

High Prevalence of Hyperuricemia in Adolescent Taiwan Aborigines

YING CHIN KO, TSU NAI WANG, LI YU TSAI, FOWN TZU CHANG, and SHUN JEN CHANG

ABSTRACT. Objective. To explore the prevalence and related factors of hyperuricemia among adolescent Taiwan aborigines in tribes with a high prevalence of adult gout, compared with adolescents of low prevalence aboriginal and non-aboriginal tribes.

Methods. The participants were aborigines and non-aborigines in Taiwan, age 12 to 15 years and free of gout. Each participant provided information on sex, age, and parents' tribal background as well as body weight and height. Serum samples were analyzed for biochemical markers. A logistic regression model was used to study factors related to hyperuricemia.

Results. In total 940 adolescents participated. The hyperuricemia rate in tribes with high gout prevalence (57.7%) was higher than in non-aborigines (48.2%) and in aboriginal tribes with low gout prevalence (34.0%). Factors statistically significantly related to hyperuricemia were tribe, sex, obesity, creatinine, and cholesterol levels in preliminary analysis. After adjustment by the logistic regression model, obese boys with higher creatinine were most likely to have hyperuricemia. Adolescents whose parents originated from tribes with high gout prevalence had a tendency to have hyperuricemia, and those aborigines from tribes with low gout prevalence had a low prevalence of hyperuricemia compared to non-aborigines.

Conclusion. The prevalence of hyperuricemia in aboriginal adolescents mirrors the incidence of adult gout, implying a predisposition for adult gout in childhood, with genetic and/or environmental components presumably contributing to the differences between tribes; this may be of potential benefit to preventive efforts. (J Rheumatol 2002;29:837-42)

Key Indexing Terms:

HYPERURICEMIA

ADOLESCENCE

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COMMUNITY

That there is a high prevalence of gout disease among adult Taiwan aborigines is well known, with incidences ranging from 15 to 44% documented for Atayal men aged over 40 years, followed by Bununs (28.1%) and Paiwans and Tsou tribes (>5%)^{1,2}. In addition to high prevalence of the disease itself among aboriginal tribes, hyperuricemia is also known to be an asymptomatic feature among the adults² and children³, but not all the subtribes of Taiwan aborigines suffer from gout. According to Bellwood⁴, the ancestral homeland of Austronesians was the agricultural heartland of Southeast Asia, from where they first radiated to Formosa (Taiwan; 4000 BC), then western Polynesia (1200 BC), central Polynesia (200 BC), and New Zealand (800 AD). Studies have shown male Micronesians to have prevalence of hyperuricemia ranging from 21 to 64%⁵⁻⁷, and in male Polynesians the figure ranges from 24.3 to 49%^{8,9}. This is

higher than in male Caucasians (6 to 23%)¹⁰⁻¹², suggesting a direct association with gout.

To our knowledge, data on the prevalence of hyperuricemia among adolescent children are limited, especially for tribes with a high prevalence of gout. Asymptomatic hyperuricemia may be present more than 20 years before disease onset¹³, with familial aggregation¹⁴⁻¹⁶. We compared the prevalence of hyperuricemia among adolescent children in tribes of Taiwan aborigines with high and low gout prevalence.

MATERIALS AND METHODS

With parental consent 940 adolescent children were enrolled in this study from 1994 to 1998. The aborigines were from the Atayal, Paiwan, Bunun, Tao, Tsou, Puyumar, and Pancah tribes, while the non-aborigines were Fukien-Taiwanese and Hakka-Taiwanese from 2 villages located near the aboriginal areas who served as controls. The adolescent children were selected from the community junior high school in their areas of residence; roughly one-third of the students were included. All the participants were aged between 12 and 15 years and free of gout. Each completed a questionnaire to give data on sex, age, parents' tribal background, and weight and height measurements. Sera were extracted from blood samples and stored at -70°C before analysis for cholesterol, triglycerides, creatinine, and uric acid with an autoanalyzer (Biotechnica; Hitachi, Tokyo).

Definition of variables. The tribal origin of both parents was assessed to classify the child's tribe; for example, an Atayal child was defined as one with both parents of Atayal lineage; 176 children were excluded as both parents did not originate from the same tribe. The children were further divided into 2 groups according to the adult gout prevalence in their tribes determined in previous studies, one from tribes with high gout prevalence

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(HG) and the other from tribes of low gout prevalence (LG). The Atayal, Bunun, Paiwan, and Tsou tribes are classified as HG, with incidences > 5%^{1,2}, whereas the Pancah, Puyumar, and Tao tribes had LG incidences < 0.3%, and the non-aboriginal adult gout prevalence was estimated to be 0.3%².

