Juvenile Gout in Taiwan Associated with Family History and Overweight

SHIH-YANG CHEN and MING-LAI SHEN

ABSTRACT. ***Objective***. To examine the clinical features of juvenile gout and its possible association with familial juvenile hyperuricemic nephropathy (FJHN).

Methods. A total of 543 cases of juvenile gout from the Ho-Ping Gout Database were enrolled, and 5269 gouty cases with onset age of 40 to 50 years were selected as a control group. Clinical and laboratory data were compared between the 2 groups.

Results. In patients with juvenile gout, body mass index, serum urate concentration, 24-hour urinary uric acid excretion, and creatinine clearance were significantly higher than those in the control group ($p < 0.0001$), while fractional excretion of uric acid was significantly lower. Only 15% of the juvenile gout cases fulfilled the features of FJHN. The percentage of familial aggregation in juvenile gout was about 1.9-fold higher than that in the control group (44.3% vs 23.8%; $p < 0.0001$).

Conclusion. Juvenile gout in Taiwan is associated with overweight and hereditary background, while FJHN may not be primarily responsible. (First Release Oct 15 2007; J Rheumatol 2007;34:2308–11)

Key Indexing Terms:
GOUT HYPERURICEMIA OBESITY FAMILY ADOLESCENT

Gout is a common rheumatic disorder in Taiwan, with a prevalence of 2.2%[1]. There is a trend that age at onset of gout is decreasing in Taiwan after 1990[2]; however, gout usually develops after middle age. Juvenile gout is a very rare disease entity and is reported scarcely. The only report of collected data of 21 patients with precocious onset of gout before age 30 years showed a high proportion of family history, reduced renal function, and reduced endogenous urate clearance[3]. Familial juvenile hyperuricemic nephropathy (FJHN) has been suggested to be responsible for these manifestations, and its genes have been mapped[4]. FJHN applies to families in which hyperuricemia appears in multiple members of both sexes early in life, in association with hypertension and progressive renal impairment, leading to death before age 40 years[5,6]. However, there has been no large study elucidating the clinical manifestations of juvenile gout and comparing it with FJHN. We performed a cross-sectional study on 543 gouty patients with onset of symptoms before age 20 years to examine the clinical features of juvenile gout and associations with FJHN.

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MATERIALS AND METHODS

The Ho-Ping Gout Database retains clinical and laboratory data of all gouty patients who have since 1983 visited the Gout Clinic at Taipei Municipal Ho-Ping Hospital. Patients came to our clinic by self-referral and not exclusively by referral from primary care doctors for severe gout. Diagnosis of gout was made according to the Wallace criteria[7]. Of a total of 28,660 cases collected in the database during the period January 1983 to December 1999, 543 (1.9%) were identified as juvenile gout, with onset before age 20 years. Since the mean age at onset of gout of the database was 46.5 years[2], a total of 5269 gouty cases with onset age of 40 to 50 years were selected from the database as the control group. Background data, clinical manifestations, inheritance pattern, and laboratory data, including creatinine clearance and daily uric acid excretion, were compared between the juvenile group and the control group. All medications affecting renal processing of uric acid such as diuretics, fenofibrate, or losartan were discontinued at least 1 month prior to the laboratory tests.

RESULTS

The mean age at onset of 543 patients with juvenile gout was 16.5 years (Table 1) and the youngest was 8 years (Figure 1). Compared with the controls, juvenile gout was significantly associated with higher serum urate concentration, height, and body weight. The percentage of females with juvenile gout was not significantly different from that in controls. Although the median duration of disease in juvenile gout was significantly longer than that in controls, once involved by gout attacks their joint counts were significantly lower than those in controls.

Among the risk factors for gout, juvenile gout was significantly associated with lower percentage of drinking alcohol and higher percentage of family history of gout than controls (Table 1). Forty-four percent of juvenile gout patients had a family history, 1.9-fold higher than that in controls. Among the cases with family history, a juvenile gout patient had a sig-

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Table 1. Clinical features of juvenile gout compared to middle-aged gout. Values are mean ± SD or percentage.

