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PLASMA AND URINE URIC ACID LEVELS: HERITABILITY ESTIMATES AND CORRELATION WITH IQ

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Summary Plasma and urine uric acid levels were measured in 37 pairs of twins aged 11 or 12 years and their parents. Effect of age differed between sexes and between plasma and urine. Assuming linear regression on age, the uric acid levels were adjusted for a fixed age, then standardized with mean 0 and standard deviation 1. The standardized values for plasma yielded a high MZ twin correlation (0.8429), a high mid-parent-offspring regression (0.7516) and a high parent-offspring regression (0.5100). Because of a high husband-wife correlation (0.3771) a model was used for estimating parameters, where effects of assortative mating and/or common within-family environment were incorporated. In plasma two sets of estimates were obtained: $V_A/V_P=0.7064$, 0.3251; $V_D/V_P=0.1010$, 0.1769; and V_{EC} (variance due to common within-family environment)/$V_P=0.0362$, 0.3416. In urine $V_A/V_P=0.4125$, $V_D/V_P=0.3556$ and $V_{EC}/V_P=-0.1106$. It was concluded that heritability of uric acid level was not less than 0.3 in plasma and not less than 0.4 in urine. The plasma uric acid level and IQ was positively correlated (between 0.17 and 0.34), but not significant.

INTRODUCTION

Apart from studies on hyperuricemias, there have been reported a few genetic studies on the level of plasma, serum or urine uric acid in normal subjects. Jensen *et al.* (1965) reported that plasma uric acid level in twins living together or apart was influenced by genetic as well as environmental factors. Boyle *et al.* (1967) found that genetic component in the control of serum uric acid level was significant only in female twins. Rich *et al.* (1978) suggested that X-linked genetic factors played a significant role in determining the level of serum uric acid, using half-sib analysis method. On the other hand, O'Brien *et al.* (1966) and Gulbrandsen *et al.* (1979) reported a low heritability of serum or plasma uric acid level, applying either of estimates from parent-offspring regression or path analysis method. Apparently

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non-genetic factors are associated with plasma, serum and urine uric acid levels. They include nutrition such as nucleic acid, purines and protein (Waslien *et al.*, 1968; Clifford *et al.*, 1976; Seegmiller *et al.*, 1963; Rauch-Janssen *et al.*, 1977), alcohol consumption (Lieber *et al.*, 1962; Brooks and Mueller, 1966; Saker *et al.*, 1967; Gulbrandsen *et al.*, 1979), body weight, obesity or body surface (Dunn *et al.*, 1963; Brooks and Mueller, 1966; Sturge *et al.*, 1977; Noppa *et al.*, 1978; O'Brien *et al.*, 1966), social status or occupation (Dunn *et al.*, 1963; Montoye *et al.*, 1967), and education (Dunn *et al.*, 1963).

Plasma, serum or urine uric acid level is also reported to be associated with intellectual performance (Stetten and Hearon, 1959; Dunn *et al.*, 1963) and behavior variables (Brooks and Mueller, 1966). It is thus suggested that there might be an association between uric acid level in body fluids and behavioral characteristics due to genetic origin, since there are accumulated evidences that some behavioral characteristics including activity (*e.g.* Inouye, 1953) and IQ (*e.g.* Erlenmeyer-Kimling and Jarvik, 1963) are influenced by genetic factors.

Present study aims at estimation of heritability of plasma and urine uric acid levels in a population of twins and their parents, applying a model incorporating the effect of assortative mating and the effect of within-family common environment. Sex and age effects and the correlations of uric acid levels with IQ, weight and height in twins were also examined.

MATERIAL AND METHODS

There are two samples of subjects, both consisting of twins of age 11 or 12 years and their parents. Twins are those who applied to the Junior High School of the Faculty of Education, University of Tokyo. Subjects of the first sample were obtained in 1978 which consist of 14 monozygotic (MZ) and 2 same-sexed dizygotic (DZ) twin pairs, an opposite-sexed dizygotic pair, 15 fathers and 14 mothers. Second sample was obtained in 1979 which consists of 18 MZ and 2 same-sexed DZ twin pairs, 18 fathers and 20 mothers. All twin subjects were selected for the area of residence, and those with low academic achievements were excluded. They were physically normal and in good health. Zygosity of twins was diagnosed by two methods of Inouye (1956, 1962). Informed consent was given by the subjects and school administration.

