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Original Article

Hyperuricaemia in congenital heart disease patients

Efrén Martínez-Quintana,[1] Fayna Rodríguez-González[2]

[1]*Cardiology Service, Insular-Materno Infantil University Hospital;* [2]*Dr. Negrín University Hospital of Gran Canaria, Las Palmas de Gran Canaria, Spain*

Abstract *Introductio:* Hyperuricaemia is associated with traditional cardiovascular risk factors such as type 2 diabetes or dyslipidaemia and a higher mortality. *Methods:* Out of 528 congenital heart disease patients, 329 patients, including 190 male and 139 female patients, in whom uric acid determination was performed, were studied and followed up to determine survival. *Results:* Male congenital heart disease patients with high serum uric acid concentrations (>7 mg/dl) showed significantly ($p < 0.05$) higher body mass index, serum creatinine, total cholesterol, low-density lipoprotein-cholesterol, triglycerides, and C-reactive protein concentrations than those male congenital heart disease patients with lower serum uric acid levels (≤7 mg/dl). Meanwhile, female congenital heart disease patients with higher serum uric acid concentrations (>5.7 mg/dl) were significantly ($p < 0.05$) younger, more hypoxaemic, more obese, and with higher C-reactive protein and N-terminal-pro-B-type natriuretic peptide levels than those female congenital heart disease patients with lower serum uric acid concentrations (≤5.7 mg/dl). During a median follow-up of 90 months, 16 out of 528 congenital heart disease patients died – 14 patients of cardiac origin and two patients of non-cardiac origin – of whom 10 were hypoxaemic. Kaplan–Meier analysis showed no significant differences in mortality between male and female congenital heart disease patients with high and low serum uric acid level concentrations. *Conclusions:* Hypoxaemia, body mass index, and C-reactive protein concentrations are higher in hyperuricaemic congenital heart disease patients, although no significant differences were seen in mortality between congenital heart disease patients with high and low serum uric acid concentrations.

Keywords: Hyperuricaemia; serum uric acid; congenital; survival

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HYPERURICAEMIA, THE CARDINAL BIOCHEMICAL feature and prerequisite for gout, is classified as primary (idiopathic/genetic) or secondary (acquired) and both may in turn classified into three functional types depending on whether there is an increased production of uric acid, a decreased excretion of uric acid, or a combination of both. However, in the past few decades overproduction has increased coinciding with a higher incidence of obesity and lifestyle factors, with the prevalence of hyperuricaemia reaching 18.0% in the Caucasian population.[1] Moreover, hyperuricemia has become a cardiovascular risk marker associated with other classic cardiovascular risk factors, atherosclerosis and mortality.[2,3]

With the objective of gaining insight into the role of serum uric acid levels in congenital heart disease patients, we measured and compared serum uric acid levels with other demographic, clinical, and analytical parameters and determined survival curves between congenital heart disease patients with low and high serum uric acid concentrations.

Methods

Data were collected from all consecutive clinically stable congenital heart disease patients who had

Correspondence to: Dr E. Martínez Quintana, Complejo Universitario Insular-Materno Infantil. Avenida Marítima del Sur s/n. 35016. Las Palmas de Gran Canaria, Spain. Tel: +0034 928441360; Fax: +0034 928441853; E-mail: efrencardio@gmail.com

serum uric acid concentration measured in our Adolescent and Adult Congenital Heart Disease Unit of the Complejo Hospitalario Universitario Insular-Materno Infantil of Gran Canaria, between January, 2006 and January, 2013. Most of the patients included in the study, or their parents, gave informed consent for routine serum and 24-hour urine analytical determinations. In the remaining patients, serum uric acid concentrations were determined by review of the medical history. Repeated measurements, other than the first, were excluded from analysis. The inclusion criteria specified patients older than 14 years with a structural congenital heart disease. On the contrary, exclusion criteria were patients who had, at the time of analytical extraction, advanced kidney disease, were under high doses of diuretic treatment or chemotherapeutic agents, or did not give prior authorisation for analytical extraction. Measurements made after emergency admissions or within 6 months after surgery were also excluded from the analysis. Clinical data were acquired from patient records; specific congenital heart disease diagnoses were previously verified by echocardiography, cardiovascular magnetic resonance, and/or cardiac catheterisation. Patients were classified into diagnostic groups according to the underlying cardiac anatomy. Patients with more than one defect were classified according to the prevalent lesion from a clinical and/or haemodynamic point of view. An additional clinical subgroup of congenital heart disease patients was created according to whether or not the patient had hypoxaemia and patients were classified as hypoxaemic when basal oxygen haemoglobin saturation was $\leq 92\%$. Hyperuricaemia was established as a serum uric acid level >7.0 mg/dl in men and >5.7 mg/dl in women.[4] Serum creatinine, glucose, C-reactive protein, N-terminal-pro-B-type natriuretic peptide, and 24-hour urine uric acid concentrations were also recorded, when available, on the same date. Missing values were $<10\%$ for all variables. All the patients were Caucasian, and the protocol of the study was approved by the hospital's ethics committee. Survival status and time to death were obtained from the National Health Service computer system or after reviewing the medical history of the patients who died at the hospital.

