The Epidemiology of Hyperuricemia in Children of Taiwan Aborigines

CHIU-SHONG LIU, TSAI-CHUN LI, and CHENG-CHIEH LIN

ABSTRACT. ***Objective.*** To explore the factors influencing serum uric acid concentrations and the prevalence of hyperuricemia in aboriginal children from an area in Taiwan with a high prevalence of gouty arthritis.

Methods. A cross sectional study of the Bunun tribe was conducted in central Taiwan from March to May 2001. Children aged 4–13 were requested to fill out a structured questionnaire with the assistance of their parents. A total of 414 children (mean age, 8.9 ± 2.1 yrs) were recruited. Uric acid was determined by colorimetry using the uricase method. Since no previous study has investigated serum uric acid concentrations in these aboriginal children, hyperuricemia was defined as uric acid > 416.5 µmol/l (7 mg/dl) in boys and > 357 µmol/l (6 mg/dl) in girls.

Results. The mean concentration of serum uric acid was 368.9 ± 83.3 µmol/l. Ninety of 224 girls (40.2%) and 56 of 190 boys (29.5%) were hyperuricemic. Children with hyperuricemia had significantly higher body mass index (BMI), blood pressure, and triglyceride and creatinine concentrations than those with normal uric acid concentrations. After adjustment for age, sex, lipid profile, and blood pressure, hyperuricemia was found to be significantly associated with serum creatinine (OR 2.40, 95% CI 1.91–3.04), BMI (OR 1.24, 95% CI 1.11–1.40), and a family history of gouty arthritis in parents (OR 2.01, 95% CI 1.02–3.96).

Conclusion. BMI, a positive family history of gouty arthritis in parents, and creatinine level correlated with hyperuricemia in aboriginal children in Taiwan. (J Rheumatol 2003;30:841–5)

Key Indexing Terms:
HYPERURICEMIA CHILDREN ABORIGINES

Hyperuricemia is a well known cause of gout and is related to cardiovascular disease and nephropathy[1,2]. The common risk factors for hyperuricemia include a genetic enzyme defect, alcoholism, intake of high purine diet, and reduced renal uric acid clearance[3]. Gout prevalence varies between different ethnic groups. The prevalence of gout among Taiwanese aborigines is around 12% and that of hyperuricemia is about 40%[4,5]. These prevalence rates are similar to Malayo-Polynesian groups[6] and are higher than those reported in Caucasians and non-aboriginal Taiwanese[7-9]. In Taiwan, there are 9 tribes of Aborigines who live in the mountainous areas and who compose 1.5% of the entire Taiwanese population. The major aboriginal tribe included in this study is the Bunun tribe, who live in central Taiwan. Previous studies of hyperuricemia have focused on prevalence and risk factors for adults. Issues relating to the prevalence and risk factors of hyperuricemia in childhood have not been examined as a separate issue. We investigated the factors associated with hyperuricemia in children from an area with a high prevalence of gouty arthritis.

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MATERIALS AND METHODS

Study population. Hsin-Yi County in central Taiwan is composed of 10 villages. In the year 2000, the total population in Hsin-Yi County was 13,753. Aborigines make up 80% of the total population and 90% of them belong to the Bunun tribe. Non-aboriginal children were excluded. With the assistance of the local health authority, we recruited 547 children, which was the total population of school age children in Di-Li, Tan-Nan, Jen-Ho, and Shuan-Long villages in the period March to May 2001. All the children were requested to fill out a structured questionnaire with the assistance of their parents. Out of this population, 5.6% did not provide useful information, 1.9% refused to participate, and 17.5% had missing laboratory data. A total of 414 (75.7%) children were finally recruited. Information collected on the children and their parents and grandparents included demographic information and medical history of gouty arthritis and other diseases. Consent was obtained from the participants' parents, and the study protocol conformed to ethics committee guidelines regarding studies of human subjects.

