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ORIGINAL ARTICLE

Renal Dysfunction in Children with Congenital Cyanotic Heart Disease

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ABSTRACT

Background: Cyanotic nephropathy (CN), was found in about 30%-50% of patients with congenital cyanotic heart disease (CCHD), causing significant proteinuria, decreasing the glomerular filtration rate (GFR) and azotemia. This study aimed to show the frequency of CN in children with CCHD and the associated risk factors.

Methods: A cross sectional study was conducted in cardiology unit, pediatric department, Zagazig University Hospitals from March 2018 to June 2019. This study included 49 children of age ranged from 2 months to 11 years selected randomly from those admitted to the pediatric cardiology unit and diagnosed as having CCHD. They were subjected to full history taking, general examination and local examination of the heart, chest X-ray and echocardiography. Early morning urine and blood sample were taken for measuring urine albumin, protein, creatinine, urinary protein to creatinine ratio [UPCR], urinary albumin to creatinine ratio, serum creatinine level, complete blood count (CBC), prothrombin time (PT), partial thromboplastin time (PTT), and serum ferritin**.**

Results: 65% of CCHD patients had renal impairment as regard to albuminuria also, 83.6% of them had CN depending on proteinuria. 37% of CCHD patients with significant albuminuria had renal insufficiency. Patients with CN had higher hematocrit (Hct)level, lower platelet count and longer time waiting for surgery.

Conclusions: Children with CCHD are in high risk of renal insufficiency. Microalbuminuria, proteinuria, increased Hct level, decreased platelet count, longer time waiting for surgery, are risk factors of renal disease.

Keywords: Nephropathy; microalbuminuria, cyanotic congenital heart disease, children ..

INTRODUCTION

Cyanotic nephropathy (CN) means renal injury in children suffering from cyanotic congenital heart disease (CCHD) [1]. Children with CCHD have risk factors for development of renal disorders and chronic kidney disease later in life, as pathophysiological changes related to abnormality in heart anatomy and circulation [2]. CN was found in about 30%-50% of patients with CCHD [3]. CN disturbs tubular activity in children during the first decade of life [4]. Also affects glomerular function in the second decade of life, causing proteinuria, nephrotic syndrome, reduced glomerular filtration rate (GFR), and azotemia [5]. Microalbuminuria is a good predictor of progressive kidney disease [6]. When microalbuminuria progresses to nephropathy, structural changes including damage or even failure to the podocyte occur in the glomerular barrier. To estimate microalbuminuria, urine samples in the early morning should be taken, and that is better than 24-h urine collection [7].This study aimed to show the frequency of renal dysfunction in children with CCHD and the associated risk factors.

METHODS

A cross sectional study was conducted in cardiology unit, pediatric department, Zagazig University Hospitals from March 2018 to June 2019. This study included 49 children (25 males and 24 females) of age ranged from 2 months to 11 years from those admitted to the pediatric cardiology unit, and well diagnosed as having CCHD. Inclusion criteria: Patients were enrolled in during the study period if their age around from 2 months to 11 years and suffering from CCHD with or without palliative surgery .

Exclusion criteria: Patients were excluded if they were out of the age group ,refused to give the full information needed , were taking drugs, such as

NSAIDs, aminoglycosides, sulfonamide, amphotericin B, penicillin and cephalosporin, that could impair renal function ,and patients of compromised urinary tract or patients with congenital renal disease. All patients subjected to chest X-ray to detect cardiac anomaly and echocardiography to confirm the diagnosis of CCHD. Urine samples were collected from these patients early in the morning by nurses using urine collection bags in non-toilet-trained children or using wide neck sterile container in older children following all infection control precautions such as, hospital environmental hygiene principles, asepsis principles, principles of hand hygiene, and use of personal protective equipment. All specimen containers were transported to Zagazig University Lab in a self-sealing polythene bag with 2 compartments for the laboratory request form and the specimen. Urine sample was taken for measuring urine albumin, protein and creatinine for diagnosis of significant microalbuminuria (urinary albumin to creatinine ratio 30– 300mg/g) ,overt proteinuria (urinary albumin to creatinine ratio [UPCR] > 300 mg/g) , significant proteinuria (UPCR >0.20mg/mg) while nephrotic-range proteinuria (UPCR >2 mg/mg) **[8]**.

