Familial Aggregation of Serum Uric Acid in Taiwan Aborigines

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Objectives. There is a high prevalence of gouty arthritis (GA) among Taiwan aborigines. This study analyzed the correlation between serum uric acid levels among siblings and familial aggregation of serum uric acid in Taiwanese aboriginal families.

Methods. This was a cross-sectional study conducted in central Taiwan. From March to May 2001, we recruited 210 aboriginal children (mean age, 8.79 ± 1.95 years) from 95 different families. All children completed a structured questionnaire which collected family information and provided blood samples for serum uric acid analysis. The associations between serum uric acid and hyperuricemia between the firstborn sibling and other siblings in families with a history of GA were assessed by multiple regression and logistic regression with generalized estimating equations (GEEs).

Results. The mean serum uric acid level was 363.12 ± 78.70 μmol/L. The adjusted correlation coefficients of serum uric acid between the firstborn siblings and other siblings were 0.74 in the families of parents with GA, and 0.33 in those with parents without GA. The families of firstborn siblings without hyperuricemia and parents without GA served as the reference group (OR = 1); the adjusted odds ratio for hyperuricemia of other siblings was 6.23 in the families with hyperuricemic firstborn siblings and parents with GA (95% CI = 1.43 to 27.6).

Conclusions. Although the possibility of recall bias cannot be excluded, our data suggests a correlation between serum uric acid levels among siblings and familial aggregation of hyperuricemia in Taiwan aboriginal families, especially in families with a history of GA. **(Mid Taiwan J Med 2004;9:219-24)**

Key words

aborigines, children, familial aggregation, serum uric acid

INTRODUCTION

The prevalence of gouty arthritis (GA) in adult Taiwanese aboriginal men is about 15.3% and in adult Taiwanese aboriginal women it ranges from 2.2% to 4.8% [1,2]; the prevalence is significantly higher than in non-aboriginal Taiwanese men and women [3]. There are 10 aboriginal tribes in Taiwan. The major aboriginal tribe included in this study was the Bunun tribe, whose members live in central Taiwan. Most studies of gout and hyperuricemia in Taiwanese aboriginal adults and children have focused on the prevalence and risk factors. The important risk factors identified in aboriginal populations include alcohol consumption, obesity, the hypoxanthine-guanine phosphoribosyltransferase (HPRT) gene and family history of gout [2,4,5]. However, few studies have reported a relationship between genetic or family factors and serum uric acid levels or hyperuricemia in these specific populations. A report which studied familial aggregation in North America noted a 43%

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Table 1. Characteristics of the firstborn siblings and other siblings of Taiwanese aboriginal children

	Firstborn siblings (N = 95)	Other siblings (N = 115)	*p*
All children			
Gender	95	115	–
Boys (%)	38 (40.0)	57 (49.6)	0.1657
Girls (%)	57 (60.0)	58 (50.5)	–
Serum uric acid (μmol/L)	373.16 ±71.71	354.83 ±83.43	0.0930
Age	9.96 ±1.67	7.83 ±1.61	<0.0001
WLI	1.02 ±0.18	0.99 ±0.15	0.1055
Triglyceride (mmol/L)	0.75 ±0.33	0.77 ±0.36	0.6192
Family of parents without gouty arthritis (GA)			
Gender	77	92	–
Boys (%)	48 (62.3)	45 (48.9)	0.0806
Girls (%)	29 (37.7)	47 (51.1)	–
Serum uric acid (μmol/L)	370.45 ±66.39	349.30 ±74.40	0.0551
Age (yr)	9.84 ±1.64	7.76 ±1.56	<0.0001
WLI	1.04 ±0.18	0.98 ±0.13	0.0136
Triglyceride (mmol/L)	0.74 ±0.34	0.75 ±0.37	0.8915
Family of parents with gouty arthritis (GA)			
Gender	18	23	–
Boys (%)	9 (50.0)	13 (56.5)	0.6777
Girls (%)	9 (50.0)	10 (43.5)	–
Serum uric acid (μmol/L)	384.77 ±92.49	376.92 ±111.97	0.8116
Age (yr)	10.44 ±1.76	8.09 ±1.83	0.0002
WLI	0.94 ±0.10	1.01 ±0.21	0.1419
Triglyceride (mmol/L)	0.76 ±0.29	0.84 ±0.31	0.3591

WLI = weight-for-length index.

heritability of fasting serum uric acid [6]. The aim of this study was to analyze the correlation between serum uric acid levels among siblings and the familial aggregation of serum uric acid levels in Taiwanese aboriginal families.

