



Original article

Myocardial Dysfunction in Children with Nephrotic Syndrome: A Tissue Doppler Study

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ABSTRACT

Background: The prevalence of chronic kidney disease (CKD) has increased steadily. Mortality and morbidity are seen more frequently in CKD compared to in healthy subjects. Cardiovascular events are the most frequent cause of mortality and morbidity in this patient group. Objectives: To assess the presence of fQRS in children with NS and to evaluate the relationship between fQRS and myocardial functions. **Methods:** 30 children with nephrotic syndrome and 30 apparently healthy children were enrolled in this study All patients in this study were subjected to: Full history taking and Full clinical examination, Laboratory investigations: (BUN), creatinine, albumin, Calcium, phosphorus, (LDL), (HDL), triglycerides and 24h urine collection for protein in urine, ECG and Echocardiography was performed to detect early pathological problems. and Tissue doppler imaging was used to detect changes occur in the heart with nephrotic Syndrome. Patient group was subdivided in to 2 groups according to presence of FQRS in ECG. **Results:** fQRS was present in 56.7% of patient group. There was significant increase in systolic and diastolic blood pressure in patient with FQRS in ECG. There were no statistically significant differences between tissue doppler parameter and Tie index with fQRS except for Em wave. By univariant analysis for patient with fQRS and all parameter, fQRS was presented with increase in systolic and diastolic blood pressure, and in patient with systolic dysfunction (decrease FS%), and in patient with diastolic dysfunction (E`). **Conclusions:** NS children generally have a high risk of cardiovascular complications. The present study revealed that fQRS, determined using ECG, an economic and easily accessible technique, can be used as an early marker of myocardial function impairment in this patient group.

Keywords: Myocardial dysfunction, A tissue doppler study.

INTRODUCTION

The prevalence of chronic kidney disease (CKD) has increased steadily. Mortality and morbidity are seen more frequently in CKD compared to in healthy subjects. Cardiovascular events are the most frequent cause of mortality and morbidity in this patient group [1].

Nephrotic syndrome (NS) is a condition characterized by severe proteinuria, hypoalbuminemia as well as dyslipidemia [2]. More cardiovascular events are seen in NS patients than in the normal population [3]. The main reasons for these increased

cardiovascular events are thought to be inflammation cascade activation due to proteinuria and malnutrition [4].

The QRS complex represents the electrical depolarization of ventricular myocardium. Abnormal electrical conduction leads to widening of the QRS complex. The block of one of the bundle branches results in a typical bundle branch block pattern. A QRS complex that cannot be classified as bundle branch block due to an atypical configuration is called nonspecific intraventricular conduction delay or pre-excitation type Wolff-Parkinson-White. If the QRS complex

has normal duration and contains notched R or S wave, various RSR' patterns in at least 2 contiguous ECG leads is called a fragmented QRS (fQRS) [5].

Fragmented QRS (fQRS) includes various RSR' patterns with different morphologies of the QRS complexes with or without the Q wave on a resting 12-lead ECG. Various RSR' patterns include an additional R wave (R') or notching in the nadir of the S wave, or the presence of >1 R' (fragmentation) in 2 contiguous leads, corresponding to a major coronary artery territory [6]. Studies to date have shown that presence of fQRS is associated with a rise in cardiovascular event incidence and cardiovascular mortality and morbidity. This association is thought to stem from myocardial scarring, ventricular arrhythmia and structural cardiac defects [7],[8].

If QRS duration is prolonged, the proper nomenclature is wide fragmented QRS (w-fQRS). The underlying pathophysiologies are manifold and include myocardial scars induced by ischemic heart disease, myocardial fibrosis due to other diseases, primary cardiac pathologies as well as systemic diseases with cardiac involvement. Pathologies on the cellular level, such as ion channel dysfunctions, also correlate with fragmented QRS. Besides the diagnostic relevance, fragmented QRS is known to have prognostic properties, for example in identifying high risk patients with coronary artery disease, cardiomyopathy, Brugada syndrome and acquired long QT syndrome; however, fQRS may also be detected in ECGs of healthy individuals [5].

fQRS is a novel ECG marker with more sensitivity and less specificity than Q wave. A combination of fQRS with Q wave in a 12-lead ECG results in up to 74% sensitivity and 92% specificity [9]. Classically, some echocardiographic parameters such as ejection fraction, peak systolic mitral annular velocity and rate of early and late mitral inflow velocities have been used to analyze systolic and diastolic myocardial functions. However, in some conditions these indices do not accurately reflect myocardial functions.

