Subjects and Methods

**Background:** Primary or idiopathic nephrotic syndrome (PNS) is the most frequent form of Nephrotic Syndrome in children. There is an increased incidence of heart disease in patients with (PNS). Protein wasting and systemic inflammatory activation during PNS may contribute to cardiac remodeling and dysfunction.

**Methods:** This study was carried out in nephrology unit jointly with cardiology unit in El-Minia University Hospital at the period between March 2015 till December 2016 and included 30 PNS patients as group I and twenty age and sex matched healthy control as group II. Both groups are subjected to full history taking, thorough clinical examination, anthropometric measurements, and lab studies, including serum albumin; renal function tests, 24 h urine protein, and serum cholesterol level. Doppler Echocardiography was used for evaluation of both ventricular hemodynamics, MPI (myocardial performance index) and LV function by LV end systolic diameter, LV end diastolic diameter, LV ejection fraction.

**Results:** The difference between both groups in conventional echo is non-significant, while it is significant in tissue echocardiography in both ventricles including IVRT, IVCT, MPI, E/A, and DT. Ventricular diastolic dysfunction was detected in 30% of patients in whom; diastolic blood pressure (DBP) was significantly higher than those with normal RV diastolic function. Also, DBP not affected by duration of illness and other biochemical parameters.

**Keywords:** PNS; Tissue echo; MPI; LV & RV diastolic dysfunction

**Introduction**

Nephrotic syndrome (NS) is the most common chronic renal disease of childhood and the most common type of NS is PNS [1]. It is caused by impaired glomerular function, characterized by protein leakage from the blood to the urine through the glomeruli, resulting in proteinuria, hypoalbuminemia, hypercholesterolemia and generalized edema [2]. There is an increased incidence of heart disease in patients with chronic PNS [3]. Protein wasting and systemic inflammatory activation during PNS may contribute to cardiac remodeling and dysfunction [4]. Acute afterload elevations would result in decreased relaxation rate and increased diastolic intolerance to afterload in children with PNS [5].

**Subjects and Methods**

This study included 50 children and adolescents who were classified into two groups: Group I: 30 patients who had already diagnosed as with primary nephrotic syndrome (18 males, 12 females) their ages ranged from (4-14 y) had regular follow up in pediatric Nephrology outpatient's clinic, jointly with cardiology unit in El-Minia University Hospital at the period between March 2015 till December 2016 and included 2 groups, and Group II: 20 apparently healthy subjects, age and sex matched to the diseased group.

All patients included were those who fulfilled the following criteria: hypoalbuminemia with serum albumin<2.5 g/dl, hypercholesterolemia serum cholesterol>250 mg/dl, generalized edema, proteinuria (urinary protein>2 gm/24 h). Patients excluded if they have congenital or acquired heart diseases, severe anemia, or chronic pulmonary diseases.

The studied groups are subjected to the followings: thorough history taking, clinical examination, and Laboratory investigations, including complete blood count, Liver function tests (serum albumin, alanine aminotransferase (ALT), aspartate amino transferase (AST)), total cholesterol, urea, and creatinine. Also fresh morning urine sample 10 ml sample was collected and examined for A/C ratio plus 24 h urine collected in a sterile container.

Echocardiography was performed using a Vivid 3 color Doppler ultrasound system General Electric with transducers of 3.75 MHz or 5 MHz, as appropriate for children or adolescents. A complete echocardiographic examination was performed to exclude the possibility of congenital heart disease with great emphasis on RV dimension, global function, and LV internal dimensions with assessment of LV ejection fraction; where recorded images for each patient was stored and analyzed offline with software (Echo PAC; GE Medical Systems, USA) blinded to the patients' data (Figure 1).

From the standard transthoracic windows, LV end diastolic diameter (LVEDD), LV end systolic diameter (LVESD), LV posterior wall (LVPW), and LV ejection fraction (EF) were measured.

Transmitral E wave velocity (E) and (A) wave velocity were obtained from the recorded data and were averaged to generate the mean value (Figure 2).
Figure 1: Comparison between the patients and the control groups as regard tissue echocardiographic parameters of left ventricle.

