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Original Article

Assessment of the Pulmonary Artery Pressure in Children With the Nephrotic Syndrome

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ABSTRACT

Background: The nephrotic syndrome (NS) is associated with a hypercoagulable state and an increased tendency for thromboembolism. The reported incidence of thromboembolic complications ranged from 1.8% to 6.6% in children with NS. Although thromboembolism may occur anywhere, deep vein thrombosis and pulmonary embolism are most frequently encountered in the clinical setting. Severe pulmonary embolism is a critical condition which needs urgent intervention, but minor embolism to the pulmonary arteries may not induce clinical symptoms, and occurs in up to 28% of patients. Recurrent pulmonary embolism may induce increased pulmonary pressure.

Objectives: Assessment of the pulmonary arterial pressure in children with the NS to find out whether it is a problem in such a category of patients.

Methods: Complete blood picture, serum total proteins, albumin and cholesterol, total proteins in 24 hours urine, coagulation profile and Doppler echocardiography was performed in 40 children with NS (aged 2 - 14 years), 17 NS responsive patients, 12 NS dependent patients, 11 NS resistant patients and 20 normal controls. Pulmonary pressure was estimated by measuring the systolic transtricuspid gradient from tricuspid regurgitation.

Results: All patients had edema, heavy proteinuria 6.98 ± 3.58 g/24 hrs, hypoalbuminaemia, serum albumin was 1.92 ± 0.48 g/dl, and hypercholesterolaemia 462.23 ± 92.84 mg/dl. Serum creatinine was 1.12 ± 0.80 mg/dl. Total platelet count was 32.6 ± 9.9 x 10^4/mm^3, PT 13.65 ± 1.31, PTT 34.32 ± 3.60 seconds and prothrombin fragments 1 & II 1.59 ± 0.46. Thirty seven of the 40 patients with NS had measurable tricuspid regurgitation with a pulmonary systolic pressure ranging from 26 to 52 mm Hg. Pulmonary systolic pressure was > 40 mm Hg in seven patients.

Conclusion: Pulmonary arterial pressure was increased in children with NS, so we recommend further studies to evaluate the etiology and clinical effects of this abnormality

INTRODUCTION

The nephrotic syndrome (NS) remains a major cause for referral to pediatric nephrologists because of the chronicity of the disorder and the complexities of its evaluation and management. The male to female ratio is approaching 1 : 1. The age at onset varies with the type of nephrotic syndrome[1]. The NS is a common condition seen in pediatric nephrology units, but is rare in the community, as its cumulative prevalence is 15.7 per 10^5 in children. The etiology of NS is not known. It is classified into primary and secondary (which is seen in the course of systemic diseases such as connective tissue disorders, neoplasia and use of drugs)[2]. Ninety percent of children with NS have idiopathic nephrotic syndrome (INS). Minimal change disease is found approximately in 85% of cases,

mesangial proliferation (MPGN) in 5% and focal sclerosis (FSGS) in 10%[1]. The NS is characterized by edema, proteinuria, hypoalbuminaemia and hypercholesterolaemia[3].

The NS has many complications mainly renal failure, hypertension, GIT disturbances, psychological disturbances, infections, growth retardation, anemia, protein malnutrition, hypovolemia, ocular hazards, thrombotic complications, iatrogenic complications and others[4]. The prognosis for children with minimal-change NS is excellent and poor with other types[1]. The NS is associated with hypercoagulability and an increased tendency for thromboembolism[5]. The reported incidence of thromboembolic complications ranged from 1.8% to 6.6% in children with NS[6]. Although thromboembolism may occur anywhere, deep vein thrombosis and pulmonary embolism are most frequently encountered in the clinical setting[7]. Severe pulmonary embolism is a critical condition which needs emergency intervention, but minor embolism to the pulmonary arteries may not induce clinical symptoms, and occurs in up to 28% of patients detected by radionuclide lung perfusion study[8]. Recurrent pulmonary embolism as well as systemic hypertension may induce increased pulmonary pressure[9]. Pulmonary hypertension (PH) is mainly diagnosed by echocardiography and other investigations as chest radiography, ECG, CT, MRI, right heart catheterization, CT, MRI, pulmonary function tests, right heart catheterization and lung biopsy[10]. By measuring tricuspid regurgitation and Doppler flow of the pulmonary artery, echocardiography has proved to be an accurate and reliable method for assessment of pulmonary artery pressure[11].