Hyperuricemia was defined as serum uric acid (SUA) concentration > 7 mg/dl for boys and > 6 mg/dl for girls¹⁷. Subgroups were generated for serum cholesterol, creatinine, and triglycerides, with cutoff concentrations of 200, 1.0, and 170 mg/dl, respectively. Since the body mass index (BMI, weight in kg/height in m²) was not distributed homogeneously between the sexes, girls having a higher mean and greater variance than the boys (girls 20.2 ± 3.5 kg/m²; boys 19.4 ± 2.9 kg/m²; p < 0.01), we defined obesity as a value greater than the 90th percentile of the distribution for the sex, i.e., if a boy's BMI was greater than 23.44 kg/m² or a girl's BMI was greater than 24.54 kg/m², they were considered obese.

Statistical analysis. The chi-square test was used to assess differences between 2 category variables, such as sex and hyperuricemia status. Analysis of variance (ANOVA) was employed for means, such as SUA for different tribal groups. The simple regression method was employed to predict the uric acid concentration from age. Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated to estimate the risks of having hyperuricemia in relation to the associated factors identified by questionnaire or biochemical markers. Those showing significant OR were subsequently examined in a multiple logistic regression model to obtain adjusted OR and the adjusted 95% CI were calculated by the Mantel-Haenszel method. Where the probability was less than 0.05 or the 95% CI did not include unity, the difference was considered statistically significant.

RESULTS

Of the 940 children who participated, 778 were aborigines and 162 were non-aborigines aged between 12 and 15 years. Of the 476 boys the mean age was 13.47 years (± 1.04) and showed no significant difference from 464 girls (13.43 ± 0.97 yrs; p = 0.464). The 778 aborigines were divided into 2 groups according to their tribal adult gout prevalence: 305 children from Atayal, Tsou, Bunun, and Paiwan tribes, and 473 children from the Pancah, Puyumar, and Tao tribes. There was no significant difference in sex frequency distribution among aborigines and non-aborigines (Table 1; p = 0.58).

The boys' mean uric acid concentration was 7.21 mg/dl (± 1.92), 1.53 mg/dl higher than that for the girls (5.68 ± 1.61 mg/dl; p < 0.01) for all the participants, and in the different tribes, boys' values were always higher than girls' (Table 2; p < 0.01). The HG boys had significantly higher mean uric acid concentration than non-aborigines or LG groups (p < 0.01). Among the girls, the HG group and non-

aborigines also had higher mean uric acid concentrations than the LG group (Table 2; p < 0.05).

The highest prevalence of hyperuricemia was in the Tsou tribe (12/17, 70.6%; Table 3) for both sexes, followed by the Atayal (74/107, 69.2%) and Bunun (63/105, 60.0%). The Tsou boys and Atayal girls also had the highest hyperuricemia rates among male and female groups, respectively (Table 3). For all participants, the HG hyperuricemia rate was significantly greater than for the LG aborigines (Table 3; 176/305 vs 161/473; p < 0.01) or for non-aborigines (78/162; p < 0.05), and there was a significant difference between the non-aborigines and LG groups (p < 0.01). However, for each sex, the HG group always had a higher hyperuricemia rate than the LG (p < 0.01).

The possible related factors for hyperuricemia were tribe, sex, age, serum cholesterol, triglycerides and creatinine, and obesity. Using the Mantel-Haenszel method to compute OR and 95% CI of factors related to hyperuricemia in the preliminary analysis, we found that all of the factors except age and triglycerides significantly affected hyperuricemia (Table 4). After adjustment by a logistic regression method, the cholesterol factor was excluded. This shows that tribe, sex, obesity, and creatinine significantly contributed to hyperuricemia; e.g., those obese boys with parents from HG tribes and with higher concentrations of serum creatinine were significantly related to hyperuricemia.

The means of SUA concentrations at different ages for each sex (Figure 1) show a gradual increase with age in SUA for LG aboriginal boys, from the mean of 5.70 mg/dl at age 12 to 7.67 mg/dl at age 15 (p < 0.01). However, no age association was found in HG aborigine and non-aborigine boys (Figure 1A). HG aboriginal girls were found to have a gradual decline in SUA with age, from 6.84 mg/dl at age 12 to 5.20 mg/dl at age 15 (p < 0.01; Figure 1B). However, girls of the other tribes showed no association with age.