Body weight and height were measured with the patients wearing light clothes and barefoot. Body mass index was determined according to the equation: weight/height^2 in kg/m^2. Blood samples were collected for subsequent laboratory analysis after an overnight fast of at least 10 hours, and during the 24-hour urine collection patients were recommended to have the usual diet and drink fluids, avoiding drinking alcohol or doing exercise strenuously before and during the urine collection. Analytical determinations were obtained for serum uric acid (normal values: 2.6–6.0 mg/dl), total cholesterol (20–220 mg/dl), low-density lipoprotein-cholesterol (0–155 mg/dl), high-density lipoprotein-cholesterol (45–75 mg/dl), triglycerides (30–200 mg/dl), C-reactive protein (0–0.5 mg/dl), N-terminal-pro-B-type natriuretic peptide (0–125 pg/ml), and uric acid in 24-hour urine (250–750 mg/24 hours) concentrations. Serum creatinine, uric acid, lipids, C-reactive protein, and 24-hour proteinuria were measured by spectrophotometry with an Olympus AU 2700 equipment (Olympus Diagnostic, Hamburg, Germany), and N-terminal-pro-B-type natriuretic peptide was measured by immunoassay using the Siemens Stratus CS Acute Care Diagnostic System (Siemens Healthcare Diagnostics Inc., Newark, Deusa, United States of America). The low-density lipoprotein-cholesterol (in mg/dl) was determined with the Friedewald formula (low-density lipoprotein = total cholesterol – [high-density lipoprotein+triglycerides/5]). Pulmonary arterial hypertension was defined as an increase in mean pulmonary arterial pressure greater or equal to 25 mmHg at rest as assessed by right heart catheterisation or echocardiography. Total mortality was defined as death from any cause, including cardiovascular.

Quantitative variables were expressed as mean $\pm$ standard deviation or median and 5th and 95th (5; 95) percentiles. Qualitative variables were expressed as percentages. Possible associations between categorical variables were evaluated using the Pearson χ^2 test or the Student's t-test for continuous data. The non-parametric Mann–Whitney U test was used to compare two independent samples when the assumption of normality or homogeneity of variance was not met. Binary logistic regression multivariate analysis was performed to compare male congenital heart disease patients with serum uric acid concentrations ≤ 7.0 mg/dl and >7.0 mg/dl and female congenital heart disease patients with serum uric acid concentrations ≤ 5.7 mg/dl and >5.7 with those independent variables that had a p-value inferior to 0.05 in the univariate analysis. The results were expressed as odds ratios with their 95% confidence intervals. The log-rank test was used to compare Kaplan–Meier survival curves. Data analysis was carried out using SPSS 20.0 (SPSS, Chicago, Illinios, United States of America).

Results

From a total of 528 congenital heart disease patients followed up in our unit, 329 patients, including 190 male and 139 female patients, fulfilled the inclusion criteria. Overall, there were 39 hypoxaemic

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Table 1. Types of congenital heart diseases and congenital heart disease patients with and without hypoxaemia.

Type of congenital malformations	Non-hypoxaemic	Hypoxaemic	Total	PAH
Ventricular septal defect	45	4	49	5
Tetralogy of Fallot	32	1	33	0
Atrial septal defect	35	2	37	3
Coarctation of the aorta	27	0	28	0
Pulmonary stenosis	29	1	30	1
Atrioventricular septal defect	18	6	24	5
Transposition of the great arteries	18	5	23	1
Aortic stenosis	12	0	12	0
Bicuspid aortic valve	11	0	11	0
Double-outlet right ventricle	4	6	10	1
Univentricular heart	3	5	8	4
Ebstein anomaly	5	1	6	0
Pulmonary atresia	6	0	6	2
Ductus	6	0	6	0
Tricuspid atresia	0	3	3	0
Truncus arteriosus	2	0	2	0
Subaortic membrane	5	0	5	0
Mitral valve prolapse	6	0	6	0
Pulmonary/systemic venous anomaly	4	1	5	1
Other types of cardiopathies	24	2	26	0
Total	292	37	329	23

PAH = Pulmonary arterial hypertension

Patients with atrioventricular septal defect included 13 patients with partial and 11 patients with complete defect. Patients with transposition of the great arteries included 12 patients with dextro-transposition and 11 patients with levo-transposition of the great arteries

congenital heart disease patients, of whom 37 patients had uric acid determination.

