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Hyperuricaemia in cyanotic congenital heart disease

Y. Hayabuchi, S. Matsuoka, H. Akita, Y. Kuroda

Department of Paediatrics, University of Tukoshima School of Medicine, Kuramoto-cho, Tokushima 770, Japan

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Abstract. This study examines the exacerbating factors of hyeruricaemia in patients with cyanotic congenital heart disease (CCHD). We studied 59 CCHD patients aged 1 month–30 years. The following variables were assessed: serum uric acid levels, red blood cell count, haemoglobin, hematocrit, partial oxygen pressure and arterial oxygen saturation. Uric acid excretion and renal function were also measured in ten patients with serum levels of uric acid greater than 8 mg/dl (hyperuricaemia group). Serum uric acid level correlated significantly with age and severity of polycythaemia. However, it did not correlate with partial oxygen pressure or arterial oxygen saturation. Uric acid excretion was measured in hyperuricaemia group. Urinary uric acid excretion (24 h) was within normal limits in infants but markedly lower in patients over 15 years of age. The aetiology of hyperuricaemia and decreased uric acid fractional excretion and clearance in infants appears to be secondary to diminished excretion of uric acid in concert with uric acid overproduction. Hyperuricaemia in adolescents and adults with CCHD, however, results mainly from age-related impairment of uric acid excretion.

Key words: Hyperuricaemia – Cyanotic congenital heart disease

Introduction

In patients with cyanotic congenital heart disease (CCHD) polycythaemia and renal dysfunction are known to develop with age. Hyperuricaemia is frequently observed in adolescence and adulthood [5, 12–14, 17]. However there have been few reports about their occurrence in infants, moreover, the age-dependent mechanism of hyperuricaemia in CCHD has not been identified precisely.

Our study examins serum uric acid levels in CCHD patients not having undergone surgical interventions. Furthermore, in patients with serum uric acid levels greater than 8 mg/dl the production and excretion of uric acid as well as renal function were evaluated to determine the aetiology of hyperuricaemia.

Correspondence to: Y. Hayabuchi

Abbreviation: CCHD = cyanotic congenital heart disease

Subjects and methods

We reviewed 59 CCHD patients (aged 1 month–30 years) prior to any surgical intervention. Cardiac lesions identified were: tetralogy of Fallot (24 cases), transposition of the great arteries (4 cases), double outlet right ventricle (6 cases), Taussig-Bing anomaly (3 cases), single ventricle (9 cases), tricuspid atresia (6 cases), and heterotaxia (7 cases). Out of 59 patients, 19 received furosemide. In these patients the following variables were studied; serum uric acid, red blood cell count (RBC), haemoglobin (Hb), haematocrit (Hct), partial pressure of oxygen in arterial blood (PaO_2), and the saturation of oxygen in arterial blood (SaO_2).

In ten patients with werum uric acid levels greater than 8 mg/dl (hyperuricaemia group; Table 1), the following additional investigation were performed: 24 h urinary uric acid excretion, uric acid clearance, fractional excretion of urid acid, creatinine clearance, proteinuria and urinary N-acetyl-β-D-glucosaminidase.

Results

Relationship between clinical background and serum uric acid level

Serum uric acid levels were found to increase significantly with age (Fig. 1.) RBC, Hb and Hct correlated significantly with serum uric acid level ($r = 0.54, 0.50, 0.51$; $P < 0.05$) (Fig. 2.), but not with age. Mean PaO_2 was 40 ± 7 mm Hg (range of 27–53), and mean $Sa0_2$ was 68% ± 15% (range of 35%–89%). PaO_2 showed no significant correlation with serum uric acid level.

Serum uric acid level of 19 patients taking furosemide (age 5.4 ± 5.5 years. RBC 598 ± 125 μl, HB 17.3 ± 4.5 g/dl, Hct 53.3% ± 13.0%. PaO_2 40 ± 6 mm Hg, SaO_2 73% ± 11%) was 7.5 ± 3.8 mg/dl. This was significantly higher ($P < 0.05$) than that of 40 patients not taking the drug (age 5.8 ± 6.6 years, RBC 588 ± 121 μl, Hb 15.6 ± 2.8 g/dl, Hct 48.7% ± 9.0%. PaO_2 39 ± 7 mm Hg, SaO_2 66% ± 17%, serum uric avid 5.6 ± 1.7 mg/dl).