	Juvenile Gout, n = 543	Middle-aged Gout, n = 5269	p	Odds Ratio*, (95% CI)
Background data				
Age at first visit, yrs	22.5± 10.3	49.9 ± 6.0	< 0.0001	—
Age of gout onset, yrs	16.5 ± 2.3	45.0 ± 2.6	< 0.0001	—
Duration of gout, median yrs (interquartile range)	4 (1, 8)	3 (1, 7)	0.0003	—
Body weight, kg	78.7 ± 17.1	71.6 ± 10.0	< 0.0001	—
Height, m	170.0 ± 7.5	166.2 ± 6.3	< 0.0001	—
Serum urate, µmol/l	642.4 ± 184.4	594.8 ± 95.2	< 0.0001	—
Female, %	2.6	4.1	0.4346	0.62 (0.32–1.06)
Clinical manifestations				
Joint counts	2.3 ± 1.3	2.5 ± 1.4	0.0040	—
Frequency of attacks > 6 times/yr	47.4%	45.4%	0.0794	1.08 (0.91–1.29)
Tophi, %	9.2	9.7	0.4882	0.95 (0.70–1.28)
Risk factors				
Alcohol drinking, %	9.5	28.4	< 0.0001	0.26 (0.20–0.36)
Family history of gout, %	43.8	23.8	< 0.0001	2.50 (2.08–2.99)
Comorbidities				
BMI, kg/m^2	27.4 ± 5.7	26.0 ± 3.7	< 0.0001	—
Hypertension, %	4.1	25.0	< 0.0001	0.13 (0.08–0.20)
Diabetes, %	2.8	9.1	< 0.0001	0.29 (0.17–0.49)
Hypertriglyceridemia (TG > 2.26 mmol/l), %	20.3	35.2	< 0.0001	0.47 (0.38–0.58)
Hypercholesterolemia (TC > 6.21 mmol/l), %	11.8	22.2	< 0.0001	0.47 (0.36–0.61)
Renal insufficiency (serum creatinine ≥ 133 µmol/l), %	8.0	24.7	< 0.0001	0.27 (0.19–0.36)
History of nephrolithiasis, %	2.6	14.4	< 0.0001	0.16 (0.09–0.27)
Laboratory				
Serum creatinine, µmol/l	106.1 ± 26.5	123.8 ± 88.4	0.0001	—

* Odds ratio for juvenile gout.

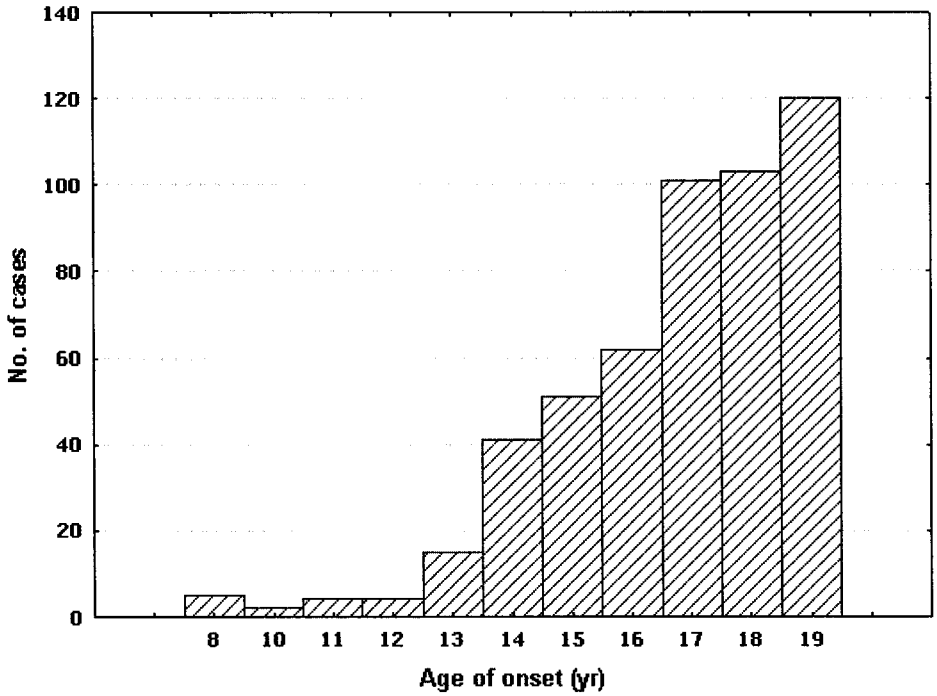

Figure 1. The mean age at onset of 543 patients with juvenile gout was 16.5 years and the youngest was 8 years of age.

