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Original Research Article

Microalbuminuria among children with congenital heart disease seen in Sokoto, North-Western Nigeria

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ABSTRACT

Background: Congenital heart disease (CHD) especially cyanotic CHD has been associated with microalbuminuria which is an early marker of glomerular nephropathy but this has hardly been studied in African children. The aim of this study was to compare mean microalbuminuria levels and associations among children with acyanotic CHD, cyanotic CHD and normal controls.
Methods: Forty-one (41) children comprising 19 acyanotic CHD, 14 cyanotic CHD and 8 without CHD aged 1 to 15 years were recruited in a cross-sectional study. Quantitative urinary microalbuminuria was measured by ELISA technique. Positive result was microalbuminuria of 30-300 mcg/mgCr. Mean levels were compared by student t-test and analysis of variance (ANOVA). Statistical significance was taken at $p<0.05$.
Results: There were 22 (53.7%) females and 19 (46.3%) males. Mean level of microalbuminuria was highest in those with cyanotic CHD at 147.7±78.8 mcg/mgCr, followed by those with acyanotic CHD at 111.8±61.5 mcg/mgCr and lowest in those without CHD at 67.3±31.6 mcg/mgCr. There was significant difference between the groups with CHD and those without CHD ($F=4.1$, $p=0.03$) and microalbuminuria had a significant but weak negative correlation with oxygen saturation implying that microalbuminuria increased with worsening cyanosis.
Conclusions: Microalbuminuria was high among the patients with CHD, though higher in cyanotic patients warranting closer follow up of these patients.

Keywords: Microalbuminuria, CHD, Acyanotic, Cyanotic, Controls

INTRODUCTION

Congenital heart diseases (CHD) are gross structural abnormalities of the heart or intrathoracic great vessels which are actually or potentially of functional significance.[1] They are the most common congenital defects accounting for about a third of major anomalies at birth. Thus they are a significant cause of mortality and also lifelong morbidity in those affected.[2] This is especially important since interventional cardiac care is increasingly available and accessible, more affected young children increasingly survive infancy.[3] They are thus exposed to more complications which may occur inherently from the disease process, from medications or from the interventions carried out.[4] These complications affect different systems as congenital heart disease is being viewed as a multi-systemic disease.[5] Complications could be cardiac and non-cardiac. Cardiac problems include congestive heart failure, infective endocarditis, and arrhythmias. Others are pulmonary hypertension, neurological and nephropathy.

Nephropathy has been shown to complicate CHD especially cyanotic CHD in several studies both in children and adults.[4,6-10] In acyanotic CHD, the structurally abnormal heart and circulation leads to effects such as cardiac volume overload, changes in intraglomerular hemodynamics, derangements in neurohormonal

activation and impairment in the autonomic nervous system.[11] This eventually leads to glomerulosclerosis with increased mesangial cellularity. In cyanotic congenital heart disease, in addition to the foregoing, chronic hypoxia stimulates erythropoiesis through the stimulation of erythropoeitin, leading to an increased blood viscosity. Hyperviscosity affects renal hemodynamics, causing increased glomerular arteriolar resistance and pressure leading to hyperfiltration and proteinuria.[11]

Microalbuminuria is a much earlier marker of renal damage before proteinuria becomes apparent and is a predictor of future cardiovascular disease even in apparently normal individuals.[12] Both markers of renal status have not been reported in children with CHD in Nigeria despite supportive evidence these patients should be followed from an early age for the development of CKD.[11] This study was carried out amongst children diagnosed with CHD in UDUTH, Sokoto to determine mean levels of microalbuminuria in the different types of CHD and associated factors. The aim of this study was to compare mean levels and associations of microalbuminuria among children with acyanotic CHD, cyanotic CHD and normal controls seen at Usmanu Danfodiyo University Teaching Hospital, Sokoto.

METHODS

Study location

The study was conducted at the paediatric cardiology unit of the Paediatrics Department of Usmanu Danfodiyo University Teaching Hospital, Sokoto. The hospital is a major referral center for paediatric cardiac cases in the North-Western region of Nigeria and the neighbouring Niger and Benin Republics. The hospital also has other major specialities and sub-specialities.

Study design

It was a descriptive cross-sectional study. It was conducted between 1st July 2017 and 31st August 2018.