The myocardial performance (Tei) index was first developed by Tei et al. [10] to evaluate combined myocardial systolic and diastolic function. Several studies have shown that the Tei index is a more reliable parameter in the evaluation of systolic and diastolic function than classic echocardiographic indices [11].

METHODS

This case control and cross section study was carried out in Pediatric Nephrology Unit and Cardiology Units at Zagazig University Hospital during the period from March to October 2018.

The study was done after taken approval from Institute Research Board of faculty of medicine, Zagazig University (IRB) and after All subjects' parents gave informed written consent to participate in the study.

The study included 60 children divided into two groups.

1- The first group thirty children with nephrotic syndrome twenty-three male and seven female ranged age from three to fifteen years old from Pediatric Nephrology Unit. we divided the patient's group into two subgroups according to presence or absence of fQRS in ECG into two subgroups:

- FQRS Positive: included 17 patients with fQRS in ECG. They were ...13 males, and ...4 females, their ages ranged from 5 to 12 years...
- FQRS Negative: included 13 patients with normal ECG. They were 10 males and 3 females, their ages ranged from 4 to 15 years.

2- The second group: thirty apparently healthy children, eleven female and nineteen male ranged age from three to fifteen years matched to cases regarding to age and sex

. All patients in this study were subjected to:

Full history taking. „Full clinical examination...Laboratory investigations: Blood urea nitrogen, creatinine, albumin, Calcium, phosphorus, Low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides and 24h urine collection for protein in urine... Electrocardiography.

Echocardiography was performed to detect early pathological problems.

Tissue doppler imaging was used to detect changes occur in the heart with nephrotic syndrome

Inclusion criteria: Children with NS.

Exclusion criteria: 1. Patients with a history of malignancy, findings of active infection or inflammation . 2. Patients with significant organic heart disease. 3. Patients with non-ischemic dilated cardiomyopathy. 4. Patients with bundle-branch block (left bundle-branch block, incomplete or complete right bundle-branch block) or intraventricular

conduction delay (duration of QRS >120 ms) on ECG. 5. Patients with permanent pacemakers, were excluded from the study

The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

RESULTS

There is no statistically significant difference in Age, sex and in anthropometric and vital sign in both studied groups

Table 1. Bivariate analysis of presence FQRS with clinical parameter.

	FQRS	Mean	Std. Deviation	P
Age	YES	5.8522	3.48371	0.587
	NO	6.2649	3.56388	
Sex	YES	Male female	15 8	0.52
	NO	Male Female	27 10	
HR	YES	98.9130	8.27325	0.245
	NO	96.3243	8.30680	
SBP	YES	118.1739	4.55923	0.036*
	NO	111.9459	3.43952	
DBP	YES	79.6957	5.48083	0.03*
	NO	70.9459	4.05480	
BMI	YES	21.4478	1.40837	0.290
	NO	21.0405	1.45152	

This table shows that there was no statistically significant predictor in Age, sex and BMI with FQRS, but there was statistically significant increase of SBP and DBP in patient with FQRS in ECG.

Table 2. Bivariate analysis of presence of FQRS with Laboratory parameter.

	FQRS	Mean	Std. Deviation	P
BUN (mg/dl)	YES	13.8394	7.83809	0.372
	NO	11.5615	5.13815	
Cr (mg/dl)	YES	.3906	.22612	0.103
	NO	.2631	.17342	
CA (mg/dl)	YES	8.0224	.51155	0.109
	NO	8.3308	.49932	
P (mg/dl)	YES	5.0482	1.45949	0.381
	NO	4.5900	1.29006	
Albumin (g/dl)	YES	2.6235	.74713	0.582
	NO	2.7638	.57182	
Protein urea/24h (mg/dl)	YES	2028.6231	1449.79584	0.848
	NO	1435.5202	1431.42908	
LDL (mg/dl)	YES	142.0588	46.80741	0.128
	NO	119.0000	28.24594	
HDL (mg/dl)	YES	51.9412	8.99632	0.533
	NO	53.7692	6.02984	
TG (mg/dl)	YES	210.7647	77.63096	0.311
	NO	179.1538	72.02181	

This table shows that there was no statistically significant predictor between LABS and presence of fQRS in ECG of cases