MATERIALS AND METHODS

Study Population

Our study population was the Bunun tribe, whose members live in Hsin-Yi Township in central Taiwan. At the end of the year 2000, there were around 9000 aborigines in Hsin-Yi. With the assistance of the local health authority, we recruited all school-aged children in four villages (Di-Li, Tan-Nan, Jen-Ho, and Shuan-Long) from March to May 2001 [4]. All children were requested to fill out a structured questionnaire with parental assistance. From this questionnaire we collected demographic information and medical history of GA and other diseases in the family. Body height and weight of all children were recorded. Every child was requested to fast for 8 hours before blood sampling. All blood samples were sent to the laboratory of the China Medical University Hospital within 4 hours. Total cholesterol, triglyceride, creatinine, and serum uric acid were analyzed by a Beckman Coulter LX-20 autoanalyzer.

In total, 236 aboriginal children provided detailed family information; 26 were excluded (12.8%) because of a lack of laboratory data. Therefore, a total of 210 children (from 95 families) were enrolled in this study.

Definition of Variables

A child whose parents and grandparents were Bunun aborigines was defined as an aboriginal child. A positive history of GA was defined when either of a child's parents had been diagnosed as having GA.

Statistical Analysis

Our analysis was performed in three stages. Three strata were used in each stage: 1) complete dataset, 2) patents with GA and 3) parents without GA.

Table 2. Correlation coefficients of serum uric acid between the firstborn siblings and other siblings, stratified by parental gouty arthritis (GA) status

	All children	Parents without GA	Parents with GA
Crude	0.52***	0.37***	0.78***
Adjusted†	0.49***	0.33*	0.74*

†Adjusted for gender, age, WLI, serum uric acid and triglyceride of the firstborn siblings and other siblings. *$p < 0.05$, ***$p < 0.001$.

Table 3. Estimated effects of the firstborn siblings' serum uric acid on the serum uric acid of other siblings, stratified by parental gouty arthritis (GA) status

	All children	Parents without GA	Parents with gouty GA
	Coefficient (S.E)	Coefficient (S.E)	Coefficient (S.E)
Crude model			
Serum uric acid	0.55 (0.12)***	0.41 (0.11)***	0.74 (0.24)**
Multivariate model			
Serum uric acid	0.52 (0.12)***	0.39 (0.11)***	0.82 (0.19)***
Sex (boy)	– 8.59 (11.63)	– 8.39 (13.55)	16.23 (21.92)
Age	0.36 (3.60)	4.78 (3.96)	– 0.70 (3.59)
WLI	53.39 (44.18)	34.64 (41.92)	77.88 (82.45)
Triglyceride	– 10.54 (17.48)	– 30.36 (15.23)*	107.39 (32.02)

WLI = weight-for-length index. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

First, the correlation between serum uric acid levels in the firstborn siblings and in the other siblings was analyzed by Pearson's correlation coefficients test. Second, we modeled the serum uric acid of other siblings by the generalized estimating equations (GEEs) approach [7] assuming an identity link. Finally, we modeled the hyperuricemia (serum uric acid > 416.5 μmol/L) of the other siblings by the GEEs approach assuming a logic link to estimate the odds ratio (OR). All statistical analyses were performed with an SAS package (Version 8.2, SAS Institute Inc., Cary, NC, USA).

RESULTS

The 210 aboriginal children came from 95 different families and included 95 firstborn siblings and 115 other siblings. Their mean age was 8.79 ± 1.95 years. The mean serum uric acid level was 363.12 ± 78.70 μmol/L. The demographic characteristics and laboratory data of the firstborn siblings and other siblings in three different strata (completed dataset, parents with GA, and parents without GA) are shown in Table 1. There were no significant differences between the firstborn siblings and other siblings in gender, triglyceride, and serum uric acid in the three strata. However, in one of the strata, parents without GA, the WLI (Weight-for-Length Index) of the firstborn siblings was significantly higher than that of other siblings.

In families with parental GA, the crude and adjusted Pearson's correlation coefficients (r = 0.78 and r = 0.74, respectively) were both greater than in families without parental GA (Table 2).

In determining the relationship between firstborn siblings' serum uric acid and other siblings', we considered that dependence existed in those siblings from the same family. Therefore, we compared the effects of serum uric acid of the firstborn siblings to that of other siblings with GEEs by assuming an identity link (Table 3). The effects of sex, age, WLI, and triglyceride of other siblings were adjusted in the multivariate regression model. The adjusted regression coefficient was 0.82 ($p < 0.001$) in the families with parental GA, and 0.39 ($p < 0.001$) in those without parental GA.