Patients (n = 10) with serum uric acid levels above 8 mg/dl

In the hyperuricaemia group, the degree of polycythaemia (RBC 738 ± 105 μl, Hb 20.6 ± 3.4 g/dl, Hct 64.8% ±

Table 1. Characteristics of hyperuricamia patients with CCHD

Case	Cardiac diagnosis	PaO_2 (mm Hg)	RBC ($\times 10^4$/mm^3)	Drugs	Status
1	TGA	41	830	Furosemide	Decreased
2	Taussig-Bing	30	825	Furosemide, allopurinol, benzbromarone	Decreased
3	Tricuspid atresia	40	662	Furosemide	Alive
4	Asplenia syndrome	42	610	Furosemide	Alive
5	Asplenia syndrome	42	550		Alive
6	Single ventricle	42	733	Furosemide	Alive
7	Asplenia syndrome	37	870	Furosemide	Alive
8	Asplenia syndrome	32	822		Alive
9	Single ventricle	40	759	Furosemide	Alive
10	DORV	47	717		Alive

TGA, Transposition of the great arteries; Taussig-Bing, Taussig-Bing anomaly; DORV, double outlet right ventricle

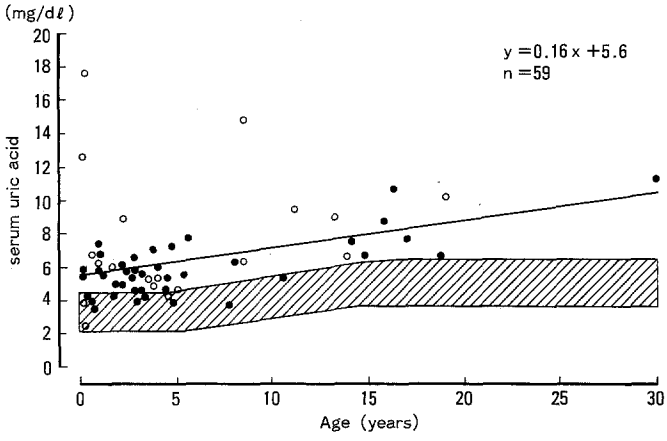

Fig. 1. Correlation between serum uric acid level and age in patients with CCHD. *Shaded area* indicates normal range (mean ± standard deviation). ○: Patients receiving furosemide; ●: patients not on furosemide

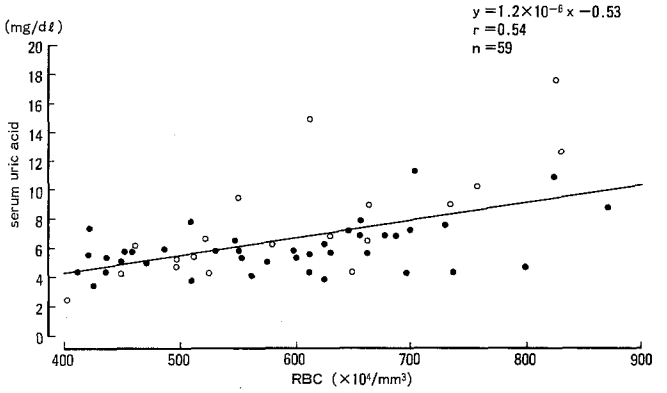

Fig. 2. Correlation between serum uric acid level and RBC value count in patients with CCHD. ○: Patients receiving furosemide; ●: patients not on furosemide

10.8%) was significantly higher ($P < 0.01$) than in patients with serum uric acid levels below 8 mg/dl (RBC 555 ± 115 μl, Hb 15.2 ± 3.2 g/dl, Hct 47.0% ± 9.4%). In contrast, no significant difference was noted between hyperuricaemia patients and others with regard to PaO_2 and SaO_2.

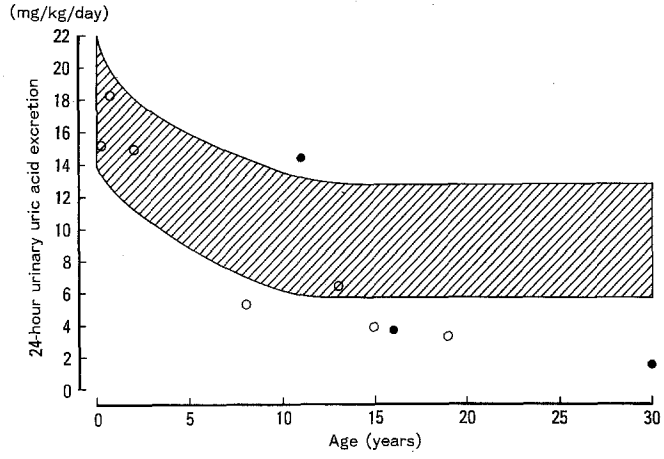

Fig. 3. Urinary uric acid (24 h) excretion in ten hyperuricaemia patients with CCHD. *Shaded area* indicates normal range (mean ± standard deviation). ○: Patients receiving furosemide; ●: patients not on furosemide

Urinary uric acid excretion (24 h) was within the normal range in hyperuricaemic patients less than 15 years old, but markedly lower in patients greater than 15 years of age (Fig. 3). Uric acid clearance and fractional excretion of uric acid in the hyeruricaemia group were notably lower. Uric acid clearance decreased with age (Table 2).