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nificantly higher proportion of heritage from his/her father ($p < 0.0001$), grandparents ($p < 0.0001$), and third-degree relatives ($p < 0.0001$), and a significantly lower proportion of heritage from his/her siblings ($p < 0.0001$) and mother ($p < 0.0001$) than controls (Table 2). Over half the juvenile gout with a family history was inherited from the father.

Among the comorbidities, juvenile gout was significantly associated with higher body mass index (BMI; Table 1) and with percentage of obesity with BMI > 30 kg/m^2 than controls (Figure 2). However, juvenile gout was significantly associated with lower percentage of hypertension, diabetes, hypertriglyceridemia, hypercholesterolemia, renal insufficiency (serum creatinine > 1.5 mg/dl), and history of nephrolithiasis than control gout (Table 1).

Since the data for 24-hour urine uric acid and creatinine excretion were not recorded in the database until 1992, the data of 292 juvenile gout cases since then were compared with control data. Juvenile gout was significantly associated with higher 24-hour urinary uric acid excretion (747.2 ± 395.8 vs 689.4 ± 338.1 mg/24 h; $p = 0.0075$) and creatinine clearance (114.4 ± 55.4 vs 91.2 ± 48.1 ml/min; $p < 0.0001$) compared with control gout. However, juvenile gout was significantly associated with lower fractional excretion of uric acid than control gout (4.3% ± 1.9% vs. 5.9% ± 2.9%; $p < 0.0001$). For the cutoff of 800 mg/day on a regular diet defining overproduction of uric acid, juvenile gout was significantly associated with higher proportion of overproduction of uric acid than control gout (32.1% vs 28.4%; $p < 0.0001$ by chi-square test).

Among the 292 juvenile gout cases, a comparison between overproduction (n = 94) and underexcretion (n = 198) groups was made. There was no significant difference between the 2 groups in the onset age, duration of gout, serum uric acid and creatinine levels, joint counts, frequency of attacks, female gout, hypertension, diabetes, hypertriglyceridemia, hypercholesterolemia, history of nephrolithiasis, or family history of gout. However, overproducers were significantly associated with higher BMI and creatinine clearance than underexcreters (29.2 ± 5.7 vs 27.7 ± 6.3 kg/m^2, $p = 0.041$; 155.1 ± 70.2 vs 97.2 ± 39.1 ml/min, $p < 0.0001$, respectively).

Only 44 cases (15%) with precocious renal insufficiency (creatinine clearance < 60 ml/min) and positive family history of gout fulfilling the features of FJHN were identified in our database. Comparing the FJHN and non-FJHN groups, the FJHN group was significantly associated with lower 24-hour urine uric acid excretion and creatinine clearance than the non-FJHN group (556.4 ± 295.0 vs 791.6 ± 427.0 mg/day, $p < 0.0001$; 72.8 ± 26.8 vs 123.7 ± 58.7 ml/min, $p < 0.0001$, respectively). However, there was no significant difference between the 2 groups in onset age, duration of gout, serum uric acid level, hypertension, diabetes, history of nephrolithiasis, or fractional excretion of uric acid.

Table 2. Percentage of familial gout in patients with juvenile gout in comparison to controls.