Table 1 shows the different types of congenital heart diseases and the number and type of congenital abnormalities that had associated hypoxaemia and pulmonary artery hypertension. The prevalence, according to the NHANES III laboratory definition, of hyperuricaemia was 30 (15.8%) patients among men and 30 (21.6%) patients among women. Table 2 summarises the demographic characteristics, the clinical data, and the laboratory test results of male congenital heart disease patients with serum uric acid levels of 7.0 mg/dl or lower and those with levels exceeding 7.0 mIU/L. Table 3 summarises the demographic and clinical data and laboratory test results of the female congenital heart disease patients with serum uric acid levels of 5.7 mg/dl or lower and those above 5.7 mIU/L. Meanwhile, when compared with non-hypoxaemic congenital heart disease patients hypoxaemic patients had significantly higher serum uric acid levels (6.3 (4.1; 12.1) versus 5.2 (3.4; 7.9) mg/dl, $p < 0.001$) and significantly lower 24-hour urine uric acid concentrations (397.2 (79.0; 759.1) versus 486.6 (209.7; 895.7) mg/24 hours, $p = 0.006$). Similarly, comparing men and women, men had higher serum uric acid levels (5.8 (3.9; 8.4) versus 4.6 (3.2; 8.8) mg/dl, $p < 0.001$) and higher urine 24-hour uric acid concentrations (528.0 (216.8; 1038.6) versus 395.9 (118.7; 733.1) mg/24 hours, $p < 0.001$) than women. Moreover, only one patient with hyperuricaemia reported having gout and being under allopurinol treatment.

In the binary logistic regression multivariate analysis performed to compare serum uric acid concentrations in male congenital heart disease patients with serum uric acid levels ≤ 7 mg/dl or >7 mg/dl, being hypoxaemic (odds ratios, 14.2; 95% confidence intervals, 3.7–55.2; $p < 0{,}001$) and having higher body mass index (1.14 (1.04–1.26); $p = 0.007$), higher serum creatinine (86.6; 3.2–3231.7, $p = 0.008$), and higher low-density lipoprotein-cholesterol (1.02; 1.002–1.04, $p = 0.026$) levels proved to be a risk factor for hyperuricaemia. On the contrary, in the binary logistic regression multivariate analysis performed to compare serum uric acid concentrations in female congenital heart disease patients, age (1.05; 1.002; 1.09, $p = 0.042$) and C-reactive protein concentrations (7.9; 2.3–26.7, $p = 0.001$) proved to be risk factors for hyperuricaemia.

During a median follow-up of 90.8 (4.5; 173.9) months, 16 out of 528 congenital heart disease patients died – 14 patients of cardiac origin and two patients of non-cardiac origin. In all of them, except in one male patient who died of cardiac cause, serum uric acid concentrations were determined. In all, 10 hypoxaemic congenital heart disease patients died in the follow-up, of whom five had pulmonary

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Table 2. Demographic data and laboratory test results from Congenital Heart Disease (CHD) male patients.

	Serum uric acid ≤7.0 mg/dl (160)	Serum uric acid >7.0 mg/dl (30)	p-value
Age (years)	30.8 ± 13.6	35.3 ± 14.2	0.098
Hypoxaemia (patients)	9 (5.6)	10 (33.3)	<0.001
PAH (patients)	9 (5.6)	3 (10)	0.399
Global mortality (patients)	5 (3.1)	3 (10)	0.092
BMI (kg/m^2)	23.8 ± 4.5	26.5 ± 5.8	0.033
Serum uric acid (mg/dl)	5.3 (3.8; 6.9)	8.2 (7.15; 33.3)	<0.001
Serum glucose (mg/dl)	95.9 ± 11.8	93.7 ± 14.1	0.361
Serum creatinine (mg/dl)	1.0 ± 0.2	1.2 ± 0.3	<0.001
Total cholesterol (mg/dl)	158.0 ± 36.6	173.0 ± 38.8	0.046
HDL-cholesterol (mg/dl)	47.5 ± 10.5	44.7 ± 9.4	0.185
LDL-cholesterol (mg/dl)	91.1 ± 31.2	105.1 ± 31.3	0.031
Triglycerides (mg/dl)	95.6 ± 48.4	120.1 ± 62.4	0.018
CRP (mg/dl)	0.11 (0.0; 1.1)	0.25 (0.0; 1.2)	0.010
NT-pro BNP (pg/ml)	34.7 (0.0; 683.8)	77.1 (0.0; 3003.4)	0.074
Uric acid in urine (mg/24 h)	545.4 (201.4; 1044.4)	454.6 (264.6; 1005.4)	0.057