Table 3. Bivariate analysis of presence of FQRS and ECHO Parameter

	FQRS	Mean	Std. Deviation	P
MPA mm	YES	17.9783	3.20978	0.955
	NO	17.9297	3.19955	
RPA mm	YES	8.4609	1.96254	0.793
	NO	8.3297	1.81779	
LPA mm	YES	8.1217	1.75938	0.829
	NO	8.0216	1.72404	
AO mm	YES	22.9957	4.45140	0.290
	NO	21.9189	3.34098	
LA mm	YES	26.7609	5.50741	0.517
	NO	25.8297	5.30424	
IVS mm	YES	8.3348	2.27448	0.017
	NO	7.7676	1.92371	
PW mm	YES	8.5957	2.24185	0.868
	NO	8.4865	2.51948	
TAPSE mm	YES	21.0304	3.51444	0.487
	NO	20.3946	3.36336	
LVDD mm	YES	38.0957	6.31517	0.994
	NO	38.0838	6.26585	
LVSD mm	YES	23.3348	4.96786	0.611
	NO	22.7324	4.07452	

This table shows that there was no statistically significant predictor between ECHO parameter and FQRS apart from thicknes IVS in patient with FQRS (P =0.017)

Table 4. Bivariate analysis of presence of FQRS with systolic and diastolic conventional.

	F QRS	Mean	Std. Deviation	P
EF%	YES	68.9743	6.71166	0.069
	NO	71.7676	4.94526	
FS%	YES	37.9435	5.15151	0.027*
	No	43.5543	6.42670	
E wave	YES	85.0043	21.79231	0.398
	NO	90.4541	25.44042	
A wave	YES	53.7348	10.93392	0.177
	NO	59.3486	17.66830	
DT OF E wave ms	YES	89.5652	20.22336	0.918
	NO	90.1351	20.94028	

This table shows that there was statistically significant decrease of EF and FS in patient with FQRS in ECG.(p =0.027) although FS is still normal (37.9 %) in patients with fragmented QRS. .

Table 5. Bivariate analysis of presence of FQRS and Tissue Doppler parameter and Tie index

	F QRS	Mean	Std. Deviation	P
S wave	YES	8.2391	1.61210	0.100
	NO	9.1622	2.31869	
E m	YES	13.3522	3.63166	0.014*
	NO	15.8027	3.66822	
A m	YES	7.4913	1.81306	0.360
	NO	8.1622	3.17161	
A (ms)	YES	380.0000	53.48917	0.311
	NO	367.2432	42.61938	
B (ms)	YES	249.3913	26.48969	0.734
	NO	245.9892	42.79608	
A-B/B	YES	.5260	.15468	0.951
	NO	.5231	.18350	

This table shows that there was no statistically significant between tissue doppler parameter and Tie index with FQRS except for E wave velocity which was found to be lower in patients with FQRS (P =0.014)

DISCUSSION

Nephrotic syndrome is primarily a pediatric disorder and is 15 times more common in children than adults. The incidence is 2-3/100,000 children per year, and the vast majority of affected children will have steroid-sensitive minimal change disease [16]. The term nephrotic syndrome is applicable to any condition with heavy proteinuria (> 40 mg/m²/hour or protein/creatinine ratio > 2), hypoproteinemia (plasma albumin < 2.5 gm/dl), edema and hyperlipidemia [17]. Tubular abnormalities seen in Minimal-Change Nephrotic Syndrome (MCNS) include protein droplets, lipid accumulation,

focal calcification and disruption by extruded casts [18]. NS is a clinical picture accompanied by biochemical (hypoalbuminemia, hyperlipidemia) and metabolic (edema) abnormalities caused by massive proteinuria [2]. Incidence of cardiovascular events increases in the NS patient group compared to the normal population. Intestinal edema developing secondary to massive proteinuria-associated hypoalbuminemia reduces nutrient absorption and leads to malnutrition and activation of inflammatory cascade. Various inflammatory mediators (such as TNF α) exhibit a negative inotropic effect on the myocardium [19]. In

this way, malnutrition and inflammation lead to an increase in cardiovascular events incidence in the NS patient group. Thrombosis frequency is known to increase in this patient group. In particular, deep vein thrombosis and pulmonary embolism secondary to this cause impairment in right ventricular functions [3]. Hyperlipidemia, one of the diagnostic criteria for NS, is known to be a cardiovascular events risk factor. Therefore, dyslipidemia, which is frequently encountered in this patient group, causes a rise in coronary artery disease (CAD) frequency [20]. Studies performed in the pediatric age group in particular have shown a greater incidence of cardiomyopathy and congestive heart failure (CHF) in patients with focal segmental glomerulosclerosis (FSGS). Researchers suggest this may be related to immune mechanisms [21].

