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Proteinuria in Congenital Heart Disease: Is It a Real Problem?

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ABSTRACT

The relationship between congenital heart disease and nephropathy has been known for a long time although its mechanism has not been understood thoroughly. Furthermore such studies have been performed in older populations. 74 children aged between two months to 168 months (20 normal as control group, 20 cyanotic and 34 acyanotic patients with congenital heart disease were investigated for their renal function and protein excretion. The data were analyzed using SPSS (version 16.1) independent t- test. Creatinine and glomerular filtration rate in cyanotic was lower than acyanotic group but these were not significant while both protein excretion incidence (65% vs 24%) and quantity (1.2 vs 0.2; measured as urine protein to creatinine ratio) were higher significantly in cyanotic group (P< 0. 001). In cyanotic children with congenital heart disease proteinuria is more common and more severe compared with acyanotic patients; this is not related to age in children as it may occur in the same nephrotic range in infants with cyanotic congenital heart disease.

1. Introduction

There is a clear association between renal function and heart failure which can affect patients' survival.[1] However the exact mechanism through which heart failure affects renal function is a matter of controversy. It may be due to hypoxia occurring in conditions such as cystic fibrosis, chronic obstructive pulmonary disease (COPD),[2] obesity, sickle cell anemia, apnea, polycythemia[3] or in some physiologic conditions such as living in high altitude[4]. Hypoxia with or without heart problems can damage glomeruli and increase permeability which ultimately leads to endothelial

swelling and sclerosis.[5,6] Pulmonary hypertension is another common problem in congenital heart defects can cause a rise in serum creatinine or result in hemodynamic problems which leads to increased mortality and morbidity in these patients especially following surgical procedures or injection of radiocontrasts for imaging.[7] In fact few studies has been done on this subject, in a similar study from Ghaffari et al[8] reported significant proteinuria in a prominent rate of children even before age two; this shows that screening should begin in lower age even in acyanotic patinets with pulmonary hypertension. In this article we aimed to evaluate the risk factors for proteinuria in cyanotic and acyanotic congenital heart disease patients with or without pulmonary hypertension.

2. Materials and Methods

Fifty four children over one month of age with no pre-existing renal disease diagnosed with congenital heart disease with or without cyanosis entered in this study. They had been diagnosed by using angiography and echocardiography. Patients who were taking drugs which could affect on urinary protein excretion and those with structural renal problems were excluded. Their second urine sample in the morning as randomly was evaluated for proteinuria by measuring protein to craetinine concentration in urine which has been measured two weeks after angiography and before they were scheduled for operation. The mentioned values above 2.5 or (protein excretion above 50 mg/kg/daily) if it is associated with hyperlipidemia and low serum albumin could be considered as nephrotic syndrome. Their serum creatinine was measured and calculated normal values as their age by using this formula:

Cr (mg/dL)= 0.18+ age(y) X 0.032.

Their glomerular filtration rate (GFR) was measured by Schwartz formula:

GFR (mL/min/1.73m^2) = K X length (cm)/ Plasma creatinine (mg/dL).

Where K was defined 0.45 for infant up to two years and 0.55 for girls and boys under the age 12. Age, sex, anthropometric characters, mean pulmonary artery and cardiac thoracic ratio were measured from the chest radiograms in addition to other blood results such as hemoglobin and hematocrit, and then these data were collected in special questionnaires. Echocardiography was performed and the type of structural defects and parameters about shunt characters, regurgitation and their gradients were reordered. In angiography pressure and blood gas were measured in main pulmonary artery, right atrium and aorta. The left and right ventricle and their valvular structures were assessed in detail in standard left lateral decubitus position by Vingemed system with 2.5 MHz probe (GE Holten, Norway) in the apical four chambers window. Right atrium diameter (RAD) and left atrium diameter (LAD), were measured at the levels of mitral and tricuspid annulus valve in millimeter (mm) which means the distance from the lateral wall of the right atrium to the interatrial septum and from the lateral wall of the left atrium to the interatrial septum. The pulmonary valve was structurally assessed in parasternal short axis window. Then the mean and peak pressure gradients over the pulmonary valve were obtained by using color wave (CW) Doppler. Pulmonary hypertension was considered as a disorder characterized by progressive elevation of pulmonary artery pressure (PAP) and vascular resistance in the absence of left sided cardiac disease, pulmonary vein compression respiratory disorders or thrombo embolic disease. It was defined by a mean PAP over 25 mmHg at rest or over 30 mmHg in exercise and a pulmonary artery occlusion pressure (PAOP) of less than 15 mmHg. For comparing of the results 20 normal children without existing renal or cardiac disease who hospitalized for elective surgery were selected. Their haemoglobin, hematocrit, anthropometric indices, protein excretion and GFR were measured and evaluated (as Table 1).