AIM OF THE WORK

Assessment of the pulmonary arterial pressure in children with the NS to find out whether it is a problem in such category of patients.

SUBJECTS AND METHODS

Forty children, 20 males and 20 females, with nephrotic syndrome at onset or relapse, ages ranging from 2-14 years, were selected randomly from the Nephrology Inpatient and Pediatrics Nephrology Outpatient Clinic of Zagazig University Hospitals, between June 2005 and June 2006. Twenty children sex- and age-matched, 12 males and 8 females, with ages ranging from 2-14 years were taken as a control group. The nephrotic range for proteinuria was defined as a urine protein/creatinine ratio greater than 2 in an early morning specimen, a value that is 10 times the upper limit of normal protein excretion[12] or a urinary protein level of more than 1 $g/m^2/d$[13].

Relapse was defined as proteinuria of more than 1 $g/m^2/d$ for 3 consecutive days[13] or proteinuria ($\geq$ 2+) for 3 consecutive days[12]. Remission in response to steroid therapy only was achieved when the urine was free of protein for 3 consecutive days[12].

Steroid-resistant NS was defined as failure to achieve response in spite of 4 weeks of prednisolone 60 $mg/m^2/d$[13].

Exclusion Criteria:

Chronic infection, malignancy, systemic disease e.g. DM., congenital nephrosis, liver

disease, congenital heart disease and chronic chest diseases as T.B.

Before starting the study an informed consent was obtained from parents of the patients.

All children and adolescents included in the study were subjected to the following: full history taking, thorough clinical examination with stress on the presence of edema, ascites, blood pressure measurement, cardiac and abdominal examination.

E.C.G. was done for all subjects for detection of signs of pulmonary hypertension in the form of right atrial dilatation and right ventricular hypertrophy.

Abdominal ultrasonography was done for all subjects for detection of ascites and renal affection[14]. Chest x-ray was done for all patients for detection of enlargement of the main pulmonary artery and major branches with marked tapering of peripheral arteries and for detection of right atrium and right ventricle enlargement[15].

Echocardiography

Echocardiography was performed on a GE, vivid 7 colour Doppler ultrasound system with transducers of 7 MHz or 3 MHz as appropriate for children or adolescents. A complete echocardiographic examination was performed. All echocardiograms were performed by the same experienced personnel. By using M-mode Echo left ventricular ejection fraction, fractional shortening, inter-ventricular septum diastolic thickness, posterior wall end diastolic thickness were calculated. In each subject tricuspid regurgitation was carefully detected by colour flow mapping and continuous wave Doppler in parasternal right ventricular inflow tract, apical four chamber view, and short axis view at the aortic valve level. By using the modified Bernoulli equation ($P = 4V^2$), the maximal transtricuspid gradient was estimated. Pulmonary systolic pressure was computed as the sum of the transtricuspid gradient and right atrial pressure[16] with right atrium pressure (RAP) assumed to be 10 mm Hg[17]. All measurements were obtained on the basis of the standards of the American Society of Echocardiography.

Laboratory investigations: Complete urine analysis for total proteins in 24 hours urine, blood urea nitrogen, serum creatinine, total serum proteins, albumin and cholesterol using automated analyzer dimension RXL (Behring), complete blood counts using cell counter (Cell-Dyn 1700), blood electrolytes (calcium, phosphorus, sodium and potassium) using analyzer (AUL 988-3), ESR, PT and PTT. Prothrombin fragment I and II were assayed using an enzyme immunoassay for the quantitative determination of human prothrombin fragment 1 + 2 provided from Behring Diagnostic Inc. USA, by Wester Green method using wave length 492 nm (49-500 nm). We calculated the mean absorbance values and plotted the reference curve on log-log graph paper (Abscise: 0.04 to 10 nmol/L, ordinate: absorbance 0-2).