Study subjects

Subjects comprised children with echocardiographic diagnosis of CHD being seen and followed up in the paediatric cardiac clinic.

Inclusion criteria

Children less than 15 years of age with echocardiographic diagnosis of CHD whose caregivers had given informed written consent.

Exclusion criteria

Those who had corrective surgery, those with febrile illnesses within 2 weeks prior to and at the time of the study, symptoms of urinary tract infection such as dysuria, frequency, urethral discharge, use of antibiotics and non-steroidal analgesics (NSAIDS) 2 weeks prior to the study, menstruating females, any other comorbidity known to affect renal function e.g. sickle cell disease, elevated blood pressure, those subjects who had taken drugs known to affect protein excretion such as radio-opaque dye and nitrofurantoin within the previous 4 weeks.

Sample size determination

The minimum sample size was determined with the formula.[13]

$$n = (Z^{2\alpha})/d^2$$

α=standard deviation of variable from a previous study=11.7 mcg/mgCr with a precision margin of 5 mcg/mgCr) =22 subjects[15]

A total of 55 subjects were enrolled comprising 22 subjects with acyanotic CHD, 22 with cyanotic CHD and 11 subjects without CHD were enrolled consecutively as they present to the clinic for follow up till the desired sample size was attained. The controls were recruited from the follow up clinics which run simultaneously in the same department but in a different section.

Instruments of data collection

Their demographic characteristics were entered into a structured questionnaire. Other data including type of CHD, year of diagnosis, weight, height, and oxygen saturation were documented. The laboratory results as obtained were entered.

Materials/equipment of data collection

Sterile universal bottles, cool box for collecting urine sample bottles, urinalysis strips, capillary tubes, microalbumin reagent, microplate reader, microhaematocrit reader, ethylene diamine tetra-acetic acid (EDTA) bottles, 2 ml and 5 ml syringes, disposable gloves, table top electronic weighing scale/Wunder beam balance table top weighing scale, Wunder beam balance floor top weighing scale, pulse oximeter.

Subject handling procedure

At presentation to the clinic, all the caregivers were initially given a general health talk about their children's condition, and the risk of life long morbidities including renal dysfunction for which they need proper monitoring. As the child was being reviewed, the required routine examination for clinic follow up including weight, height, and cardiovascular examination including pulse oxygen saturation will be done. After the child has been attended to, the caregivers were given more information and consent for the study sought for. Those who consented (plus assent for children above 7 years) were given a sterile universal bottle which was properly labelled. For infants

and children below 5 years, their caregivers were instructed on how to carefully collect about 10 ml of their random urine (clean catch specimen) into the bottle. The older children were given an explanation on how to collect a mid-stream urine specimen in the presence of their caregivers who supervised them.

Laboratory procedures

Proteinuria

Testing for proteinuria was done semi quantitatively by urine dipstick analysis by using Combi-10 strips by Macherey-Nagel Plc. The reagent strips was dipped in the urine specimens, and completely immersed for 2-3 seconds.

The test pad colour for protein was compared visually with colour chart on the bottle containing the strips after 30 seconds for all the urine samples. Those that tested positive were further excluded from microalbuminuria test.

Microalbuminuria

Microalbuminuria was measured quantitatively in the urine by immunoturbidometry using an ELISA technique. The albumin concentration in the urine sample is proportional to the turbidity and this was analysed by a micro plate reader. Results of microalbuminuria were reported positive if spot urine microalbumin/urine creatinine was >30 milligram/milligram creatinine while >300 milligram/milligram creatinine was macroalbuminuria.[12]

Packed cell volume

Packed cell volume was determined done using the microhematocrit method on a blood sample taken in a capillary tube. This was centrifuged at 10,000 rpm for 5 minutes and the result read by a microhaematocrit reader.

Data analysis

Data was analyzed using statistical package for social science (SPSS) statistical software (version 22.0). Chi square test was used to determine associations between categorical variables and Fischer's exact test was used when an expected cell value is less than 5.

Student t-test was used to assess the mean differences, and if more than 2 groups, analysis of variance (ANOVA) was used. The level of statistical significance was set at p value <0.05.