For each year, heparinized blood was taken in a morning. Fasting urine specimens were also collected in the same morning. Uric acid assay was made on the same day by a colorimetric method at OD 410 nm, using Boehringer Mannheim uric acid uricase color test. Standard solution was 6 mg/dl. Results of intelligence test (Shin-Tanaka B2 Test) of twins were provided by the school.

The model

The following model is a part of that proposed by Inouye (1979).

We assume

$$V_P = V_A + V_D + V_{EC} + V_{EW}$$

where V_P is phenotypic variance, V_A additive variance, V_D dominance variance, V_{EC} within-family variance, and V_{EW} between-family variance. Four equations (1) to (4) below are used to estimate the above four parameters, where assortative mating was taken into consideration. Here r denotes intra-class correlation, and b regression coefficient.

1. Monozygotic twins (MZ) living together

$$r_{MZ} = V_A + V_D + V_{EC}. \qquad (1)$$

2. Husband-wife

Let A additive value, D dominance deviation. E_C (within-family environmental deviation) is devided into E_{C_1} (common environment between husband and wife before marriage having effects lasting to the time of examination) and E_{C_2} (common environment between husband and wife after marriage having the same effects). Intra-class correlation coefficient of husband and wife at the time of marriage is

$$\rho = (\mathrm{Cov}A_HA_W + \mathrm{Cov}D_HD_W + \mathrm{Cov}E_{C1H}E_{C1W}) \div 0.5(V_{PH} + V_{PW}),$$

where H denotes husband, and W wife. Intra-class correlation coefficient at the time of examination is

$$r_{HW} = (\mathrm{Cov}A_HA_W + \mathrm{Cov}D_HD_W + \mathrm{Cov}E_{C1H}E_{C1W} + \mathrm{Cov}E_{C2H}E_{C2W}) \div 0.5(V'_{PH} + V'_{PW}).$$

We assume

$$V_{PH} + V_{PW} = V'_{PH} + V'_{PW}$$

and

$$V_{PH} = V_{PW}.$$

Then

$$r_{HW} = \rho + V_{EC2} \div 0.5(V_{PH} + V_{PW}) = \rho + V_{EC2} \div V_P. \qquad (2)$$

3. Mid-parent-offspring

We assume

$E_{C1} = 0$. Assortative mating has no effect (Reeve, 1956), and there is no contribution of dominance deviation.

Let $\bar{P}$ the mean of phenotypic deviations of the parents, then

$$\bar{P}=0.5(A_F+A_M+2E_{C2}+E_{WF}+E_{WM})\text{ , and}$$

$$V_{\bar{P}}=0.25V_{AF}+0.25V_{AM}+V_{EC2}+0.25V_{EWF}+0.25V_{EWM}$$

where F denotes father, and M mother.

Since E_W is random, we assume

$$0.25V_{EWF}+0.25V_{EWM}=0.5V_{EW}$$

and

$$V_{AF}=V_{AM}\ .$$

Then

$$V_{\bar{P}}=0.5V_A+V_{EC2}+0.5V_{EW}=0.5V_P+V_{EC2}\ .$$

Since

$$\mathrm{Cov}\bar{P}O=\mathrm{Cov}0.5A_FA_O+\mathrm{Cov}0.5A_MA_O+\mathrm{Cov}E_{C2}E_{C2}$$

and

$$\mathrm{Cov}A_FA_O=\mathrm{Cov}A_MA_O=0.5V_A\ .$$

Then

$$\begin{aligned} b_{\bar{P}O}&=\mathrm{Cov}PO\div V_{\bar{P}}=(0.25\times 2V_A+V_{EC2})\div(0.5V_P+0.5V_{EC2})\\ &=(V_A+2V_{EC2})\div(V_P+V_{EC2})\ . \end{aligned} \qquad (3)$$