Table 4 is a 2 × 2 × 2 contingency table which classifies the status of parental GA, and children with and without hyperuricemia. The families of parents without GA and the firstborn siblings without hyperuricemia served as the reference category (OR = 1). In comparison with

Table 4. Odds ratio and 95% confidence interval of hyperuricemia of other siblings, based on parental gouty arthritis (GA) and the firstborn siblings' hyperuricemia status

	Variables	OR (95% CI)
Crude OR		
Parental GA status	Hyperuricemia of firstborn sibling	
No	No	1.00 (–)
No	Yes	2.67 (0.76–9.32)
Yes	No	4.00 (0.98–16.34)
Yes	Yes	6.67 (1.65–26.93)**
Multivariate model		
Parental GA status	Hyperuricemia of firstborn sibling	
No	No	1.00 (–)
No	Yes	2.83 (0.67–12.02)
Yes	No	3.90 (0.90–16.97)
Yes	Yes	6.23 (1.43–27.16)*
Sex (boy)		0.69 (0.24–1.97)
Age		0.99 (0.76–1.26)
WLI		3.41 (0.11–103.36)
Triglyceride		1.01 (1.00–1.02)

WLI = weight-for-length index. *$p < 0.05$, **$p < 0.01$.

reference category, after adjusting for gender, age, WLI, and triglyceride of other siblings, the adjusted ORs of hyperuricemia of other siblings were higher in the other three categories. It is noteworthy that only the last category (parents with GA and the firstborn siblings with hyperuricemia) reached the criterion of statistical significance (OR = 6.23, 95% CI = 1.43 to 27.6).

DISCUSSION

Gout is one of the most important health problems in Taiwanese aborigines. The risk factors of gout have been explored extensively; however, the familial aggregation of serum uric acid has not been adequately investigated. This study revealed a strong familial aggregation of serum uric acid in families with GA history. The finding could prove helpful in educating the public about how to prevent hyperuricemia, GA and their subsequent complications.

In our population of Bunun children, the correlation coefficient of serum uric acid among siblings was 0.52. In North American populations, the correlation coefficient of serum uric acid among siblings reported previously ranged from 0.14 to 0.30 [6,8]. The conflicting results suggest that serum uric acid and familial aggregation differ between ethic groups. The aggregation was stronger in the families with GA history than in those without GA history. These results were reproduced by the GEEs models. Furthermore, we found an interaction between parents' GA status and firstborn siblings' hyperuricemia in the multivariable analysis. Individuals with both of these conditions (parents' GA history and firstborn siblings' hyperuricemia) showed a significantly higher odds ratio for hyperuricemia than those with only one or without these conditions.

It has been shown that hyperuricemia is caused by both genetic and behavoral factors (e.g. food preference, and alcohol consumption) [2,4,6,8]. A mutation site contributing to hyperuricemia in the HPRT gene in Taiwanese aborigines was reported by Chang et al [5]. In our study, the phenomenon of familial aggregation of hyperuricemia also supported the importance of genetic heritability.

Nevertheless, this cross-sectional study had its limitations. First, recall bias might have influenced the accuracy of parental GA status. Second, selection bias existed because children who were unable to provide detailed family information were excluded from this study. The cooperativeness and ability to complete the questionnaire might, to an extent, reflect

the family's education level, lifestyle or socioeconomic status. Third, the relevant risk factors of other family members were not collected for analysis, such as obesity, alcohol consumption, food preference, blood lipids and uric acid, and genotypes pertinent to gout.

Therefore, the mechanism underlying the phenomenon of familial aggregation of hyperuricemia needs further exploration. In conclusion, an apparent correlation exists between uric acid and siblings of aboriginal childern, particularly in families with GA history.

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探討原住民血中尿酸值之家族聚集性

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目的 痛風性關節炎爲台灣原住民一重要之疾病，在本研究中我們將使用台灣原住民的家族資料來評估同一家庭學童其血中尿酸值的相關性與家族聚集性。

方法 本研究爲橫斷面研究。我們於西元2001年三月至五月間在中台灣地區進行此研究。本研究最後樣本爲來自95個家庭的210位布農族學童(平均年齡爲8.79 ± 1.95歲)。所有學童我們都要求完成一份結構式問卷、提供家族相關資料和收集學童的血液樣本，此血液樣本主要用於分析學童血中尿酸濃度。我們在使用廣義估計公式(generalized estimating equations，GEEs)來評估第一出生順序學童(長子/女)與其他出生順序學童(次子/女)血中尿酸值和高尿酸血症相關性。

結果 學童血中尿酸值平均值爲363.12 ± 78.70 μmol/L。長子和其次子血中尿酸值其調整相關因子後的相關係數，在「父母有痛風性關節炎家庭」和「父母無痛風性關節炎家庭」分別爲0.74和0.33。我們以長子沒有高尿酸血症並且其家庭爲「父母無痛風性關節炎家庭」這一組當基準組（OR = 1)，發現長子有高尿酸血症的並且其家庭爲「父母痛風性關節炎家庭」這一組，其次子有高尿酸血症的調整後勝算比爲6.23 (95% CI = 1.43至27.6)。

結論 雖然本研究沒辦法排除可能的回憶偏差，但我們資料顯示台灣原住民家庭中學童其血中尿酸值有強的相關性和家族聚集性可能是需被注意的，特別在其家中父或母患有痛風時。（**中台灣醫誌2004;9:219-24**）

關鍵詞

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