Clinical and laboratory examination. The clinical examination included measurement of sitting blood pressure (with a random-zero sphygmomanometer), height, and weight. The children fasted for more than 8 h on the day of the examination. Blood was drawn with minimal trauma from an antecubital vein and was sent for analysis to the clinical laboratory of the China Medical College Hospital within 4 h. Total cholesterol and triglyceride concentrations were determined by the enzymatic method using commercial kits (Beckman Coulter Inc., Fullerton, CA, USA). Uric acid was determined by the colorimetry method using the uricase method

(Beckman Coulter). Creatinine was measured by the alkaline picrate method. All analyses were performed with a Beckman Coulter LX-20 auto-analyzer. All of the laboratories participate in the American College of Pathologists' external quality control program for their automated analyses.
Definition. An Aborigine was defined as a person whose parents were both Aborigines. Uric acid concentrations in healthy adult Chinese subjects range from 178.5 to 415.5 µmol/l in men and 119 to 357 µmol/l in premenopausal women. Hyperuricemia was defined as uric acid levels > 416.5 µmol/l (7 mg/dl) in boys and > 357 µmol/l (6 mg/dl) in girls. The measure of body fat was determined by body mass index (BMI), calculated as body weight (kg)/body height $(m)^2$. Family history of gouty arthritis in parents was defined as either of the participant's parents being diagnosed with gouty arthritis by a medical practitioner.

Statistical analysis. Pearson correlation coefficients were used to assess the linear relationship between uric acid concentrations and other measurements. Comparisons of continuous data among 3 or more groups were based on analysis of variance (ANOVA) for independent variables. Student t test was used to compare the differences of continuous data between 2 groups. To test the explanatory effects of all the independent variables on hyperuricemia by controlling the other independent variables, a multivariate logistic was applied. The significant effect of each variable was then determined by Wald statistic. Statistical analyses were performed with an SAS package (Version 6.06, SAS Institute Inc., Cary, NC, USA).

RESULTS

Of 414 children who participated, 190 were boys and 224 were girls. The mean age was 8.9 ± 2.1 years (range 4–13 yrs). Basic characteristics and results of biochemical tests are summarized in Table 1. There were no significant differences between boys and girls in age, blood pressure, body weight and height, BMI, and biochemical tests except for triglyceride and creatinine levels. In addition, the physical examinations and routine blood tests did not disclose any illness known to elevate uric acid levels.

The mean concentration of serum uric acid was 368.9 ± 83.3 µmol/l. The uric acid concentration correlated well with blood pressure, BMI, and creatinine concentration in both boys and girls (all Pearson correlation coefficients > 0.15, $p < 0.05$). There was significant correlation between uric acid concentrations and age in boys ($r = 0.31$, $p < 0.001$) but not in girls. Serum uric acid concentrations in different age and sex distributions are shown in Figure 1. There was no significant difference between boys and girls except for those over 9 years (t test, t value = –3.1, p = 0.002). A 2-age group *post hoc* comparison (Scheffe's test) was statistically significant at $\alpha = 0.05$ only in > 9 years versus 7–9 years and > 9 years versus < 7 years in boys.

Ninety of the 224 girls (40.2%) and 56 of 190 boys (29.5%) were hyperuricemic. Table 2 shows the biochemistry tests and other data according to the status of uric acid concentrations. Children with hyperuricemia had significantly higher BMI, blood pressure, and triglyceride and creatinine concentrations than those with normal uric acid concentration. Children with hyperuricemia had significantly lower HDL cholesterol concentrations than those with normal uric acid levels. Children with hyperuricemia tended to have higher prevalence of family history of gouty

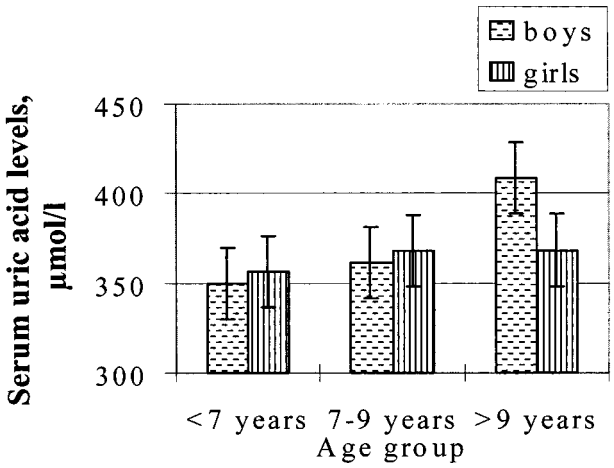

Figure 1. Serum uric acid concentrations in different age and sex distributions of Taiwan aboriginal children. There was no significant difference between boys and girls except those over 9 years (t test, t value –3.1, p = 0.002). A 2-age group *post hoc* comparison (Scheffe test) was statistically significant at $\alpha = 0.05$ only in groups aged > 9 years vs 7–9 years and > 9 years vs < 7 years in boys.

Table 1. Anthropometric and biochemical data of Taiwan aborigine children.

