	.0675
Creatinine (mg/dL)	1.33 ± 0.46 (n = 4,334)	1.36 ± 0.66 (n = 10,486)	.0119

NOTE. Values are means ± SD.

effect of genetic association, while some other environmental factors shared by these disorders may play a more important role. Several dietary factors, including alcohol consumption and lipid-rich diet, could be attributed. In our results, the lower percentage of alcohol consumption with lower serum TG in familial gout could suggest the role of alcohol in hypertriglyceridemia. Alcohol consumption has been demonstrated to be able to elevate serum TG[24-26] and cause both increased uric acid production and decreased uric acid excretion.[1] In addition to alcohol, Chinese food that is rich in fatty acids, cholesterol, and purines may also be attributed. These dietary factors could link hyperlipidemia and gout together, and their effects are more than that of genetic association.

Similar to the results of hyperlipidemia, we found that the concurrence of hypertension with gout is also mainly caused by environmental factors shared by these 2 disorders, but not by genetic association. Diuretic use could be 1 of the attributed factors, because diuretics may decrease uric acid excretion in renal tubules by the action of fluid depletion.[1] Hypertensive patients might take diuretics as antihypertensive agents for a long time with the consequence of hyperuricemia and gout.[1] Furthermore, alcohol consumption could be another important factor, because alcohol consumption can cause not only hyperuricemia and hypertriglyceridemia, but also hypertension.[27] In this study, the higher percentage of drinking habit in nonfamilial gout could suggest the role of alcohol. Alcohol and diuretics should be the main factors linking hypertension and gout together. However, further studies are needed to demonstrate this.

Table 4. Comparison of Associated Conditions Between Familial and Nonfamilial Gout by χ^2 Test

Associated Conditions		Dependent Variable		*P* (χ^2)
		Familial Gout (%)	Nonfamilial Gout (%)	
Gender	Female	170 (4.02)	349 (3.34)	.0423
	Male	4,060 (95.98)	10,113 (96.66)	
Drinking history	Positive	909 (22.49)	2,532 (27.34)	<.0001
	Negative	3,133 (77.51)	6,728 (72.66)	
Hypertension	Yes	874 (19.57)	2,374 (22.56)	<.0001
	No	3,591 (80.43)	8,147 (77.44)	
Type 2 DM	Yes	248 (5.56)	587 (5.58)	.986
	No	4,216 (94.44)	9,935 (94.42)	

NOTE. Values are the case numbers and their percentage in each dependent variable.

Contrary to the results of hypertension, we found that genetic association is as important as shared environmental factors for the concurrence of both obesity and type 2 DM with gout. High-caloric intake, which is often purine-rich in Chinese foods, can result in both obesity and type 2 DM in susceptible people with subsequent development of insulin resistance,[28] while insulin resistance can cause decreased renal clearance of uric acid.[29,30] Therefore, a high-caloric diet should be the most important environmental factor for obesity and type 2 DM in their concurrence with gout. In addition to the dietary factor, our results suggest that the effect of genetic association should not be neglected. Some loci of gene(s) for gout linked with those for obesity and type 2 DM might be present, or there might be some common defective genes responsible for the development of both obesity and gout, and some for both type 2 DM and gout, while we think the latter may be more likely. In people who have inherited these common defective genes, obesity and type 2 DM could develop first, and these 2 disorders would result in hyperuricemia secondarily by the action of insulin resistance.[28] However, further studies are needed to determine the existence and action of these common defective genes.

In addition to the above metabolic disorders, we found that the effect of defective genes on the concurrence of renal insufficiency and gout is equivalent to that of environmental factors. Aging, hypertension, DM, and nonsteroidal anti-inflammatory drug (NSAID) use may be among these environmental factors contributing to renal function deterioration[1,31] in gouty patients. This study also suggests that the effect of defective gene(s), which is not transmitted by autosomal dominant inheritance as reported, should not be neglected. Although these genes have not been mapped and their function is still unclear, we think these genes might normally code for some molecules regulating the process of both uric acid and creatinine excretion, and their mutation would lead to underexcretion of both substrates in affected cases. Further studies are needed to map these genes and to determine their function.

In conclusion, we have shown that familial gout is associated with precocious onset, and that the contributory effect of the genetic association to the concurrence of hyperlipidemia and hypertension with gout is less than that of environmental association, while the effect of genetic association to the concurrence of obesity, type 2 DM, and renal insufficiency with gout is equivalent to that of environmental factors. To our knowl-

edge, this is the first analytic study verifying the precocious onset of familial gout and determining the effect of genetic association to the concurrent disorders in gout. Therefore, this work is very important for future studies concerning the hereditary aspects of gout and for those concerning the relationship between gout and its related disorders.

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