Statistical Analysis

Data are presented as mean ± SD. Means between two groups were compared with the paired or unpaired Student's t test as appropriate. Non-parametric data were compared using the Pearson test or Fisher exact test. The 95% confidence intervals (CI) were calculated as appropriate. Linear correlation and regression were used to test

the correlations between pulmonary systolic pressure and the independent variables. The Mann-Whitney U test was used to compare data that were not normally distributed. SPSS 10.0 for Windows (SPSS Inc., Chicago) was used for the analysis. A p value of 0.05 was regarded as significant.

RESULTS

There were forty patients; 32 at onset of NS and 8 during relapses after remission. Their clinical characteristics are shown in Table 1. The time from onset of the disease ranged from 4 days to 7 years with a median of 5 weeks. At the time of admission, all patients had edema, heavy proteinuria (6.98 ± 3.58 g/24 hrs), hypoalbuminaemia, (serum albumin was 1.92 ± 0.48 g/dl) and hypercholesterolaemia (462.23 ± 92.84 mg/dl). Serum creatinine was 1.12 ± 0.80 mg/dl. Total platelet count was 32.6 ± 9.9 x $10^4/mm^3$, PT 13.65 ± 1.31, PTT 34.32 ± 3.60 seconds and prothrombin fragments I & II 1.59 ± 0.46. Chest x-rays showed that 13 patients had pulmonary congestion and 10 had pleural effusion. A total of 29 patients had a response during initial treatment; 17 patients were steroid sensitive (10 males & 7 females, their ages were 4.3 ± 2.1 years), 12 patients were steroid dependent (8 males & 4 females; their ages were 5.8 ± 1.6 years) and 11 were steroid resistant (5 males & 6 females; their ages were 8.9 ± 2.1 years). ECG was abnormal in 7 patients. Of these, one had atrial premature beats, 2 had LVH and 4 had RVH. In comparison to normal controls, patients with NS had a larger left atrial and right ventricular dimension by echocardiography, and higher systolic and diastolic blood pressures (Table 2). Pulmonary artery pressure as estimated through the tricuspid valve regurgitation from the 40 patients; 37 had tricuspid regurgitation. The maximal regurgitant velocity was 2.0 - 3.3 m/sec, with a transtricuspid gradient of 16.0 - 42.5 mm Hg (28.3 ± 7.2 mm Hg). Right atrial pressure was assessed as 10 mm Hg.. Pulmonary systolic pressure ranged from 26.0 to 52.5 mm Hg. Pulmonary systolic pressure was > 30 mm Hg in 13 patients (32.5%), and > 40 mm Hg in 7 patients (17.5%). Of 20 normal controls, 12 had tricuspid regurgitation. Pulmonary systolic pressure ranged from 16.0 to 30 mm Hg (22.4 ± 4.7 mm Hg), and was significantly lower than that in the patients with NS ($p < 0.01$) (Table 2).

Table 3 shows a significant difference between patients and controls as regards the serum levels of urea, creatinine, calcium and WBCs and a highly significant difference as regards the serum level of albumin, cholesterol, urinary proteins in 24 hours, phosphorus, prothrombin fragments I & II, Hb level and ESR.

Table 4 shows a significant positive correlation between prothrombin fragments I and II and urea, urinary proteins in 24 hours, serum phosphorus and Hb level. It also shows a significant negative correlation between prothrombin fragments I and II and serum calcium level, and a highly significant positive correlation between prothrombin fragments I and II and serum cholesterol and shows highly significant negative correlation between prothrombin fragments I and II and serum albumin level.