3 cm^3 venous blood sample were taken from each case. Serum creatinine for diagnosis of renal disorder. Estimated Chronic Kidney Disease in Children (CKiD) bedside equation [GFR ($mL/min/1.73m^2$) = 0.413 height (cm)/creatinine serum (mg / dL) < 90 mL / min/1.73 m^2] **[8]**.

CBC, PT, PTT, and serum ferritin level to identify factors associated with CN.

STATISTICAL ANALYSIS

Data was collected, coded, updated, and entered into version 20 of the Statistical Package for Social Science (IBM SPSS). For the qualitative, data presented as number and percentage and for quantitative data with parametric distribution and interquartile range (IQR) median for quantitative data with non-parametric distribution, data were presented as numbers and percentages. The Chi-square test was used to compare two groups of qualitative data, and the exact Fisher test was used instead of the Chi-square test when the predicted count in any cell was found to be less than five.

In the comparison between two groups with quantitative data and parametric distribution, independent t-test was used, and Mann-Whitney test was used in the comparison between two groups with quantitative data and non-parametric distributions. The confidence interval was set at 95 percent and the agreed margin of error was set at 5 percent. The p-value was therefore assumed to be the following:

P > 0.05: significant, P < 0.05: important, P < 0.01: highly significant.

Ethical Clearance: Written Informed consent for inclusion in the study was received from the patient's parents. Approval for the research was received from the departments of pediatrics, Zagazig University Hospitals, following approval by the Institutional Review Board (IRB). The research was carried out for studies involving humans in compliance with the code of ethics of the World Medical Association (Decleration of Helsinki).

RESULTS

This cross sectional study included 49 patient, 49% of them were females and 51% males . **(Figure 1)**.

Echocardiography of the studied cases showed that , 53.1% of cases had Fallot tetralogy , transposition of the great arteries(TGA) represented a percent of 24.5%, pulmonary atresia+ atrial septal defect (ASD) represented 4.1% of cases, pulmonary atresia+ ventriclar septal defect (VSD) represented 10.2% of cases, Pulmonary atresia alone represented 2% of cases tricuspid atresia represented 6.1% of cases.**(Figure 2)**.

51% of the studied cases had palliative operations such as shunting operations, while 24.5% of them had total correction of the heart anomaly and the rest had no operation. .**(Figure 3)**.

Significant albuminuria was found in 65.0% of cases with UPCR (30– 300mg/g). **(Table 1**)

83.6% of patients had significant proteinuria with UPCR (>0.20mg/mg) and 4.1% of the studied cases had nephrotic syndrome with UPCR >2 mg/mg. **(Table 2**).

There is high significant difference between CCHD with significant albuminuria and CCHD without significant albuminuria as regard serum creatinine , protein creatinine ratio and GFR ,but there is no significant relation between significant albuminuria and PT, PTTor serum ferritin. **(Table 3**).long waiting time for surgery, high Hct level and low platelet count increase the risk for significant albuminuria and can properly predict significant albuminuria. **(Table 4**).

Table (1): Micro albuminuria findings of the studied cases

Variable	N	%
Significant albuminuria	27	65.0
No albuminuria	22	45.0

Table (2): Proteinuria findings of the studied cases

Variable	N	%
No proteinuria	6	12.3
Significant proteinuria	41	83.6
Nephrotic syndrome	2	4.1

Table (3): Relation between laboratory data and albuminuria:

Variable	CCHD with significant Albuminuria	CCHD without Albuminuria	T test	P value
Serum creatinine(mg/dl):				
Mean ± SD	**0.46±0.12**	**0.31±0.1**	**4.77**	**<0.001**
Range	**0.31-0.62**	**0.24-0.34**		**(HS)**
GFR(ml/min/1.73m^2) :				
Mean ± SD	**82.8±19.2**	**93.4±13.1**	**2.29**	**0.02**
Range	**39-108.9**	**72.1-119.9**		**(S)**
Protein creatinine ratio(mg/mg):				
Mean ± SD	**0.4±0.11**	**0.12±0.03**	**12.68**	**<0.001**
Range	**0.13-0.7**	**0.1-0.4**		**(HS)**
PT(sec):				
Mean ± SD	**0.47±0.13**	**0.45±0.11**	**0.573**	**0.569**
Range	**0.31-0.62**	**0.29-0.60**		
PTT(sec):				
Mean ± SD	**28.8±7.19**	**29.9±7.09**	**0.535**	**0.594**
Range	**20-46**	**19-45**		
Serum ferritin(ng/ml):				
Median ± SD	**120.16±101.7**	**121.03±101.8**	**MW**	**0.891**
Range	**21-478**	**20-469**	**12.3**	