The MPI, also called Tei index, and is calculated by dividing the sum of IVRT and IVCT by Ejection time (ET). Normally (0.39 ± 0.05) it increases in diastolic dysfunction [6].

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LV\ MPI = (IVCT + IVRT)/LVET
\]

Whereas the prejection time (PEP) derived MPI was defined as the ratio of PEP along with IVRT to ET [7].

We evaluate right ventricular and left ventricular function by MPI. Measurement of the Tei index is noninvasive and easily obtained, it does not require the presence of an echocardiographer with great experience and it does not materially prolong the time required for the examination (Figure 3).

The study was carried out according to the principles of declarations of Helsinki, and its appendices [8] and was approved the hospital ethical review board in El Minia university hospital (code 75a, March, 2015). Written informed consents from patients’ caregivers were obtained for the use of their study-related information and for participation in the ongoing research.

Table 1 showed no significant difference between patient and control groups as regard age, sex, weight, height, and SBP and serum creatinine, while there are high significant differences as regard DBP, serum levels of albumin and cholesterol and 24 h urine protein.

Table 1: Comparison between patients and control groups in demographic, clinical and laboratory data; DBP: Diastolic Blood Pressure; SBP: Systolic Blood Pressure.

| Parameters          | Case            | Control         | P value |
|---------------------|-----------------|-----------------|---------|
| Age                 | Mean ± SD       | 7.83 ± 3.36    | 7.05 ± 3.33 | 0.4 |
| Range               | 4 – 14          | 3 – 14          |         |
| Sex                 | Number          | 18              | 10      | 0.5 |
| Male                | Percentage      | 60%             | 50%     | 0.5 |
| Female              | Number          | 12              | 10      | 0.5 |
| Weight (Kg)         | Mean ± SD       | 23.17 ± 7.58    | 19 ± 8.54 | 0.07 |
| Range               | 15 – 40         | 11 – 40         |         |
| Height (cm)         | Mean ± SD       | 106.5 ± 18.2    | 104.3 ± 23.5 | 0.7 |
| Range               | 84 – 150        | 66 – 145        |         |
| SBP (mmHg)          | Mean ± SD       | 118 ± 12        | 115 ± 12 | 0.5 |
| Range               | 100 - 140       | 100 - 130       |         |
| DBP (mmHg)          | Mean ± SD       | 92.75 ± 4.7     | 75 ± 15 | 0.001* |
| Range               | 60 – 70         | 50-95           |         |
| Albumin (g/dl)      | Mean ± SD       | 1.8 ± 0.5       | 4.2 ± 0.5 | 0.0001* |
| Range               | 0-25            | 3.5-5           |         |
| Cholesterol (mg/dl) | Mean ± SD       | 374 ± 46.9      | 155 ± 8.6 | 0.0001 |
| Range               | 280 – 490       | 140 – 170       |         |
| Creatinine (mg/dl)  | Mean ± SD       | 0.713 ± 0.15    | 0.725 ± 0.16 | 0.7 |
| Range               | 0.4 – 1         | 0.4 – 1         |         |
| 24 h Urine Protein  | Mean ± SD       | 6.62 ± 3.85     | 0.041 ± 0.04 | 0.0001* |
| Range               | 1.3 – 15        | 0 – 0.11        |         |
Regarding disease diagnosis, 33.3% patients were steroid responsive NS; 43.3% patients were in relapse after remission; 16.7% patients were SDNS; and 6.7% patient was SRNS.

As shown in Table 2 there was no significant difference between case and control as regard conventional echo parameters, LAD, LVEDD, LVESD, LVPWD, EF and Left DT.

Table 3: Comparison between the patients and the control as regard tissue echocardiographic parameters of both right and left ventricles; A: A wave; DT: Deceleration Time; E: E wave; E/A: E/A ratio; ET: Ejection Time; IVCT: Isovolumic Contraction Time; IVRT: Isovolumic Relaxation Time; MPI: ventricular Myocardial Performance Index.