Ethical considerations

Ethical approval for the study was obtained from the ethics committee of Usmanu Danfodiyo University Teaching Hospital Sokoto. Ethical approval number: UDUTH/HREC/2017/No 613.

RESULTS

Out of the 22 subjects with acyanotic CHD enrolled, 3 had abnormal urinalysis and were excluded from further tests likewise, 8 of those with cyanotic CHD and 3 of the normal subjects without CHD. Forty-one (41) children comprising 19 acyanotic CHD, 14 cyanotic CHD and 8 controls without CHD aged 1 to 15 years were tested and analyzed.

Demographic characteristics

There were 22 (53.7%) females and 19 (46.3%) males. Mean age 41.6 (25.1) months, with a range of 1 month to 156 months. Median age at diagnosis of CHD was 14 months. 78.8% were aged below the age of 5 years. The age and sex distributions of those with CHD were similar (X^2=0.4, P=0.67) (Table 1).

Table 1: Showing age and gender distribution of the subjects.

Distribution	ACHD n (%)	CCHD n (%)	No CHD n (%)	Total
Age (years)				
<5	14 (73.7)	12 (85.7)	5 (62.5)	31 (100)
>5	5 (26.3)	2 (14.3)	3 (37.5)	10 (100)
Gender				
Male	6 (31.6)	8 (57.1)	5 (62.5)	19 (100)
Female	13 (68.4)	6 (42.9)	3 (37.5)	22 (100)

Echocardiographic diagnosis of the study subjects

The commonest CHD were VSD and TOF accounting for 30.3% and 24.2% respectively (Table 2).

Mean microalbuminuria levels

Mean level of microalbuminuria was highest in those with cyanotic CHD at 147.7±78.8 mcg/mg Cr, followed by those with acyanotic CHD at 111.8±61.5 mcg/mgCr and lowest in those without CHD at 67.3±31.6 mcg/mgCr as shown in Figure 1.

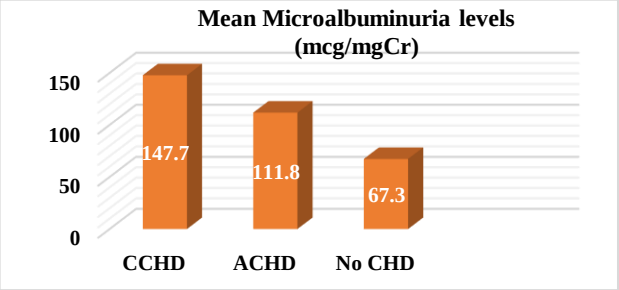

Figure 1: Mean levels of microalbuminuria among study subjects.

Table 2: Echocardiographic diagnosis of the study subjects.

Type of CHD	Frequency
ACHD	
VSD	10 (30.3)
ASD	4 (12.1)
VSD/ASD	2 (6.1)
PDA	1 (3.1)
AVC	1 (3.1)
DORV	1 (3.1)
CCHD	
TOF	8 (24.2)
DORV/PS	4 (12.1)
TGA	1 (3.1)
TA	1 (3.1)

VSD = Ventricular septal defect; ASD = Atrial septal defect; PDA = Patent ductus arteriosus; AVC = Atrioventricular canal defect; DORV = Double outlet right ventricle; TOF = Tetralogy of Fallot; PS = Pulmonary stenosis; TGA = Transposition of great arteries; TA = Truncus arteriosus

There was no significant difference of level of microalbuminuria between the groups with cyanotic and acyanotic CHD (t=1.47; p=0.15), however, there was a significant difference between the groups with CCHD, ACHD and those without CHD (F=4.1, p=0.03) as shown in Table 3.

Proportion of study subjects positive for microalbuminuria

All 14 subjects with CCHD (100%) had microalbuminuria with levels between 30-300 mcg/mgCr, while 17 (89.5%) subjects with ACHD and 6 (75%) of normal subjects) were positive for microalbuminuria (30 – 300 mcg/mgCr). Only one subject with large septal defects had macroalbuminuria>300mcg/mgCr.

Correlation of microalbuminuria with other parameters

The correlation of microalbuminuria with age, height, weight and oxygen saturation was assessed with Pearson's correlation. All showed negative correlation which ranged from weak to moderate. Only oxygen saturation had a weak negative correlation with microalbuminuria that was statistically significant (r=-0.33, p=0.04) implying that microalbuminuria increased with worsening cyanosis. The correlation coefficients are shown in Table 4.