CCHD (Cyanotic congenital heart disease) -GFR (glomerular filtration rate) -PT (Prothrombin Time)
PTT (Partial Thromboplastin time)

Table (4): Logistic regression for significant albuminuria and other variables:

Variable	Wald test	SE	Exp(B) Odds ratio	95%CI	P value
Waiting time for surgery:					
	0.454	**0.03**	**2.1**	**1.3-4.1**	**0.023 (S)**
Hematocrit level > 40%:					
	0.705	**0.08**	**3.069**	**2.5-5.7**	**0.011 (S)**
Platelet count <290,000 /mm3:					
	0.607	**0.08**	**2.4**	**2.1-4.3**	**0.034 (S)**

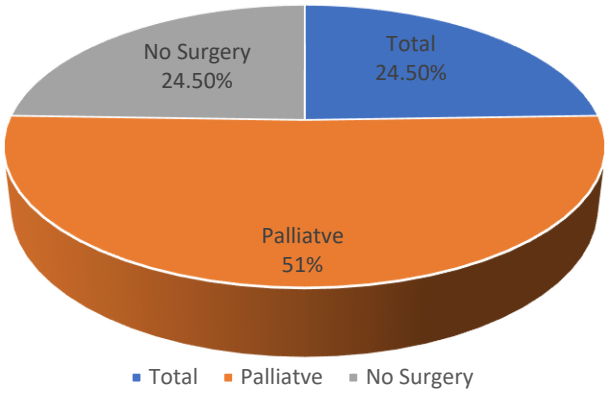

Figure 1: Sex of the studied cases**.**

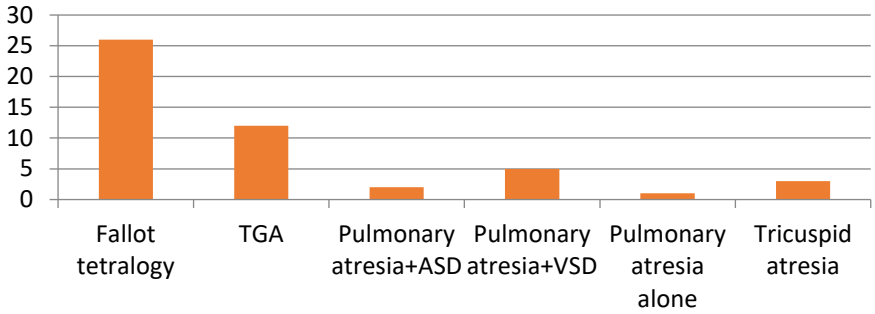

Figure 2: Echocardiographic findings of the studied cases

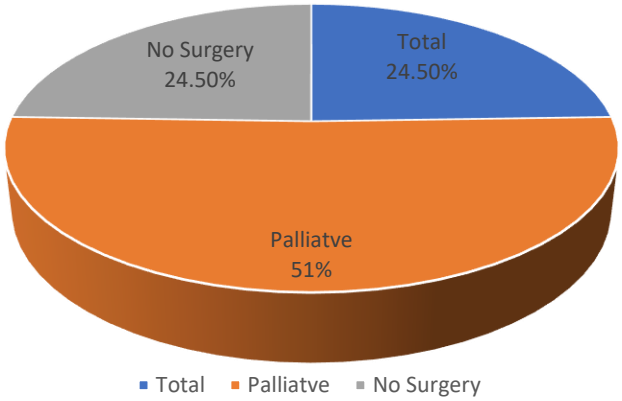

Figure 3: operations of the studied case**.**

DISCUSSION

Children with congenital heart disease have high risk factors for potential development of nephropathy and chronic kidney disease later in life, as pathophysiological changes related to abnormal heart and circulation**[2]**. These include cyanosis, chronic hypoxia, changes in renal blood flow, derangements in neurohormonal activation and intraglomerular hemodynamics **[9].**