Table 4: Correlation between duration of disease and conventional echocardiographic parameters; DT: Deceleration time; EF: Ejection Fraction; LVEDD: Left Ventricular End Diastolic Diameter; LVESD: Left Ventricular End Systolic Diameter; LVPWD: Left Ventricular Posterior Wall Diameter.

Table 5: Comparison between the patients and the control as regard tissue echocardiographic parameters of both ventricles; A: A wave; DT: Deceleration Time; E: E wave; E/A: E/A ratio; ET: Ejection Time; IVCT: Isovolumic Contraction Time; IVRT: Isovolumic Relaxation Time; MPI: Myocardial Performance Index.

As regard tissue echo findings there are significant differences between case and control groups, Lt ventricle (IVRT (P 0.001 ), IVCT (P 0.006), MPI (P 0.001), DT (P 0.02) and E/A Ratio( P 0.002); and in the Rt ventricle, significant differences include, IVRT(P value 0.02), IVCT (P value 0.02) , MPI (P value 0.0001), DT (P value 0.03) and E/A ratio(P value 0.0001) (Table 3).

Table 4 shows fair association between LVEDD and Right DT and the duration of the disease and this association is significant (p 0.04, 0.014) respectively.

Table 5 shows fair association between Right A , Right E/A Ratio , Right IVCT and the duration of the disease this association is significant (p value 0.042 , 0.034, 0.019) respectively. Fair association between Right A, Right E/A Ratio, Right IVCT and the duration of the disease this association is significant.
0.50-0.74 (moderate association)
≥ 0.75 (strong association)

Show fair association between Left A, Left IVCT, Left MPI and the duration of the disease this association is significant.

Table 6 Frequency of diastolic dysfunction among nephrotic syndrome patients

| Echo parameter              | Frequency | Percentage |
|-----------------------------|-----------|------------|
| Diastolic dysfunction       | 9         | 30%        |
| Normal diastolic function   | 21        | 70%        |
| Total                       | 30        | 100%       |

Table 7: Comparison between patients with normal ECHO and those with RV diastolic dysfunction

| Duration of disease (mo)   | ECHO     | N     | Mean ± SD       | P value |
|---------------------------|----------|-------|-----------------|---------|
| Normal                    | 21       | 22.57 ± 18.12 | 0.12    |
| RV diastolic dysfunction  | 9        | 20.66 ± 11.27  |         |
| SBP (mmHg)                |          |       |                 |         |
| Normal                    | 21       | 116.19 ± 13.22 | 0.17    |
| RV diastolic dysfunction  | 9        | 123.33 ± 11.18 |         |
| DBP (mmHg)                |          |       |                 |         |
| Normal                    | 21       | 69.76 ± 14.62  | 0.002** |
| RV diastolic dysfunction  | 9        | 87.78 ± 9.72   |         |
| S albumin (g/dl)          |          |       |                 |         |
| Normal                    | 21       | 1.9 ± 0.398    | 0.56    |
| RV diastolic dysfunction  | 9        | 1.87 ± 0.409   |         |
| S cholesterol (mg/dl)     |          |       |                 |         |
| Normal                    | 21       | 369.04 ± 42.27 | 0.38    |
| RV diastolic dysfunction  | 9        | 385.56 ± 57.47 |         |
| S creatinine (mg/dl)      |          |       |                 |         |
| Normal                    | 21       | 0.74 ± 0.12    | 0.1     |
| RV diastolic dysfunction  | 9        | 0.64 ± 0.19    |         |

Table 7: Comparison between patients with normal ECHO and those with RV diastolic dysfunction; DBP: Diastolic Blood Pressure; mo: months; S: Serum; SBP: Systolic Blood Pressure.

Discussion

Our study is a case control one, and included 30 patients with PNS and twenty age and sex matched normal children.

We found significant increase in diastolic blood pressure in patient group than control group (Table 1). Alpert et al. and Bagga et al. found same results especially with steroid resistant NS. This could be due to long term steroid ± cytotoxic therapy, and also due to increased susceptibility of development of chronic renal failure [9-11].