Table 3: Comparison of the mean levels of microalbuminuria among the study subjects.

	ACHD (n=19)	CCHD (n=14)	No CHD (n=8)	Test of significance	P value
Microal-buminuria level	111.8±61.5	147.7±78.8	67.3±31.6	F=4.07	0.03
	111.8±61.5	147.7±78.8	-	t = -1.5	0.51

Table 4: Showing correlation of microalbuminuria with other parameters in those with CHD.

Parameters	Pearson correlation coefficient	P value
Age	-0.15	0.40
Weight	-0.5	0.07
Height	-0.34	0.23
Packed cell volume	+0.51	0.05
Oxygen saturation	-0.33	0.04

DISCUSSION

This study found that subjects with cyanotic CHD had the highest levels of microalbuminuria followed by those with acyanotic CHD while the normal subjects had much lower mean values. This is similar to what was reported by Roginska amongst hospitalized children with CHD where those with CCHD had the highest levels among the 3 groups.[4] CCHD through chronic hypoxia affects renal tubular and mesangial cells by impairing differentiation of fibroblasts and inducing cellular proliferation which eventually affects both tubular and glomerular function, resulting in proteinuria.[6,14]

Mean levels of microalbuminuria of 111.8 mcg/mgCr among those with ACHD in this study was similar to the values obtained in a study in India which reported mean levels of 106.6 mcg/mgCr.[15] Likewise, mean levels among the normal study participants of 67.3±31.6 mcg/mgCr was similar to 62.7+7.6 mcg/mgCr reported in the same study even though the subjects age range was lower in this study probably supporting higher racial predisposition to microalbuminuria among the subjects in this study.[16]

The proportion of subjects with microalbuminuria in this study was high (100% in CCHD, 84.2% in ACHD) compared to a similar study comparing 3 groups of subjects by Agras in Turkey where 17.3% of CCHD and 10% of ACHD had microalbuminuria while none of the normal subjects had microalbuminuria.[3] Similarly, the study from Poland showed subjects with CCHD had higher levels of microalbuminuria of 45.7%, while only 16.4% of those with ACHD were positive.[14] Cyanotic nephropathy (CN) which is a sequelae of prolonged cyanosis has also been reported in nearly 30–50% of CCHD patients.[4]

The overall high prevalence of microalbuminuria among the subjects and controls in this study compared to other reports may be due to the genetic predisposition of

Africans to higher rates of microalbuminuria though this is more in adolescent children than the younger age group.[16,17] Microalbuminuria which is a marker of glomerular dysfunction was less common in younger children with CHD than markers of tubular dysfunction in other studies.[8,18]

Cyanotic CHD patients had more prevalence and higher abnormal biochemical markers for renal dysfunction than those of acyanotic CHD in another study though there was no difference in mean levels of microalbuminuria as seen in this study between the two groups.[18] However, markers of tubular dysfunction were not assessed in this study.

In this study, a weak negative correlation which was significant was observed between oxygen saturation and microalbuminuria while in a cohort studied by Hongswang in Thailand among 94 patients, duration of diagnosis, PCV >40% and high platelet were predictive of microalbuminuria.[19] The observation of significant correlation with low oxygen saturation in this study further corroborates the association with CCHD of which hypoxemia is a major manifestation and this may also be supported by association with other markers of bone marrow response to hypoxemia in form of polycythemia and thrombocytosis seen in the similar reports.[8]

Therefore, with the high rate of microalbuminuria seen in this study, patients with CHD in our environment who do not have the benefit of early corrective intervention should be followed up carefully in terms of markers of early renal damage so that this may not constitute an additional morbidity to them.[20,21]

Limitations of the study include relatively small sample size, lack of direct supervision of collection of urine samples and non-exclusion of those on angiotensin converting enzyme (ACE) inhibitors which may also contribute to proteinuria.

CONCLUSION

In conclusion, microalbuminuria was high among subjects with CHD, though higher in cyanotic patients warranting closer follow up of these patients and efforts geared towards early surgical interventions in all the patients.

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