Table 5 shows a significant positive correlation between pulmonary tension and

duration of illness, steroid resistance, creatinine, systemic blood pressure, pulmonary congestion, serum cholesterol level, urinary proteins and prothrombin fragments I and II and also shows a significant negative correlation between pulmonary tension and serum albumin level.

Table 1: Clinical characteristics of children with nephrotic syndrome.

		Mean ± SD	
Age		8.2 ± 5.8	
Duration of illness		2.47 ± 1.22	
		Frequency	**Percentage**
Steroid response	Sensitive	17	42.5
	Dependant	12	30
	Resistant	11	27.5
Blood pressure	Normal	9	22.5
	Mild	8	20
	Moderate	14	35
	Severe	9	22.5
Ascites	Minimal	17	42.5
	Moderate	18	45
	Tense	5	12.5
FCG	Normal	33	82.5
	RVH	4	10
	LVH	2	5
	Premature atrial beats	1	2.5
Chest x-ray	Normal	17	42.5
	Pulmonary Congestion	13	32.5
	Pleural effusion	10	25

Table 2: Clinical and echocardiographic data of children with nephrotic syndrome compared with controls.

	Patient with NS	Control	p value
HR (beat/min)	95 ± 12	94 ± 11	0.884
SBP (mm Hg)	106 ± 16	96 ± 8	0.004
DBP (mm Hg)	84 ± 9	65 ± 12	0.001
Left atrial diameter	23.8 ± 2.9	20.4 ± 2.3	0.001
LVEDD	35.8 ± 4.6	35.2 ± 4.4	0.872
LVEF	68.7 ± 4.6	69.1 ± 3.9	0.524
RVEDD	11.8 ± 2.4	10.67 ± 2.1	0.032

Table 3: Comparative study showing some routine investigations among studied groups.

	Control	Patients	t	p
Urea	12.60 ± 4.03	31.30 ± 20.95	2.651	0.012
Creatinine	0.60 ± 0.15	1.12 ± 0.80	2.140	0.034
AST	18 ± 4.41	30.40 ± 11.28	1.557	> 0.05
ALT	20 ± 4.85	37.43 ± 11.46	1.468	> 0.05
Albumin	3.68 ± 0.25	1.92 ± 0.48	-11.142	< 0.001
Cholesterol	216.00 ± 30.03	462.23 ± 92.84	7.824	< 0.001
Urinary proteins in 24 hrs	0.48 ± 0.20	6.98 ± 3.58	5.214	< 0.001
Ca	9.66 ± 0.53	9.01 ± 0.89	-2.124	0.041
Ph	2.57 ± 0.69	4.34 ± 0.78	6.136	< 0.001
Na	132.50 ± 7.23	131.24 ± 7.16	-0.852	> 0.05
K	3.98 ± 0.49	4.43 ± 0.86	1.598	> 0.05
PT	11 ± 0.82	13.65 ± 1.31	-0.413	> 0.05
PTT	25 ± 1.67	34.32 ± 3.60	-0.351	> 0.05
Prothrombin fragments I & II	0.80 ± 0.33	1.59 ± 0.46	4.994	< 0.001
WBCs (x 10^3)	7.640 ± 2108	9.940 ± 3374	2.018	0.049
Hb	14.08 ± 2.05	11.52 ± 1.55	3.598	< 0.001
PLT (x 10^3)	287.500 ± 87.999	300.433 ± 93.941	0.383	> 0.05
ESR	6 ± 9.89	43.03 ± 14.69	5.102	< 0.001

Table 4: Correlation coefficient of prothrombin fragments I and II and some studied parameters among the patient group.

	Prothrombin Fragments I & II	
	r	p
Age	-0.039	> 0.05
Duration of illness	-0.005	> 0.05
Urea	0.368	0.020
Creatinine	0.160	0.05
Albumin	-0.555	0.000
Cholesterol	0.524	0.001
24 hours urinary protein	0.461	0.003
Ca	-0.370	0.019
Ph	0.428	0.006
Hb	0.403	0.010

Table 5: Correlation coefficient of pulmonary artery pressure and some studied parameters in the patient group.