4. Parent-offspring

According to Fisher (1918; see also Crow and Felsenstein, 1968),

$$b_{PO}=(0.5V_A+V_{EC}+0.5\rho V_A)\div V_P. \qquad (4)$$

RESULTS

The mean and standard deviation of plasma and urine uric acid levels are shown in Tables 1 and 2. Plasma uric acid level is higher in males than in females, except in twins in the 1979 sample. The sex difference in twin is significant in the 1978 sample, but not in the 1979 sample, if first- and second-born twins are pooled ($t=2.66$, $p<0.025$ and $t=-1.27$, ns, respectively). In parents sex difference of plasma uric acid level is significant in both samples ($t=4.78$, $p<0.001$ and $t=6.19$, $p<0.001$, respectively). On the other hand urine uric acid indicated a sex difference only in the 1979 sample, male twins being lower than female twins ($t=-2.27$, $p<0.05$), but fathers being higher than mothers ($t=2.52$, $p<0.025$).

Table 1. The mean and standard deviation of plasma uric acid (mg/dl).

	1978 sample			1979 sample		
	No.	Mean±SD	Min–Max	No.	Mean±SD	Min–Max
Males						
1st-born twins	10	4.17±1.53	2.09–7.57	8	3.51±1.07	2.31–5.51
2nd-born twins	10	3.70±1.40	1.57–6.23	8	3.81±1.57	1.54–6.67
1st+2nd twins	20	3.93±1.44	1.57–7.57	16	3.66±1.30	1.54–6.67
Fathers	15	4.81±1.62	1.99–8.74	18	5.89±1.50	2.65–8.98
Females						
1st-born twins	5	2.46±0.99	1.21–3.78	12	4.17±1.23	1.97–6.26
2nd-born twins	7	2.72±1.39	0.42–4.43	12	4.07±0.74	2.27–4.79
1st+2nd twins	12	2.61±1.19	0.42–4.43	24	4.12±0.99	1.97–6.26
Mothers	14	2.46±0.95	0.98–4.27	20	3.44±0.78	2.24–5.32

Table 2. The mean and standard deviation of urine uric acid (mg/dl).

	1978 sample			1979 sample		
	No.	Mean±SD	Min–Max	No	Mean±SD	Min–Max
Males						
1st-born twins	11	35.68±15.48	18.77–69.72	8	56.65±13.72	40.51–76.52
2nd-born twins	10	34.09±15.04	17.77–70.73	8	53.64±18.17	26.74–73.87
1st+2nd twins	21	34.92±14.91	17.77–70.73	16	55.15±15.63	26.74–76.52
Fathers	16	31.74±15.97	5.10–60.34	18	57.25±18.36	23.30–86.80
Females						
1st-born twins	6	43.18±18.06	26.82–74.08	12	69.76±19.98	27.66–95.44
2nd-born twins	7	41.99±12.22	26.15–62.68	12	67.05±19.74	29.39–95.10
1st+2nd twins	13	42.54±14.52	26.15–74.08	24	68.41±19.48	27.66–95.44
Mothers	16	38.40±18.70	12.74–81.45	20	42.67±17.30	10.85–68.81

As to the effect of age on plasma uric acid level, fathers indicated a higher mean than male twins, but mothers indicated a lower mean than females twins, suggesting an increase of the level with age in males and a decrease in females. In urine twins indicated a higher mean than parents except in males of the 1979 sample. Assuming linear regression of uric acid level on age, analysis was made separately for each sex and each sample. The result is shown in Table 3, which also shows correlation coefficient between uric acid level and age. It is seen in Table 3 that regression coefficient of plasma uric acid level on age is positive in males and negative in females, and correlation coefficients are significant in both sexes in the 1979 sample. In urine decrease of uric acid level with age is significant in females in the 1979 sample.

Next the values were adjusted for age of 150 months, separately for each sex and each sample, using equations in Table 3. The age-adjusted values were then standardized by

$$z=(x-\bar{x})/\sigma$$

again separately for each sex and each sample (x is the age-adjusted value, $\bar{x}$ and σ are mean and standard deviation of x).