	Boys (n = 190)		Girls (n = 224)		
	Mean	SD	Mean	SD	p
Age, yrs	9.0	2.1	8.8	2.0	NS
Body height, cm	128.2	13.0	128.2	13.4	NS
Body weight, kg	30.7	10.2	31.2	10.8	NS
Body mass index, kg/m^2	18.2	3.0	18.4	3.1	NS
Systolic blood pressure, mm Hg	113.9	20.1	110.0	20.5	0.05
Diastolic blood pressure, mm Hg	69.8	15.9	69.4	15.8	NS
Total cholesterol, mmol/l	4.1	0.8	4.1	0.7	NS
Triglyceride, mmol/l	7.3	3.5	8.2	3.6	< 0.05
HDL cholesterol, mmol/l	1.3	0.3	1.2	0.3	NS
Uric acid, µmol/l	374.8	83.3	368.9	83.3	NS
Glucose. mmol/l	4.6	0.4	4.4	0.4	NS
Creatinine, µmol/l	51.3	8.8	48.6	8.0	< 0.01

HDL: high density lipoprotein.

Table 2. Anthropometric and biochemical data by serum uric acid level of Taiwan aboriginal children (mean ± SD).

	Hyperuricemia, n = 146	Normal Uric Acid, n = 268	p
Age, yrs	8.7 ± 2.1	9.2 ± 2.0	< 0.05
Sex, % of boys	38.4	50.0	< 0.05
Family history of gout, %	27.9	13.5	< 0.001
Body mass index, kg/m^2	19.4 ± 3.7	17.7 ± 2.5	< 0.001
Systolic blood pressure, mm Hg	116.7 ± 20.4	109.1 ± 19.9	< 0.001
Diastolic blood pressure, mm Hg	72.1 ± 15.3	68.3 ± 16.0	< 0.05
Total cholesterol, mmol/l	4.1 ± 0.8	4.1 ± 0.7	NS
Triglyceride, mmol/l	8.3 ± 3.7	7.5 ± 3.5	< 0.05
HDL cholesterol, mmol/l	1.1 ± 0.2	1.3 ± 0.3	< 0.05
Glucose, mmol/l	4.4 ± 0.4	4.5 ± 0.4	NS
Creatinine, µmol/l	52.2 ± 7.9	48.6 ± 7.9	< 0.001

arthritis (27.9%) than those with normal uric acid levels (13.5%; $p < 0.001$, chi-square test). There were no significant differences between these 2 groups in total cholesterol and fasting glucose concentrations.

We examined the effects of the significant risk factors for hyperuricemia with the multivariate logistic regression model. The odds ratios (OR) and 95% confidence intervals (CI) are presented in Table 3. Factors such as age group, sex, lipid concentrations, and blood pressure were not found to be associated with hyperuricemia. After adjusting for age, sex, lipid profile, and blood pressure, hyperuricemia was found to be significantly associated with serum creatinine (OR 2.40, 95% CI 1.91–3.04), BMI (OR 1.24, 95% CI 1.11–1.40), and a family history of gouty arthritis in parents (OR 2.01, 95% CI 1.02–3.96).

DISCUSSION

Taiwan's population is heterogeneous and is made up of indigenous people (1.5%), Minnan and Hakka (91%), and mainland Chinese (7.5%). The ancient Aborigines in Taiwan probably moved from southern mainland China and then migrated from Taiwan to the Philippines, Timor, and the Mariana Islands through Micronesia and New Zealand[10]. Taiwan's 9 indigenous tribes are highly homogeneous within each tribe, which is evidenced by many HLA-A, B, C alleles having the world's highest reported frequencies[11]. This study is derived from a school health program in Hsin-Yi, Taiwan. The selection bias due to nonrespondents was inevitable, but not to an important degree, as the response rate was 75.7%.

The normal uric acid concentration for prepubertal Taiwanese children (3–7 yrs) is 261.8 ± 5.9 µmol/l (4.4 ± 0.1 mg/dl)[12], lower than adult concentration. The prevalence of hyperuricemia among Aborigine children may be higher than reported in the study, if age related normal limits are used. The mean serum uric acid concentration found in this study was higher than in a survey of adult Chinese in Shanghai[13] and ethnic Chinese in Taiwan[9]. Moreover, the mean serum uric acid concentration of girls in our study was similar to adult female Taiwan Aborigines[5], although that of boys was lower than adult male Taiwan Aborigines. The mean serum uric acid concentrations, as well as the prevalence of hyperuricemia, remained stable among different age groups in girls. However, in boys, it increased to a significant difference in the group aged > 9 years. Decreased secretion of estrogen is known to increase the risk of coro-

Table 3. Multivariate logistic regression analysis on hyperuricemic factors of Taiwan aboriginal children.