DISCUSSION

A number of studies have shown the prevalence of gout in Taiwan aborigines was very high in adults of the Atayal, Bunun, Tsou, and Paiwan tribes aged over 40 years^{1,2}, but low in the Pancah, Puyumar, and Tao tribes. Only serum uric acid concentrations of children whose parents originated from the same tribe were studied. In this study, we did not classify the children according to their parents' gout status but by the tribal adults' gout prevalence. Since encroachment by non-aborigines on aboriginal villages had been prohibited by law for many years, inbreeding had presumably been proceeding until the last 10 years. Thus, gout prevalence of the participant's parents can be considered essentially the same as that of the tribe.

Like the incidence of gout in adult aboriginals in Taiwan, the prevalence of hyperuricemia in aboriginal children was not uniformly distributed in tribes; the prevalence of adult

Table 1. Subject distribution according to tribal background and sex. There was no significant variation in the sex ratio (p = 0.58).

	HG n (%)	LG n (%)	Non-Aborigines n (%)	Total n (%)
Sex				
Boys	151 (49.5)	237 (50.1)	88 (54.3)	476 (50.6)
Girls	154 (50.5)	236 (49.9)	74 (45.7)	464 (49.4)
Total	305 (100)	473 (100)	162 (100)	940 (100)

HG: high gout prevalence tribes; LG: low gout prevalence tribes.

Table 2. Uric acid concentrations by tribal background and sex.

	Boys		Girls		Total	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Tribal background*						
HG	151	7.96 ± 2.10	154	6.30 ± 1.69	305	7.12 ± 2.07
LG	237	6.72 ± 1.69	236	5.29 ± 1.46	473	5.96 ± 1.75
Non-aborigines	88	7.24 ± 1.75	74	5.96 ± 1.43	162	6.66 ± 1.73
Total	476	7.21 ± 1.92	464	5.68 ± 1.61	940	6.45 ± 1.93

* Boys' serum uric acid (SUA) was higher than girls' in each of these 3 groups ($p < 0.001$).
 HG: high gout prevalence tribes; LG: low gout prevalence tribes.

Table 3. Hyperuricemia distribution by tribal background and sex. Percentages are given in parentheses.

	HG				LG			Non-Aborigines		Total
	Atayal	Tsou	Bunun	Paiwan	Puyumar	Tao	Pancah	Hakka	Fukien	
Boys' hyperuricemia	57 (68.4)	10 (80.0)	48 (62.5)	36 (47.2)	16 (43.8)	64 (65.6)	157 (31.2)	58 (55.2)	30 (53.3)	
Subtotal*		151 (62.3)				237 (41.4)		88 (54.6)		476 (50.4)
Girls' hyperuricemia	50 (70.0)	7 (57.1)	57 (57.9)	40 (25.0)	22 (40.9)	69 (46.4)	145 (15.2)	40 (45.0)	34 (35.3)	
Subtotal*		154 (53.3)				236 (26.7)		74 (40.5)		464 (37.7)
Hyperuricemia	107 (69.2)	17 (70.6)	105 (60.0)	76 (35.5)	38 (42.1)	133 (55.6)	302 (23.5)	98 (51.0)	64 (43.8)	
Total*		305 (57.7)				473 (34.0)		162 (48.2)		940 (44.2)

* There were significant differences in statistics in hyperuricemia rate among the 3 different tribal groups ($p < 0.01$). HG: high gout prevalence tribes; LG: low gout prevalence tribes.

Table 4. Risk factors for hyperuricemia among Taiwan aboriginal adolescents.

	Hyperuricemia		OR	95% CI†	Adjusted OR	Adjusted 95% CI
	Yes n (%)	No n (%)				
Sex						
Boys	240 (50.4)	236 (49.6)	1.68	1.30–2.18*	1.59	1.21–2.09*
Girls	175 (37.7)	289 (62.3)	1.0		1.0	
Age, yrs						
>14	77 (46.4)	89 (53.6)	1.12	0.80–1.56	ND	
≤14	338 (43.7)	436 (56.3)	1.0			
Tribes**						
HG	176 (57.7)	129 (42.3)	1.47	1.0–2.15*	1.48	1.01–2.18*
LG	161 (34.0)	312 (66.0)	0.56	0.39–0.80*	0.51	0.35–0.74*
Non-aborigines	78 (48.2)	84 (51.8)	1.0		1.0	
Obesity						
Yes	60 (64.5)	33 (35.5)	2.52	1.63–3.89*	2.03	1.27–3.23*
No	355 (41.9)	492 (58.4)	1.0		1.0	
Creatinine, mg/dl						
>1.0	30 (81.1)	7 (18.9)	5.77	2.74–12.14*	7.56	3.21–17.84*
≤1.0	385 (42.6)	518 (57.4)	1.0		1.0	
Cholesterol, mg/dl						
>200	14 (66.7)	7 (33.3)	2.58	1.07–6.24*	1.76	0.67–4.63
≤200	401 (43.6)	518 (56.4)	1.0		1.0	
Triglycerides, mg/dl						
>170	12 (35.3)	22 (64.7)	0.68	0.33–1.39	ND	
≤170	403 (44.5)	503 (55.5)	1.0			