	Systolic Pulmonary Artery Pressure	
	r	p
Age	0.044	> 0.05
Duration of illness	0.372	0.019
Steroid resistant	0.398	0.013
Creatinine	0.412	0.009
Systemic blood pressure	0.370	0.019
Pulmonary congestion	0.404	0.010
Serum albumin	-0.554	0.000
Serum cholesterol	0.531	0.001
24 hours urinary proteins	0.532	0.001
Prothrombin fragments I & II	0.368	0.002

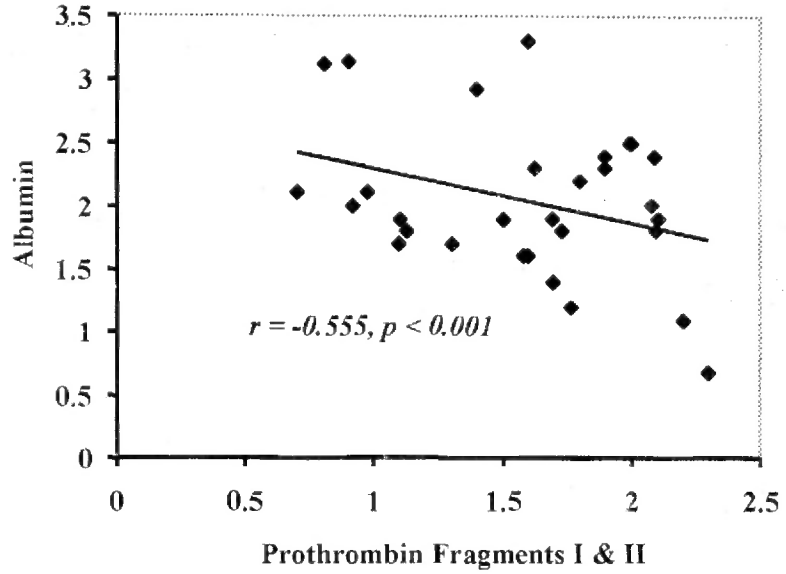

Fig. 1: Correlation coefficient of prothrombin fragments I & II and albumin.

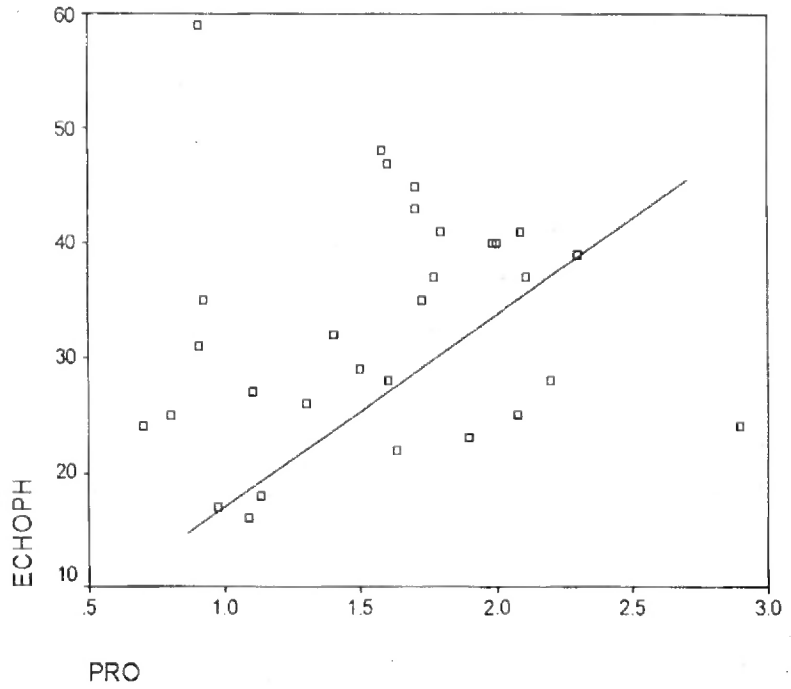

Fig. 2: Correlation coefficient of pulmonary hypertension with prothrombin fragments I & II and albumin.