	Father	Mother	Siblings	Grandparents	Children	Other Third-degree Relatives
Juvenile gout (n = 213) (%)	126 (59.2)	7 (3.3)	20 (9.4)	21 (9.9)	3 (1.4)	36 (16.9)
Control gout (n = 1217) (%)	468 (38.5)	148 (12.2)	463 (38.0)	14 (1.2)	87 (7.1)	37 (3.0)

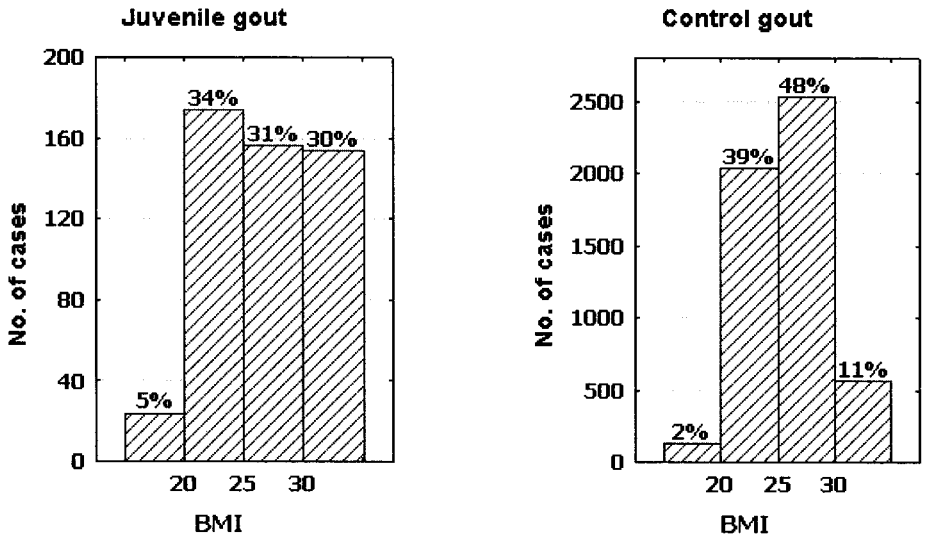

Figure 2. Among the comorbidities, juvenile gout was significantly associated with higher body mass index (BMI) and with percentage of obesity with BMI > 30 kg/m^2 than controls.

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DISCUSSION

Our study involving 543 juvenile gout patients from a large database has demonstrated that juvenile gout is associated with more obesity, hereditary background, and overproduction, with relative underexcretion of uric acid, than those with middle-aged gout. We found the serum urate level and BMI of patients with juvenile gout were significantly higher than corresponding data for age-equivalent juveniles in the national survey on the general population of Taiwan[8]. Obesity can result in hyperuricemia and consequent gout by both overproduction and underexcretion of uric acid[9]. Considering the combined overproduction and relative underexcretion of uric acid in juvenile gout, obesity could be responsible for the precocious onset of hyperuricemia and gout in Taiwanese teenagers. In addition to the effect of obesity, overintake of a high-purine diet may also contribute to precocious onset of gout[10]; however, our previous study comparing daily purine consumption between gouty patients and normal controls found no significant difference[11], while central obesity as well as family history of gout was associated with gout. Therefore, the interplay of both obesity and hereditary factors appear to be more responsible for the precocious onset of gout in Taiwan.

Several studies have indicated the role of FJHN genes for development of juvenile familial gout[4,12,13]; however, only a minority of juvenile gout cases in our database showed the feature of FJHN. For most of the juvenile gout in Taiwan, the proportions of renal insufficiency and hypertension are fairly low, which is different from the previously reported manifestation of FJHN. As well, for previously reported FJHN families, an autosomal-dominant inheritance pattern with equal penetrance to both sexes could be identified in the pedigrees[6]. However, juvenile gout in Taiwan is rarely inherited from the mother. FJHN is a very rare disease entity, and it could not account for the increasing prevalence of juvenile gout in Taiwan.

Since juvenile gout is predominant in males and inherited mainly from the father, there are 2 possible modes for inheritance of the responsible genes. The first is an autosomal-dominant mode, with low penetrance to females, and the second is a Y-linked mode of inheritance. However, the well established genes for gout, like the genes for hypoxanthine-guanine phosphoribosyltransferase deficiency and increased activity of PP-ribose-P synthetase, have an X-linked inheritance mode[9]. Therefore, the genes for juvenile gout have not been defined clearly and further studies are needed to elucidate the genetic defect as well as its interaction with obesity.

This study is the first to demonstrate that juvenile gout is mainly associated with overweight and a high proportion of family history of gout, but not with renal insufficiency or apparent underexcretion of uric acid.

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