BMI = body mass index; CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NT-pro BNP = N-terminal-pro-B-type natriuretic peptide; PAH = Pulmonary arterial hypertension
Quantitative variables are expressed as mean ± standard deviation or median and 5th and 95th (5; 95) percentiles; qualitative variables are expressed as percentages of total

Table 3. Demographic data and laboratory test results from congenital heart disease female patients.

	Serum uric acid ≤5.7 mg/dl (109)	Serum uric acid >5.7 mg/dl (30)	p-value
Age (years)	28.4 ± 13.3	38.8 ± 16.4	0.001
Hypoxaemia (patients)	10 (9.2)	8 (26.7)	0.020
PAH (patients)	5 (4.6)	6 (20)	0.021
Total mortality (patients)	3 (2.7)*	3 (10)**	0.054
BMI (kg/m^2)	24.4 ± 5.5	29.3 ± 5.7	0.004
Serum uric acid (mg/dl)	4.2 (3.1; 5.7)	6.7 (5.2; 20.4)	<0.001
Serum glucose (mg/dl)	93.1 ± 10.9	94.3 ± 26.8	0.757
Serum creatinine (mg/dl)	0.9 ± 0.1	1.0 ± 0.2	<0.001
Total cholesterol (mg/dl)	168.8 ± 38.7	178.8 ± 45.6	0.231
HDL-cholesterol (mg/dl)	53.2 ± 48.9	49.0 ± 14.2	0.138
LDL-cholesterol (mg/dl)	96.1 ± 31.4	107.6 ± 34.9	0.088
Triglycerides (mg/dl)	93.2 ± 62.8	103.5 ± 41.4	0.398
CRP (mg/dl)	0.15 (0.0; 1.2)	0.8 (0.2; 3.6)	<0.001
NT-pro BNP (pg/ml)	96.2 (0.1; 1157.8)	262.6 (21.9; 7824.1)	0.010
Uric acid in urine (mg/24 hours)	379.7 (118.6; 751.1)	398.1 (81.1; 735.1)	0.680

BMI = body mass index; CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NT-pro BNP = N-terminal-pro-B-type natriuretic peptide; PAH = Pulmonary arterial hypertension
Quantitative variables are expressed as mean ± standard deviation or median and 5th and 95th (5; 95) percentiles; qualitative variables are expressed as percentages of total
*One death of cardiac origin and two deaths of non-cardiac origin
**All deaths were of cardiac origin

arterial hypertension. Overall, the highest mortality was observed between patients with atrioventricular septal defect (three patients) and double-outlet right ventricle (three patients), of whom two and one patient, respectively, had pulmonary arterial hypertension. The mean age from birth to serum uric acid determination was 29.2 ± 14.3 years. The median time to death was 50.2 (2.5; 123.5) months, and median age at death was 31.1 (15.0; 63.6) years. Kaplan–Meier survival analysis showed no significant differences between male congenital heart disease patients with low and high serum uric acid concentrations (≤7.0 and >7.0 mg/dl) (p = 0.633). However, it showed differences between hypoxaemic and non-hypoxaemic male congenital heart disease patients (p = 0.045) and almost significant differences between male patients with and without pulmonary artery hypertension (p = 0.053). No significant differences were seen between female congenital heart disease patients with high and low (≤5.7 and >5.7 mg/dl) serum uric acid concentrations (p = 0.189), between hypoxaemic

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and non-hypoxaemic female patients ($p = 0.768$), and between female patients with and without pulmonary artery hypertension ($p = 0.364$).