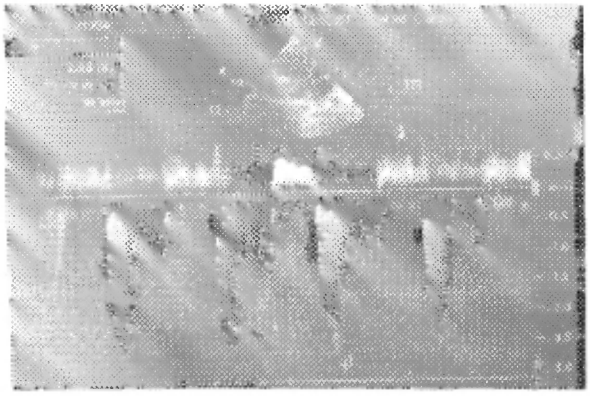

Fig. 3: CWF Doppler echocardiographic examination apical 4 chamber view showing tricuspid valve regurgitation with a maximum velocity of 2.88 m/s with recorded pressure gradient of 33.18 mm Hg giving rise to an estimated systolic pulmonary artery pressure (ESPAP) of 43.18 mm Hg.

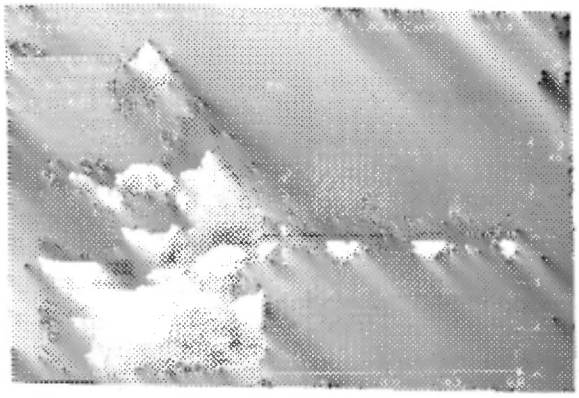

Fig. 4: CWF Doppler echocardiographic parasternal short axis view showing pulmonary regurgitation with a maximum velocity of 2.55 m/s with recorded pressure gradient of 26.06 mm Hg giving rise to an estimated diastolic pulmonary artery pressure of 36.06 mm Hg.

DISCUSSION

NS is associated with hypercoagulability and an increased tendency for thromboembolism[7]. The reported incidence of thromboembolic complications ranged from 1.8% to 6.6% in children with NS[7]. Although the NS is associated with hypercoagulability and an increased tendency for thromboembolism may occur anywhere, deep vein thrombosis and pulmonary embolism are most frequently encountered in the clinical setting[8]. Severe pulmonary embolism is a critical condition which needs emergency intervention, but minor embolism to the pulmonary arteries may not induce clinical symptoms, and occurs in up to 28% of patients by radionuclide lung perfusion study[8]. Recurrent pulmonary embolism as well as systemic hypertension may induce increased pulmonary pressure[18].

Doppler echocardiography has been proven to be a reliable non-invasive method for assessing pulmonary arterial pressure[19]. Although it is not an accurate direct measurement by itself, it has been suggested as the diagnostic method for early detection of primary pulmonary hypertension[20].