2.1. Statistics

The relationship between parametric numerical variables was evaluated by independents t test for parametric data and Man-Whitney U test for non parametric data. Categorical variables were compared by χ 2 test using SPSS software (version 16.1) a less than 0.05 was considered as significant.

3. Results

Thirty four acyanotic and 20 cyanotic patient and 20 normal children as control group entered in the study; (35 female, 19 male), mean serum creatinine and GFR in cyanotic group were 0.44±0.16 mg/dl and 101±47 mL/min/1.73m^2 while in acyanotic group serum creatinine and GFR were 0.45±0.11 and 103±30 (Table 1). There is not any relationship between the presence of cyanosis and creatinine level or GFR. Mean age of (mean±SE) was 38±6.1 months in acyanotic group and 34±9.6 months in cyanotic group. By increasing age there is an increase in GFR which was not different among cyanotic, acyanotic and control groups. Hemoglobin and hematocrit was higher in cyanotic patients compared with acyanotic ones but there was not any relationship between hemoglobin (Hb) or hematocrit (Hct) to renal dysfunction indices as creatinine level increase or GFR decrease or proteinuria severity (quantity). Twenty-one out of 54 patients had significant proteinuria related to their age (table 2). In cyanotic group 13 out of 20 and in cyanotic group 8 out of 34 patients had significant proteinuria. The amount of protein excretion and the incidence of significant proteinuria are related to the presence of cyanosis (Pr/Cr ratio was 1.2 vs. 0.2 and the incidence of significant excretion was 65% vs. 24% in cyanotic and acyatonic patients, respectively). Significant proteinuria occurs more

frequently in cyanotic group compared with acyanotic and control group but there is not a difference between acyanotic and control group (P was insignificant). In patients with significant proteinuria hematocrit level was significantly higher (P=0.01) but hemoglobin was not significantly different (P=0.057) (Table3).

Group (Patient number)	Age(month) Mean±SD Min- Max	Hemoglobin (g/dl) Mean±SD Hematocrit Mean±SD	GFR mL/min1.73m^2 Mean±SD Creatinine (mg/dl) Mean±SD	Urine proteine to creatinine; mean±SD Min -Max
Cyanotic (20)	34±9(mo) 6:2-168	15±3.6 48.3±11 P<0.01	104±50 0.41±0.1mg/dl P insignificant(0.8)	1.2 ± 0.54 0.05 -10 P <0.01
Acyanotic group children (34)	38±6.1(mo) 3-168	12.5±2 36.8±6.5 P<0.01	101±32 0.45 ±0.11 P insignificant	0.2 ± 0.03 0.03 -1 P<0.01
Control (20)	58±41 (mo) 13-103	11.8±1.8 34.5±5.6	116±40 0.5±0.19	0.15 ± 0.01 P insignificant to acyanosis group

Table 2 – Normal value of protein excretion as a function of age (9).

	Proteinuria	
Age (yr)	g/mol creatinine	g/g creatinine
0.1-0.5	80	0.70
0.5-1.0	60	0.55
1-2	45	0.40
2-3	30	0.30
3-5	20	0.20
5-7	19	0.15
7-17	18	0.15

Table 3- Cyanosis, acyanosis incidence, Hemoglobin, Hematocrit, Age, Glomerular filtration rate (GFR) were compared in two groups of significant and non significant proteinuria.