Discussion

Previous reports indicate that serum uric acid levels increase with age[1] and that the difference in serum uric acid levels between genders could be in relation to an increased renal urate clearance by oestrogen in women, particularly before menopause.[5] However, the serum uric acid levels have increased in parallel, over the past few decades, in both men and women probably in relation to an increasing burden of obesity, metabolic syndrome, lifestyle factors such as alcohol consumption, medications that increase uric acid concentrations such as aspirin or diuretics, and dietary habits.[1] In fact, incorporating massively fructose in the diet in relation to sugar added to foods or sugar-sweetened drinks[6] seems to favour obesity and hyperuricaemia in relation to a decreased renal clearance of uric acid, an increased rate of purine synthesis de novo, and an accelerated degradation of purine ribonucleotides.[7]

In fact, multiple studies have associated hyperuricaemia with obesity and the metabolic syndrome in adults,[8] adolescents,[9] and children,[10] linking hyperuricaemia among younger adults with the risk of subsequent hypertension, insulin resistance, diabetes, and dyslipidaemia.[11] In our study, the average body weights of the hyperuricaemic patients were greater than those of non-hyperuricaemic patients, which may explain the higher levels of serum triglyceride seen in the hyperuricaemic group. Moreover, those male congenital heart disease patients with high serum uric acid concentrations also had significantly higher total cholesterol and low-density lipoprotein-cholesterol levels than those male congenital heart disease patients with lower serum uric acid concentrations, which may also explain the higher incidence of metabolic syndrome seen in hyperuricaemic patients. However, no significant differences were seen in serum glucose concentrations between male and female congenital heart disease patients with high and low serum uric acid concentrations.

In addition, we found, both men and women, higher serum creatinine levels among the hyperuricaemic patients. Owing to the fact that ~70% of uric acid is excreted from the kidney, abnormal renal haemodynamics, commonly seen in the initial stages of the disease, account for the increased serum urate concentration. However, hyperuricaemia seen in such renal diseases may also play a role in the progression of renal disease inducing renal arteriolopathy and the development of renal failure.[12] On the other hand, hypoxaemia in congenital heart disease patients could be in relation to renal impairment, diuretic treatment, and renal hypoperfusion, which increases renal uric acid reabsorption.[1,13,14]

In relation to C-reactive protein concentrations, increases in C-reactive protein levels are known to be a risk factor not only for cardiovascular diseases, but also for renal dysfunction.[15,16] Moreover, uric acid has been shown to directly stimulate the production of inflammatory mediators, such as C-reactive protein, in vascular cells, which is why it has been suggested that uric acid is an endothelium-injuring factor.[17] Thus, these results imply that uric acid induces endothelial dysfunction and vascular inflammation reaction, which play pivotal roles in the pathogenesis of atherosclerosis.[18]

With regard to morbi-mortality, data in the literature indicate that men with serum uric acid concentration above 6.7 mg/dl have a significantly higher incidence of congestive heart failure and stroke mortality than men with serum uric acid concentration below 4.6 mg/dl.[19] Similarly, women over 50 years of age and a serum uric acid level above 5.4 mg/dl have an increased mortality risk of coronary heart disease, congestive heart failure, and stroke when compared with women under 3.7 mg/dl.[20,21] However, although most studies support the association between serum urate levels and cardiovascular mortality, some authors have reported negative results.[22] In this context, Krishnan et al[23] found no association between hyperuricaemia and cardiovascular mortality when comparing middle-aged patients with and without hyperuricaemia. Similarly, Culleton et al[24] found no significant associations in men and women after adjustment for cardiovascular risk factors and diuretic treatment, raising the question whether hyperuricaemia and cardiovascular disease and cardiovascular death is confounded by other factors in the cardiovascular disease causal pathway.

For this reason, it should be noted that hyperuricaemia itself does not appear to be a risk factor as commonly believed, despite serum uric acid stimulating oxidative stress, endothelial dysfunction, inflammation, and vasoconstriction, but a risk marker signalling the risk for the development of additional clinical complications such as coronary artery disease, renal failure, or hypertension.[24,25] In our series, no significant differences were seen in survival, probably because it was a young population, with little or no associated cardiovascular risk factors and no previous history of cardiovascular events.

Although asymptomatic secondary hyperuricaemia is not an indication for routine therapy, we should look to those patients with hyperuricaemia

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to avoid overweight and obesity and a sedentary lifestyle. This is particularly true in hypoxaemic congenital heart disease patients because their hearts make them more vulnerable to adverse cardiac events, and in patients with coarctation of the aorta because they have a significant prevalence of hypertension by adolescence, sometimes despite surgical or percutaneous correction, leading to a subsequent risk of early morbidity and death.[26]

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Conflicts of Interest

None.

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