† Mantel-Haenszel method.

*Significant difference ($p < 0.05$). **The HG and LG compared with non-aborigines separately.

HG: high gout prevalence tribes; LG: low gout prevalence tribes. ND: factor was not included in the adjusted model.

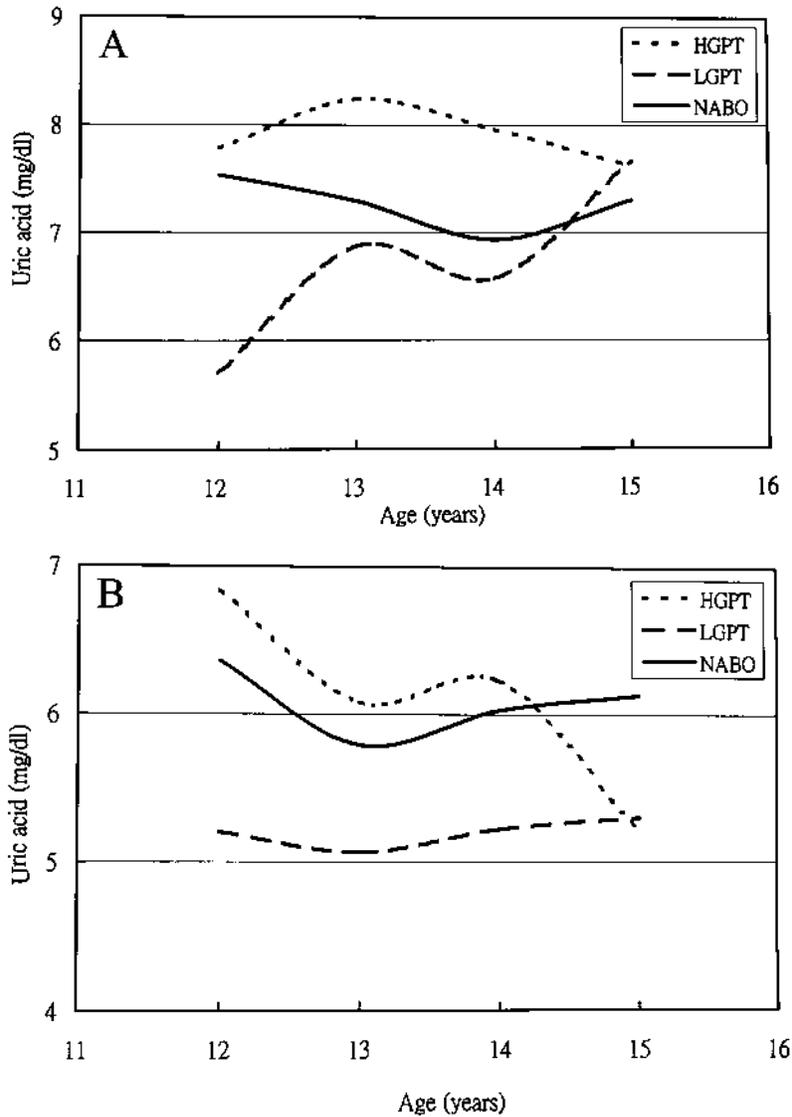


Figure 1. The relationships between mean serum uric acid (SUA) concentration and age. A. Mean SUA gradually increased by age among LG boys ($p < 0.05$). B. Mean SUA gradually declined with age among HG girls (simple regression method; $p < 0.05$). HGPT: high gout prevalence tribes; LGPT: low gout prevalence tribes; NABO: non-aborigines.

gout and adolescent hyperuricemia were correlated. This implies that the adult gout disease appears after a long preclinical period commencing in childhood, and that genetic and/or environmental components contribute to the differences between LG and HG tribes. However, the tribes we classified with a higher prevalence of adult gout (HG) live in the highland areas that always had a low temperature, while the LG tribes live in seaside areas. Temperature differences caused by altitude may therefore affect the prevalence of hyperuricemia and gout. The other inland and coastal difference between HG and LG tribes was dietary, i.e., high fish diet on the coast.