Correlations and regressions of the age-adjusted and standardized values are shown in Tables 4 and 5, which suggest a high heritability of plasma uric acid level, if husband-wife correlation was disregarded. When we apply the model for husband-wife correlation (equation (2)), we obtain two values of ρ (0.3415 and 0.0361) and therefore two values of V_{EC}/V_P (0.0362 and 0.3416) for plasma uric acid level. Putting these values to equations for mid-parent-offspring regression (3) and parent-offspring regression (equation (4)), we obtain $V_A/V_P=0.7064$ and 0.3251. Corresponding V_D values derived from equation for MZ twin correlation (1) are 0.1010 and 0.1769.

In urine two values of ρ are 0.3140 and -0.0616, and corresponding V_{EC}/V_P values are -0.1106 and 0.2650, but the second values yielded a minus value of V_A/V_P, thus were disregarded. From the first values V_A/V_P is estimated to be 0.4125, and V_D/V_P 0.3556. The above results are summarized in Fig. 1.

Table 3. Regression of uric acid level(y) on age in months(x).

	No.		Correlation coefficient	Probability
Plasma				
1978 sample				
Male	35	y= 0.0022x+3.6335	0.2640	ns
Female	26	y=−0.0003x+2.6392	−0.0524	ns
1979 sample				
Male	34	y= 0.0055x+2.8584	0.6325	0.001
Female	44	y=−0.0016x+4.3201	−0.3112	0.05
Urine				
1978 sample				
Male	37	y=−0.0060x+35.4113	−0.0754	ns
Female	29	y=−0.0097x+43.4675	−0.0975	ns
1979 sample				
Male	34	y= 0.0064x+53.9329	0.0789	ns
Female	44	y=−0.0715x+79.1967	−0.5931	0.001

Table 4. Intra-class correlation(r) and regression(b) for plasma uric acid level, age-adjusted and standardized.

	No.	Intra-class correlation	Regression
MZ			
Male	16	r=0. 8478***	
Female	15	r=0. 8386***	
Male+Female	31	r=0. 8429***	
Mid-parent-offspring	62		b=0. 7516
Parent-offspring	130		b=0. 5100
Father-son	32		b=0. 6070
Father-daughter	32		b=0. 5878
Mother-son	34		b=0. 3461
Mother-daughter	32		b=0. 4909
Husband-wife	31	r=0. 3771*	

* $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Table 5. Intra-class correlation(r) and regression(b) for urine uric acid level, age-adjusted and standardized.

	No.	Intra-class correlation	Regression
MZ			
Male	17	r=0. 6459*	
Female	15	r=0. 6452*	
Male+Female	32	r=0. 6465**	
Mid-parent-offspring	68		b=0. 2152
Parent-offspring	140		b=0. 1468
Father-son	35		b=0. 0493
Father-daughter	33		b=0. 1297
Mother-son	37		b=0. 2368
Mother- daughter	35		b=0. 1675
Husband-wife	34	r=0. 2028	

* $p<0.01$, ** $p<0.001$.

The mean and standard deviation of IQ are 129±19 in male and 116±16 in female twins in the 1978 sample, sex difference being not significant. In the 1979 sample corresponding values are 117±11 and 124±14 without sex difference.

Positive but not significant correlations are seen between plasma uric acid level and IQ in twins, where both values are standardized ($r=0.3408$, $n=27$ in

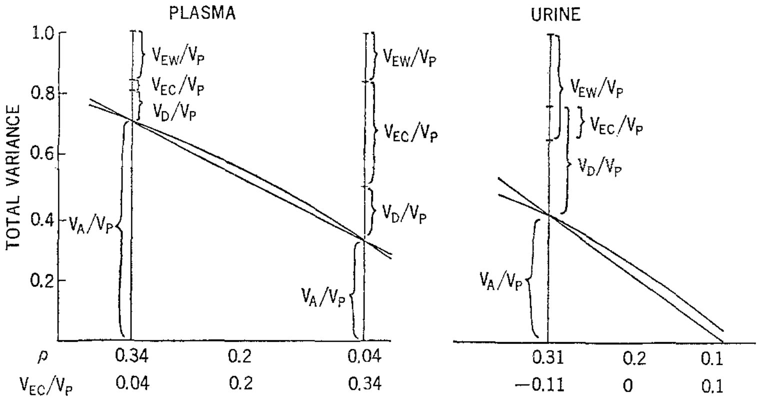

Fig. 1. Estimated components of uric acid phenotypic variance.