This clinical study was carried out to assess the presence of fQRS in children with NS and also to evaluate the relationship between fQRS and myocardial functions.

This study included 60 subjects who were subdivided into 2 groups: The first group included 30 patients with nephrotic syndrome. The second group included 30 apparently healthy subjected.

In our study, the range for age of NS patients was 2-15 years with the median 4.5, and the male represented about (76.7%) of patients. There was no statistically significant difference between cases and control as regarding age and sex ($p > 0.05$). This result was in agreement with Hooman et al. [22] and Saleh et al. [23] who found that there was no significant difference between patient and control group as regard age and sex. We found no significant difference in heart rate, BMI, systolic and diastolic blood pressure between patient group and control group. This came in agreement with Saleh et al. [23] who found that there was no significant difference in systolic blood pressure and BMI between patient group and control group while he was disagreed with us as regard diastolic blood pressure because he found highly significant difference as regard to diastolic blood pressure. Also, Candan et al., (2014) found

that there was no significant difference between patient and control group as regard BMI. But Hooman et al. [22] found significant difference as regard BMI. On the other hand, Alpert et al. [24] and Bagga et al. [25] found significant increase in diastolic blood pressure in patient group than control group especially with steroid resistant NS. This could be due to long term steroid \pm cytotoxic therapy, and also due to increased susceptibility of development of chronic renal failure. Also, Qin et al. [3], Hooman et al. [22] found that there was a statistically significant difference in systolic and diastolic blood pressure between patient group and control group while, Qin et al., [3] found that there was no significant difference in heart rate.

Echocardiographic assessment was done for all study group including case and control. As regard structural Echocardiographic variable measurement, our study showed there was no significant difference between patient and control group as regard conventional echocardiographic parameters MPA, RPA, LPA, AO, LA, PW, TAPSE, LVDD, LVSD, but there was a statistically significant increase in IVS size in patient group in comparison to control group. This result was in disagreement with Saleh et al. [23] who found that there was no significant difference between patient and control group as regard all conventional echocardiographic parameters including IVS. Assessment of left ventricular systolic function, in the present study showed that was no significant difference between case and control group as regard L.V Systolic function, this was agreement with Qin et al. [3] who found that there was no significant difference between patient and control group as regard, LVEF. Assessment of left ventricular diastolic function, in our study showed that there was a significant decrease in E wave in patient than control group (p value= 0.021). This came in agreement with Saleh et al. [23] who found that E-wave was decreased in patient group than in control group with a statistically significant difference (p value= 0.0001. While there was no significant difference between

patient and control group as regard A- wave and deceleration time of E-wave. This came in disagreement with Saleh et al., [23] who found that there was a statistically significant difference between patient and control group as regard to A-wave and deceleration time of E-wave. Doppler tissue imaging is concerning TDI systolic function, we found non-significant difference between case and control as regard peak systolic velocity (s') And also, we used TDI velocities for assessment of LV diastolic function and found non-significant difference between case and control as regard (E') and (a'). There are known to be many limitations to classic echocardiographic index evaluation of myocardial functions [11]. New techniques are therefore being developed in order to be able to better evaluate cardiac functions. One such is the Tei index [10]. Also known as the myocardial performance index, the Tei index is used in the analysis of myocardial systolic and diastolic functions [11]. In the present study there was no significant difference between patient and control group as regard to Tie index ($p > 0.05$). This came in disagreement with Saleh et al., [23] who found that there was a statistically significant difference between patient and control group as regard to Tie index (p value= 0.045).