Hyperuricemia is the major direct risk factor causing gout^{18,19}; other associated factors that have been documented are age, sex, diuretic usage, lead exposure, alcohol abuse, and obesity^{20,21}. Seegmiller²² concluded that the age of puberty in males could influence hyperuricemia and gout. However, the boys showed a higher hyperuricemia rate than girls. Age did not show a sufficient association with the hyperuricemia rate in this study as the age period studied was limited. All the participants aged between 12 and 15 years were in puberty, and a non-puberty group was not included for comparison. In addition, obesity and serum creatinine were also found to have an influence in this study,

consistent with the results of Jackson, *et al*²³ for Western Samoans. In our study serum creatinine contributed the highest risk to hyperuricemia. The serum creatinine level is the most widely used measure not only of renal function, but also of the production, intake, and metabolism of creatinine. Reimold showed that serum creatinine level increased directly with the progression of renal failure²⁴. However, the renal function decline among these participants may be doubtful, and a further followup study of measurement on renal function should be performed.

Two enzymes involved in uric acid metabolism are documented to be important, hypoxanthine-guanine phosphoribosyltransferase (HPRT) and phosphoribosyl pyrophosphate synthetase (PRPS). HPRT^{25,26} and PRPS²⁷⁻²⁹ are constitutionally expressed enzymes that function in the purine salvage pathway. Partial deficiency of HPRT activity or upregulation of PRPS causes accumulation of uric acid, so that the subject becomes hyperuricemic. Associations between HPRT mutants and gout have been well documented³⁰⁻³², and the authors also found a new HPRT mutation in a family predisposed to gout in the Tsou tribe of Taiwan aborigines (G152A)³³. This and previous findings² indicate that genetic effects are likely to play a role in hyperuricemia or gout in Taiwan aborigines.

Although Bellwood⁴ considered that Taiwanese aborigines originated from the proto-Polynesian expansion by linguistic evidence, Melton, *et al*³⁴ also showed that their results from studying mitochondrial DNA polymorphisms (Polynesian motif) were consistent with Bellwood's result. Healey, *et al*³⁵ showed hyperuricemia was caused by the interaction of heredity and environment in Filipinos. Studies from Neel, *et al*³⁶ and Wyngaarden and Kelley³⁷ also considered gout to be a disease caused by multiple genetic disorders. We show the causality of hyperuricemia in adolescent Taiwan aborigines was favored by tribal effects that combined both environment and heredity. Bellwood⁴ and Melton, *et al*³⁴ reported that Taiwan aborigines and Filipinos are Austronesians, suggesting that they may share the same genetic risk of hyperuricemia.

The triglyceride level did not significantly influence hyperuricemia in this study. This contrasts with our previous findings² and the studies of Chou, *et al*³⁸. Both these studies were of adult Taiwan aborigines. Al-Arfaj³⁹ showed that uric acid levels did not correlate with triglycerides and cholesterol in female adults, but correlation was found for hyperuricemic males and non-hyperuricemic males. Jiao, *et al*⁴⁰ reported that cholesterol and triglycerides increased in primary gout, and suggested that alcohol intake and uric acid were the major predictors of serum triglycerides. In our previous study⁴¹, the prevalence of alcohol abuse and alcohol dependence in Taiwan aborigines was roughly 10 times the rate in Fukien Taiwanese. The correlation between hypertriglyceridemia and hyperuricemia in Taiwan adult aborigines probably relates with alcohol consumption.

However, most of the adolescent Taiwan aborigines in this study were considered free of alcohol consumption. The influence of triglycerides on hyperuricemia may be due to alcohol consumption following adolescence.

The age range covered in this study was so narrow there was no overall age effect. Analysis with reference to sex and tribe (Figure 1) revealed LG aboriginal boys had an increase in uric acid concentration with age ($p < 0.01$). In contrast, aboriginal HG girls demonstrated a decline as they became older ($p < 0.01$). Since the prevalence of hyperuricemia in adults is influenced by age as an independent factor⁴², further work clearly needs to be performed to explain the apparent anomaly.

In conclusion, those at high risk of developing gout demonstrate a higher rate of hyperuricemia in adolescence; this finding may be of potential benefit to preventive efforts. This observation of high prevalence of uric acid level in Taiwan aboriginal adolescents suggests that an age adjustment in puberty is needed for a segregation analysis in family studies⁴³.

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