males; r=0.1719, n=25 in females and r=0.2482, n=52 in all twins). As to correlation between standardized urine uric acid and IQ it is negative in females (r=−0.3139, n=25) and positive in males (r=0.1428, n=27), both are not significant.

The non-adjusted and non-standardized plasma uric acid level reveal non-significant correlations with body weight in female twins (r=0.1542, n=36) as well as in male twins (r=−0.0221, n=36). In urine correlations with weight are non-significant both in male and female twins (r=−0.2750, n=37; r=0.0713, n=37, respectively). Similarly correlations with height were also non-significant in plasma and urine in both sexes.

DISCUSSION

The present study is in agreement with previous reports in that males had a higher mean level than females (Rich *et al.*, 1978; Jensen *et al.*, 1965; Seegmiller *et al.*, 1963; O'Brien *et al.*, 1966; Mikkelsen *et al.*, 1965). In males a positive age effect on plasma uric acid level was revealed, but it was negative in females. Several studies have shown that age as well as sex are related to serum uric acid level. Mikkelsen *et al.* (1965) reported that the mean serum uric acid level of the age of pre-puberty was different from that of the age of puberty in both sex. Dunn *et al.* (1963) reported that there was no evidence of an age effect in adult population.

As to heritability ($=V_A/V_P$) of plasma uric acid level it seems to be quite high because of a high MZ twin correlation, a high mid-parent-offspring regression and a high parent-offspring regression (from Table 4 they are 0.8429, 0.7516 and 0.5100, respectively). However, a considerable amount of husband-wife correlation was revealed (0.3771), and therefore, the effects of assortative mating and/or common within-family environment were examined, applying the model incorporating the two variables. This analysis yielded two sets of estimates. One is a high heritability (0.7064) with a considerable phenotypic correlation between husband and wife (ρ=0.3415), a low ratio of common environmental variance to phenotypic variance (V_{EC}/V_P=0.0362), and a low ratio of dominance variance to phenotypic variance (V_D/V_P=0.1010). The other is a medium heritability (0.3251) with a low phenotypic correlation between husband and wife (0.0361), a medium V_{EC}/V_P (0.3416) and a low V_D/V_P (0.1769). It seems that there is no evidence as to which estimate is more accurate.

Inouye *et al.* (1979) reported a high heritability of plasma uric acid level of around 0.8 or 0.9, applying half-sib analysis method. In this study a minus husband-wife phenotypic correlation ($\rho = -0.2411$) was reported and V_{EC}/V_P had also a minus sign. This and the present studies disagree in several point, and it is premature to draw a definite conclusion.

As to urine uric acid level heritability was estimated to be around 0.4. A medium amount of ρ was seen (around 0.3), and V_{EC}/V_P had a minus sign. Rather strange is a considerable amount of V_D/V_P (around 0.35). Corresponding values in the half-sib study were $V_A/V_P \fallingdotseq 0.8$, $\rho \fallingdotseq 0$, and $V_{EC}/V_P \fallingdotseq 0.1$, but V_D/V_P was not estimated. Again two studies disagree. Conservative conclusion would be that heritability of uric acid level is not less than 0.3 in plasma and not less than 0.4 in urine, but the effects of assortative mating and/or within-family common environment are to be evaluated in future.

As to correlation between uric acid level and IQ, plasma indicated a positive correlation of the magnitude between 0.17 and 0.34, though not significant. In urine unequivocal result was not obtained. Similarly, correlation between uric acid level and non-genetic factors was equivocal. Further studies on a larger sample are clearly needed.

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