Proteinuria severity (Patients number)	Affected to significant proteinuria Cyanosis condition Ratio -percent	Hemoglobin (mean±SD) Min –Max	Hematocrite mean±SD Min-Max	Age month (mean±SD) Min –Max	GFR (mean±SD) Min –Max
Significant proteinuria (21)	Cyanosis 13/21 (65%) Acyanosis: 8/34(24%)	14.6±3.6 g/dl 10.4-23 p;0.052	45.2 ± 12 32.7- 72 p;0.01	47.8±44 2-168 p;0.97	122.8±44 mL/min/1.73m^2 57-223 p;0.46
Insignificant proteinuria (33)	Cyanosis 7:20(35%) Acyanosis 26:34(76%)	12.8±2.5 10-20	38.5±8.2 24-61	28.7±33.2 2-168	104.2±26.2 52-168

4. Discussion

Glomerular enlargement in congenital cyanotic heart disease was first described in 1953[10] and confirmed by others later.[11] Initially glomerular enlargement was described on the basis of visual inspection but subsequent semiquantitive morphometric studies confirmed the increased glomerular size.[12] Although pathogenesis of glomerulomegaly and FSGS associated with CCHD is still unclear, a large number of reports have described potential mechanisms. Many causative factors, such as elevated hematocrit, hyperviscosity, chronic hypoxia, increased venous pressure and glomerular hyperfiltration, seem to be involved in the glomerulopathy associated with CCHD. Although proteinuria is the major urinary abnormality in patients with CCHD, nephrotic syndrome is an uncommon complication and renal biopsy has been seldom performed.[13] Flanagan et al[14] reported that nephrotic

syndrome with symptomatic edema developed in 5 of 83 patients with CCHD (6%) after the age of 21 years. Nephropathy is a well known complication of congenital heart disease and the risk of developing renal impairment is particularly high in patients with cyanotic congenital heart disease. Although this complication occurs with long duration of disease, tubular injury may occur even in the first decade.[15] Dittrich et al concluded that in cyanotic congenital heart disease serum uric acid and microalbuminuria are correlated with age which occurred in their 6 oldest patient (15 to 28 years).[16] In another study children with persistent congenital cyanotic heart disease have substantial risk of developing a glomerulopathy if the cyanosis remains unchanged for more than ten years. Patients with persistent CCHD have a substantial risk of developing glomerulopathy. Significant proteinuria may occur in as high as 70% of them in patients over 10 years of age.[17] In our study which was performed on children aged below 10 it has been shown that in cyanotic group 65% of patients and in acyanotic group 24% had significant proteinuria which met the nephrotic syndrome criteria in two cases. Their age were lower than our expectation and both of them were infants and cyanotic. In our study there was not any relationship between age and severity of proteinuria as Figure 1 depicts. Proteinuria in cyanotic group will decrease as their age advances like general population but with a lesser steep. Figure 1 shows there is not any relationship between age and proteinura (p; in significant). Polycythemia and its consequence as hyperviscosity in patients with cyanotic nephropathy (CN) occurred more than those without CN.[13,18] Because arterial oxygen transport was higher at normal hematocrit compared with high volumes of packed red cells.[19] Increased hematocrit or polycythemia can cause hypoxemia and renal damage in these patients. In our study hemoglobin and hematocrit in cyanotic patients were significantly higher compared with acyanotic group but there was not a relationship between protein excretion values (quantity) to Hb or Hct levels but the occurrence rate of significant proteinuria (as Table 3) happened more frequently in higher hematocrit (p=0.01). This relationship was not significant for hemoglobin level (p=0.052). Although Fabrizia et al reported the association of pulmonary hypertension and nephrotic syndrome in a case report and referred it to hypoxia and increased glomerular size in a maladaptive compensation mechanism with glomerular pathology described as mesangial proliferative.[20,21] During this phase, with marked, maladaptive right ventricular hypertrophy and variable degrees of interstitial fibrosis, diastolic function may be impaired, altering the right ventricular diastolic pressure-volume relationship and leading to increased pressure in right ventricular end-diastolic and right atrium. With persistent pressure overload, the right ventricle undergoes a remodeling process, eventually leading to right ventricular failure. The right ventricular chamber dilates and the concentric hypertrophy transits to eccentric hypertrophy, resulting in increased wall stress and systolic dysfunction. Increased heart rate and right ventricular wall stress lead to significant increase of oxygen consumption in right ventricular myocardium. This, in combination with reduced right ventricular endomyocardial coronary perfusion (due to reduced right coronary artery pressure, increased right ventricular mass, and rising right ventricular end diastolic pressure), leads to right ventricular ischemia, and worsening right ventricular diastolic and systolic function. The right ventricular ischemia may be clinically manifested as chest pain. Subsequently the right ventricle and the tricuspid valve annulus dilate and functional tricuspid regurgitation will occur.[22-24] Most patients in this study affected to pulmonary hypertension although the mean of pulmonary pressure was significantly higher in cyanotic patients compared with acyanotic patients (69±22 vs 39±13 mmHg) but GFR levels does not have any relationship to cyanosis (104.7 ± 50 vs 101.5 ± 32.5), in other word although pulmonary hypertension and hypoxia besides high hematocrit, are more severe in cyanotic groups but these will not guarantee to decrease GFR in childhood period.