Renal impairment progresses with age, and cyanotic nephropathy is a common complication in adults**[9]**. The incidence of GFR reduction has been reported to be35-fold higher in adults with CCHD than in other population **[10].**

With microalbuminuria , glomeruler damage and loss of the podocyte may occure**[11].** To prevent or treat CN, early diagnosis of high-risk patients is required but, several days are required to confirm a diagnosis of CN using GFR but significant microalbuminuria provides earlier recognition of cyanotic nephropathy **[2].** It appeared from this research that microalbuminuria (glomerulopathy)

can be expressed as early as the first decade of life, and the youngest case of CCHD with microalbuminuria was only 2 months old and there was no significant difference between patients with or without albuminuria as regard to sex. This agreed with Hongsawong et al., **[2]** who aimed to determine the prevalence and associated factors of significant albuminuria in CCHD patients. A cross-sectional study was conducted. A total of 116 patients aged 1 month to 15 years with CCHD at Chiang Mai University Hospital between 2015 and 2016 were assessed and 94 patients were enrolled (54 boys and 40 girls) with no significant difference between them as regard to sex.

CN incidence in children was 65% or 83.6% depe nding on albuminuria or proteinuria, respec tively. This was in agreement with the results of Hongsawong et al., **[2]** who found that the prevalence of CN in children with CCHD was 92.55 percent according to the proteinuria staging with or without GFR decreased. Nevertheless, the prevalence of CN in these patients was 58.51 percent depending on the staging of albuminuria with or without impairment GFR.

This study showed that as regards serum creatinine and GFR, there was a significant difference between CCHD with significant albuminuria and CCHD without significant albuminuria. This was in line with the findings of Hongsawong et al. **[2]** who found that the incidence of decreased renal function in patients with severe albuminuria was more than patients with no significant albuminuria. This study found that 37% of CCHD patients with significant albuminuria had renal insufficiency with GFR lower than 90 mL/min/1.73 m2.

This agreed with Hongsawong et al. **[2]** who found that one third of the patients with significant albuminuria had renal insufficiency In this study Hct was higher in CCHD patients with significant albuminuria.This was in line with Agras et al. **[12]**, who enrolled 20 children with a CCHD, 23 children with CCHD and 13 healthy children. Blood and early morning urine samples from each subject were obtained to measure sodium, microalbumin, creatinine, ß2-microglobulin, and N-acetyl-ß-D-glucosaminidase (NAG) urinary concentrations, assuming that hematocrit values and severity and duration of hypoxia were important factors in the development of renal impairment in CHD patients. In this study the group of pediatric CCHD patients with significant albuminuria had a lower platelet count than the other group. This was in line with Lill et al. [13] who found that platelet count decreased with albuminuria.In line with Hongsawong et al. [2] this study found that waiting time for surgery showed significant correlation with significant albuminuria while early cardiac surgery decreased the risk of developing significant albuminuria. This study showed that there was no significant relationship between significant albuminuria and PT, PTT. This is consistent with Hongsawong et al., [2] who also found no significant difference in PT, PTT. This study showed that, there was no significant relation between significant albuminuria and serum ferritin level, this agreed with Hongsawong et al., **[2].**

Study limitation: The sample size was small as the total number of patients who fulfill the inclusion criteria in this short duration were limited.

CONCLUSIONS

According to the findings of our analysis we concluded that CN may occur in 65% or 83.6% of patients with CCHD depending on albuminuria staging or proteinuria staging respectively. Microalbuminuria decreased platelet count, proteinuria, long time waiting for cardiac surgery and increased hematocrit level are considered risk factors of CN.

Recommendations: From the study, we recommend that all pediatric patients with CCHD should have routine monitoring of microalbuminuria and regular calculations of GFR. Early total corrective or palliative operation decreases the risk of developing CN. Also, pediatric cardiologists, nephrologists, and intensivists must work with each other for earlier diagnosis of cyanotic nephropathy.

Declaration of interest

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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