As regard serum albumin, cholesterol, creatinine and 24 h urine proteins as in Table 1 were in accordance with that of Kaan et al. and Ismail et al. [12,13]. Also with Russo et al. who stated that High glomerular permeability leads to hyperalbuminuria and, eventually to hypoalbuminemia [14]; that in turn lowers the plasma colloid osmotic pressure, causing greater transcapillary filtration of water and the development of edema.

Also, regarding Structural changes in the heart (Table 2) were in accordance with the results Qiang Qin et al. who stated that patients with PNS had larger RV dimension by echo compared to normal controls [3]. Also they found out of 50 patients with PNS, RVEDD was increased by average of 20% in 39 patients. In addition, they found that cardiac output & stroke volume were maintained indicating compensation at the expense of increased RVEDD and RVESD.

As regards to left ventricle tissue echocardiographic (Table 3), our results are going with that of Lindblad et al. [9] who found that tissue Doppler imaging (TDI) echo detected early LV diastolic dysfunction, also Correia Pinto et al. [15-17] who stated that afterload elevation could contribute to diastolic dysfunction in the left ventricle and with Tie E Dajardin et al. [18] who reported that systolic dysfunction of the left ventricle increases IVCT and decreases ET, whereas IVRT increases in both systolic and diastolic dysfunction. Egan et al. [19,20] postulated that Cardiac edema could also account for myocardial dysfunction. Where it increases myocardial stiffness and induces contractile dysfunction.

We suggest that increased RV peak pressure and RV end diastolic pressure in children with PNS could be attributed to the following: Impaired functional reserve was highlighted by hemodynamic stress with increased RV end-diastolic pressure, acute afterload elevations would result in decreased relaxation rate and increased diastolic intolerance to afterload in children with PNS. The hemodynamic disturbance was caused by increased diastolic intolerance to afterload. This response to acute afterload can be a precarious sign of dysfunction, preceding overt heart failure Correia Pinto et al. [5]. Second, the elevated RV peak pressure and RV end diastolic pressure could be caused by pulmonary arterial hypertension.
Hypercoagulability can be caused by profound abnormalities in almost all coagulation factors and clotting inhibitors, as well as by defects in platelets and the fibrinolytic system. Although pulmonary embolism appears to be rarer in children than in adults [21]. Its incidence might be underestimated because of the high number of asymptomatic or subclinical events in children with PNS [20].

Our results were unable to identify any relationship between increased pulmonary pressure and the biochemical indicators of thromboembolism studied. This could be because of wide variations in these indicators, or because of the small number of patients with increased pulmonary pressure.

The duration of systemic hypertension might be a more important contributory factor in the increased RV peak pressure and RV end-diastolic pressure than the BP itself, because patients with increased RV peak pressure and RV end-diastolic pressure had longer durations since PNS onset. However, we cannot exclude the possibility that sympathetic activity may have influenced heart function in this study. Further studies are needed to determine the role of sympathetic activity.

Disturbed cardiomyocyte calcium kinetics has also been implicated in myocardial dysfunction during heart failure progression [5].

Conclusion

- RV functions were affected in 30% of children with PNS.
- Elevation of diastolic blood pressure in patients.
- LV and RV dysfunction were significantly correlated with the long duration of the disease

Recommendation

Further studies are needed with larger number of patients, and need long term follow up period, to understand the etiology, clinical implications, and long term prognosis of this abnormality. Also we recommend additional investigation as CT pulmonary angiography. Laboratory studies for better assessment of associated hypercoagulable state and activated cytokines tumor necrosis factor alpha.

Authors’ Contributions

SMS & KEM gives us the idea and suggest plan of work. AM & SMS planned the study. AM, HSM and KEM conducted the study; AM & HSM did analysis data and wrote the paper. AM and KEM are the one responsible for final content. All authors have read and approved the final manuscript.

Ethics Approval and Consent to Participate

The study was carried out according to the principles of declarations of Helsinki, and its appendices [8] and was approved the hospital ethical review board in El Minia university hospital (code 75a, March, 2015). Written informed consents from patients’ caregivers were obtained for the use of their study-related information and for participation in the ongoing research.

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