Urinary N-acetyl-β-D-glucosaminidase was abnormally high in all hyperuricaemia cases. A decrease in creatinine clearance as well as the existence of proteinuria was noted in all patients above 13 years of age.

Discussion

Our findings confirm that hyeruricaemia is prevalent in adolescents with CCHD and worsens with age [5, 12–14, 17]. Moreover, our data also demonstrate that hyperuricaemia is already observed in infants with CCHD. Polycythaemia, renal dysfunction as well as hypoxia have all

Table 2. Maximum serum uric acid level, uric acid excretion, and renal function in ten hyperuricaemic patients with CCHD

Case	Age	Maximum serum urate level (mg/dl)	Uric acid excretion			Renal function		
			Cua (ml/min/ 1.73 m^2)	FEua (%)	24-h urate excretion (mg/kg/day)	Ccr (ml/min/ 1.73 m^2)	NAG (U/mmol · creatinine)	Proteinuria
1	1 month	12.6	2.2	3.4	13.7	62	3.8	–
2	3 months	17.7	2.4	5.6	18.1	40	1.4	–
3	2 years	9.0	2.3	4.7	14.9	50	0.6	–
4	8 years	14.8	1.5	5.6	5.2	28	1.4	–
5	11 years	9.5	3.8	4.9	14.6	77	1.2	–
6	13 years	9.0	2.1	7.6	6.5	28	1.3	3 +
7	15 years	8.7	1.4	3.4	4.0	42	0.8	2 +
8	16 years	10.7	1.3	3.6	3.8	36	0.8	2 +
9	19 years	10.2	1.1	3.5	3.5	33	1.3	3 +
10	30 years	11.3	0.5	1.7	1.6	29	2.0	3 +

Cua, Uric acid clearance; FEua, fractional excretion of uric acid; Ccr, creatinine clearance; NAG, N-acetyl-β-D-glucosaminidase; Proteinuiria, –: negative +: positive

Normal range (mean ± standard deviation) [references: 1, 6, 8, 10, 11]

Serum uric acid level (mg/dl)

Newborn	2.0–4.5
3–4 years	2.5–4.5
5–9 years	3.0–5.0
10–14 years	3.0–5.5
Adults	3.5–6.0

Cua (ml/min/1.73 m^2) 9–11

FEua (%)

Newborn	24–52
3–4 years	8–16
4–9 years	7–13
9–14 years	4–11
Adults	5– 9

24-h urate excretion (mg/kg/day)

Newborn	14–22
3–4 years	10–17
5–9 years	8–15
10–14 years	5–13
Adults	5–13

Ccr (ml/min/1.73 m^2)

Newborn	40– 65
6 months–1 year	65–110
1–2 years	70–130
2 years–adults	80–140

NAG (U/mmol · creatinine) 0.41–0.47

Proteinuria – (negative)

been implicted in the pathogenesis of hyperuricaemia [5, 12–17]. During hypoxia, adenosine monophosphate accumulates in organs due to the suppression of the tricarboxylic acid cycle and electron transfer. Ultimately adenosine monophosphate is catabolized to uric acid. Hyperuricaemia in CCHD therefore reflects increased purine catabolism [15, 16]. In our study, two infants with abnormally high levels of serum uric acid (cases 1, 2), required mechanical ventilation and intermittent pressor support prior to dying from heart failure (case 1), and pulmonary haemorrhage (case 2).

Uric acid clearance and fractional excretion of uric acid was notably low in all patients with hyperuricaemia. The 24 h urinary uric acid excretion was normal in infants, but extremely low in patients older than 15 years of age. In infants, hyperuricaemia and low uric acid clearance and reduced fractional excretion are thought to be due to impaired urinary excretion in concert with uric acid overproduction. Hyperuricaemia in adolescents and adults, however, results mainly from renal dysfunction and concomitant impairment of uric acid excretion. Renal biopsies of patients with CCHD demonstrate remarkable enlargement, hypercellularity, and dilatation of glomerular capillaries [3, 7]. Uric acid collection within tubules also contributes to renal dysfunction [2, 9]. A decrease in creatinine clearance and proteinuria is noted in severe cases.

The serum uric acid values of paitents taking furosemide was also significantly higher than those not taking the medication as is consistent with previous reports [4].

In summary, serum uric acid level correlated significantly with age and the degree of polycythaemia. Hyperuricaemia in infants with CCHD reflected impaired uric acid excretion in concert with overproduction. Hyperuricaemia in adolescents and adults with CCHD results mainly from age-related renal dysfunction and impairment of uric acid excretion.

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