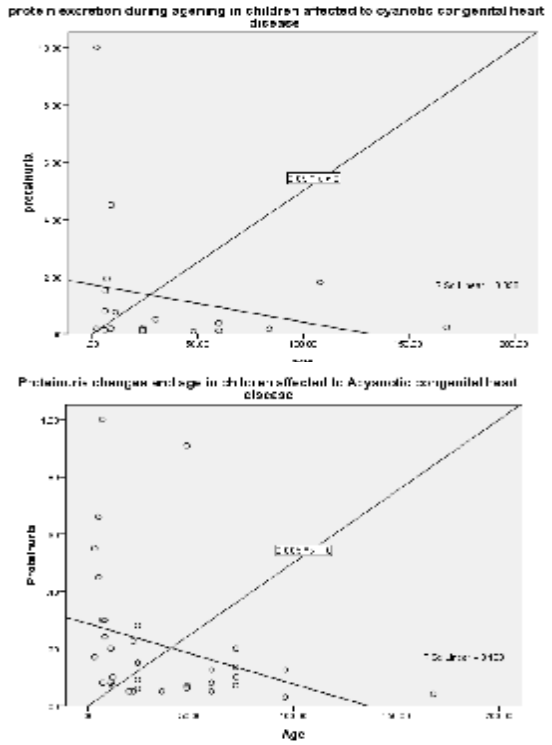

Fig 1 a, b - (above: Cyanotic group, below: Acyanotic group):
Fig 1 a - Age (month) and proteinuria (urine protein /creatinine randomly) showed there is not any relation between ageing and proteinura (p: insignificant)
Fig 1 b - proteinura decreases with age more steeply in acyanotic patients.

5. Conclusion

In children with acyanotic or cyanotic pulmonary hypertension proteinuria is a common problem and quantity of protein excretion is significantly higher in cyanotic patients. This is not related to age, hemoglobin or hematocrit levels. On the other side, in patients with significant proteinuria including those with or without cyanosis Hct level was significantly higher. Age was not different between the two groups of significant or insignificant proteinuria. GFR level was higher in those with more protein excretion which may indicate hyperfiltration. In summary although cyanosis leads to higher and significant incidence of proteinuria and their Hb and Hct were significantly higher, other contributory factors should be considered for progression and development of this ominous process.

Ethical issues

The study was approved by the Ethical Committee of the University.

Conflict of interests

No conflict of interest to be declared.

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