Tei index, shown in previous studies was used to provide a better analysis than older echocardiographic indices, to analyze myocardial functions. Tei index is more sensitive than classic echocardiographic parameters, particularly in showing subclinical myocardial function compromise [19]. Fragmented QRS demonstrates scarred myocardium and is linked to ventricular dysfunction. In Coronary artery disease, fQRS represents previous myocardial infarction and is an independent predictor of adverse cardiac events [27]. In the present study, fQRS was present in 56.7% of patient group, and absent in the other 43.3% with a statistically significant increase in presence in case than control. (p value= 0.003). Moreover, we think that the presence of fQRS in an NS patient group can be a marker of impaired myocardial performance. This came in agreement with

Özkan et al. [19] who that identified that fQRS at a level approaching 50% in NS patient group. So, we divided the cases group into two sub group according to presence of FQRS. There was no significant association between age, sex and BMI and presence of FQRS in ECG in patient with nephrotic syndrome. There was significant increase in systolic and diastolic blood pressure in patient with FQRS in ECG. This came in agreement with Litwin and Niemirska, [28] who reported that these patients frequently have several additional risk factors, such as hypertension, obesity, insulin resistance, inflammation, long-term treatment with steroids and other immunosuppressive drugs, such as cyclosporine A, hypercoagulability, and oxidative stress. All of these risk factors may act in concert to produce atherosclerotic vascular lesions

There was no significant difference between patients with or without fQRS in Heart rate, kidney function tests, Ca, P, albumin, urinary protein or lipid parameters. This came in agreement with Özkan et al., [19] who found that there were no demographic or biochemical factors affected incidence of fQRS, with the exception of proteinuria. fQRS incidence was higher in patients with a higher level of proteinuria. Clear proteinuria is today accepted as being related to a rise in incidence of cardiovascular events, for which reason they constitute one of the risk factors for cardiovascular events [29]. The median of protein excretion in 24-h urine in the patients with fQRS was 2028.62 mg/day, compared to 1435.5 mg/day for those without ($p < 0.05$). Microalbuminuria is a marker of endothelial damage, which gives rise to inflammatory cascade activation. Proteinuria in NS patients causes inflammatory cytokine release during endothelial injury, tubular reabsorption and tubular catabolism [30]. In addition, malnutrition developing secondary to hypoalbuminemia leads to inflammatory cascade activation and cytokine release [31]. Studies have shown that inflammatory cytokines cause myocardial injury. Although inflammation markers could not be assessed, due to this being a cross-sectional study, in

the light of this information, one of the probable reasons for the relation between the fQRS and proteinuria may be a rise in inflammatory cytokines [4]. Previous studies have shown that fQRS is a predictor of cardiovascular events in a variety of populations [15]. The cardiovascular events increasing effect is thought to be associated with myocardial scarring and/or the presence of fibrosis, leading to nonhomogeneous myocardial electrical activity [7]. Indeed, studies have revealed that the presence of fQRS is correlated with cardiac structural abnormality, ventricular arrhythmia, myocardial scarring and fibrosis [8]. Also, Eddy and Symons, [32] found that the duration of nephrotic dyslipidemia appears to be a critical factor for initiating vascular damage and, therefore, an increased risk of premature atherosclerosis exists in patients with unremitting NS. In the present study, there was no significant difference in TAPSE between patients with and without fQRS. This came in agreement with Özkan et al. [19] who found that there was no significant difference in TAPSE, a right ventricle function marker. In the present study, there was no statistically significant predictor between ECHO parameter and FQRS. There was no significant difference between cases with and without FQRS as regard ECHO parameter and diastolic function. But there was significant decrease in systolic function (FS%) and non-significant decrease in (EF%) in cases with FQRS in ECG. This come in agreement with Özkan et al. [19] who found that there was no significant difference in classic echocardiographic and diastolic function markers at echocardiographic examinations performed in order to assess the relationship between fQRS and myocardial functions. In the present study there was no statistically significant differences between tissue doppler parameter and Tie index with FQRS except for Em wave. On the other hand, Özkan et al., [19] found that in terms of the association between fQRS and myocardial functions, a correlation was only determined between Tei index and fQRS. We perform univariant analysis for patient with FQRS and

all parameter and detect FQRS was presented with increase in systolic and diastolic blood pressure, and in patient with systolic dysfunction (decrease FS%), and in patient with diastolic dysfunction (E[´]). We identified fQRS at a level approaching 56.7% in this patient group, in which the presence of fQRS has not been investigated before. Presence of fQRS being not in relation with Tei index and no relation with other parameters being identified suggests that was because of low number of our patient in this study.

CONCLUSION

NS children generally have a high risk of cardiovascular complications. The present study revealed that fQRS, determined using ECG, an economic and easily accessible technique, can be used as an early marker of myocardial function impairment in this patient group

Declaration of interest

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

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