Variables	ß (SE)	OR	95% CI	p
Age, yrs	–0.27 (0.10)	0.76	0.62–0.93	< 0.01
Sex, male = 1	–0.44 (0.34)	0.64	0.33–1.24	NS
Triglyceride, mmol/l	0.00 (0.01)	1.00	0.99–1.01	NS
HDL cholesterol, mmol/l	–0.02 (0.02)	0.98	0.95–1.02	NS
Systolic blood pressure, mm Hg	0.01 (0.01)	1.01	0.99–1.03	NS
Diastolic blood pressure, mm Hg	0.00 (0.01)	1.00	0.98–1.03	NS
Serum creatinine, µmol/l	0.88 (0.12)	2.41	1.90–3.05	< 0.001
Body mass index, kg/m^2	0.26 (0.06)	1.30	1.15–1.48	< 0.001
Family history of gouty arthritis, yes = 1	0.76 (0.36)	2.13	1.06–4.29	< 0.05

ß: parameter estimate of the logistic regression model, SE: standard error.

nary heart disease and hyperuricemia in postmenopausal women[14]. The role of sex hormones that might explain the mechanism of gender effect on the age-hyperuricemia relationship in children needs further investigation.

Increased prevalence of childhood overweight and obesity becomes a significant problem in many developed countries, as well as in Taiwan[15]. Chang, *et al* reported that children of the Bunun tribe had a higher prevalence of obesity than those of non-aboriginal children in both sexes (boys 15.4% vs 9.5%; girls 16.7% vs 7.6%)[16]. As expected, our results showed that BMI is related to uric acid concentrations, although numerous confounders such as age and sex have been controlled for. A similar finding was reported by Ko, *et al* among aboriginal adolescents: that the high prevalence of hyperuricemia is related to obesity, tribe, and creatinine levels[17]. Also, Nakanishi, *et al* reported that obesity, alcohol intake, and multimetabolic disorders are independent predictors for the development of hyperuricemia in Japanese men[18]. Alcoholism is widespread among Taiwan Aborigines; however, no child in our study admitted a history of alcohol drinking.

Another significant association of hyperuricemia in our study was family history of gouty arthritis in parents. Twin and family studies have shown the importance of polygenic traits in uric acid concentrations[19,20]. Wilk, *et al* reported that the heritability estimate for serum uric acid is 40%[21]. Chang, *et al* reported a mutation in the hypoxanthine-guanine phosphoribosyltransferase (HPRT) gene in a Taiwanese aboriginal family with severe gout[22]. This report suggests the possibility that variants in HPRT gene may explain the high uric acid concentrations in this population, both in adults and in children. Further, obesity may compound a possible genetic predisposition to hyperuricemia. Investigation to clarify the genetic as well as lifestyle effects is required.

In addition, serum creatinine was also found to have an influence in this study. Simmonds, *et al* observed that a high prevalence of hyperuricemia among Polynesian women resulted from a reduced fractional uric acid clearance[23]. Ko, *et al*[17] and Jackson, *et al*[24] reported that serum creatinine concentrations were associated with hyperuricemia in Taiwan aboriginal adolescents and Western Samoans, respectively. In our study, although concentrations of creatinine remained in the normal range (< 1.0 mg/dl), they contributed the highest risk of hyperuricemia. Further evaluation of the creatinine-hyperuricemia relationship is needed.

Uric acid seems inextricably linked to hypertension, dyslipidemia, and diabetes mellitus, which play a causal role in the pathogenesis of cardiovascular disease[1,2]. Uric acid has been considered as a physiologic antioxidant[25], and Nieto, *et al* reported that uric acid has an antioxidant capacity to counteract oxidative damage related to atherosclerosis[26]. There were no cases of diabetes mellitus or gouty arthritis in our study, and the association between lipid concentrations and blood pressure with hyperuricemia was not statistically significant in the final logistic regression model. The significance of hyperuricemia in children is therefore unclear.

Our findings indicate that BMI, a family history of gouty arthritis in parents, and creatinine concentration are closely correlated with hyperuricemia. However, the findings must be interpreted with caution as the cross sectional study design does not determine causality. Our findings provide the basis for further study of the relationship of serum uric acid and incidence of gout in childhood.

Body mass index, a positive family history of gouty arthritis in parents, and creatinine concentration correlated with hyperuricemia in aboriginal children in Taiwan. The significance of hyperuricemia in children needs further investigation.

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