In our present study serum albumin level, urinary protein in 24 hours and serum cholesterol level showed a highly significant statistical difference between the patient and control groups, which is considered as an integral part for the definition of nephrotic syndrome ($p < 0.001$). Also there was a significant statistical difference between the two groups regarding urea ($p = 0.011$) and creatinine ($p = 0.039$) which were higher in patients than in controls. This difference may be attributed to a reduction in the GFR owing to intravascular hypovolemia. These results were in agreement with White et al.[21]. Regarding calcium level there was a significant statistical difference between the two groups as the calcium level was

significantly lower in patients ($p = 0.043$). This difference may be attributed to albuminuria and loss of the non-ionized calcium in urine. These results were in agreement with Ormeci et al.[22], as well as the phosphorus which was significantly higher in patients than controls ($p < 0.001$). This difference may be attributed to renal impairment in patients. These results were in agreement with Ormeci et al.[22]. As regards hemoglobin level, it was significantly lower in patients than in controls ($p < 0.001$). This difference may be due to loss of transferrin in urine. It was found that in the acute stage of the nephrotic syndrome there is a decrease in erythropoietin level, as well as gastrointestinal edema with poor absorption of nutrient elements needed for haemopoiesis. These results were in agreement with Feinstein et al.[23].

A hypercoagulable state is present in the nephrotic syndrome[24]. PT, PTT and prothrombin fragments I and II are considered important in the diagnosis of hypercoagulability in nephrotic syndrome[25]. In our study there was no significant statistical difference between the patients and controls regarding PT and PTT, although their levels were lower in patients than in controls. Regarding prothrombin fragments I and II, there was a highly significant statistical difference between patients and controls, being much higher in patients with nephrotic syndrome $p < 0.001$. These results were in agreement with Malyszko et al.[26], who found that hypoalbuminaemia leads to hepatic hyperfunction with subsequent increase in production of coagulation factors II, V, VII and X and fibrinogen which is activated to prothrombin fragment I and II. These coagulation factors lead to the hypercoagulable state of NS.

In this study, we evaluated the pulmonary pressure in children with NS using Doppler echocardiography. By measuring the systolic transtricuspid gradient, we found that pulmonary artery systolic pressure was > 30 mm Hg in 13 patients (32.5%), and > 40 mm Hg in 7 patients (17.5%). This indicated that 17.5% of the children with NS had increased pulmonary arterial pressure according to the newly recommended criteria of pulmonary hypertension[19]. Our findings were in agreement with that of Du et al.[27]. Our study showed that there was a high degree of correlation between systemic hypertension and pulmonary hypertension. These results were in agreement with Du et al.[27], who found that blood pressure was higher in children with NS compared to controls. Correlation between pulmonary pressure and duration of illness showed a significant relationship between both. These results were in agreement with Du et al.[27], who found that prolonged use of corticosteroids in treatment may be complicated by systemic hypertension which subsequently lead to pulmonary hypertension. Correlation between pulmonary pressure and hypoalbuminaemia showed a very strong relationship between both. These results were in agreement with Du et al.[27], who found that there is a high degree of statistical correlation of pulmonary hypertension and hypoalbuminaemia as hypoalbuminaemia may lead to generalized edema which consequently leads to interstitial pulmonary edema. Regarding hemoglobin level there was a

significant negative statistical correlation with pulmonary hypertension. These results were in agreement with Kemper et al.[28], who found that red blood cell breakdown releases red-cell arginase, which limits the availability of arginine to nitric oxide synthetase, resulting in a relative deficiency of nitric oxide. Nitric oxide is a very important regulator of pulmonary vascular tone and these results was in agreement with Sandoval[29], who found that prolonged anemia leads to heart failure with subsequent pulmonary hypertension.

Correlation between pulmonary pressure and level of prothrombin fragments I and II showed a very strong relationship between both. This indicates that the hypercoagulable state in nephrotic syndrome may be an important cause in the development of pulmonary hypertension.

In conclusion, pulmonary artery pressure is increased in children presenting with the nephrotic syndrome and may be due to systemic hypertension, hypercoagulability, hypoalbuminaemia and anemia. So, we recommend further studies over a large scale of patients and performing lung perfusion scanning or pulmonary artery angiography as well as measuring other procoagulable states such as factor V Leiden, protein C, protein S, and lupus anticoagulant to clarify the possible etiology of such an abnormality.

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