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STUDY ON THE ROLE OF VENTILATION-PERFUSION SCAN IN DETECTION OF SILENT PULMONARY EMBOLISM IN NEPHROTIC SYNDROME CHILDREN

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ABSTRACT **INTRODUCTION:** Clinically silent pulmonary thromboembolism is commoner than symptomatic one in children with nephrotic syndrome. The present study was done to look for the occurrence of asymptomatic pulmonary thromboembolism in children with nephrotic syndrome using V IQ scan, which is noninvasive, cost effective. **MATERIALS AND METHODS:** This prospective study conducted at a tertiary care centre over a period of one year on one hundred children with nephrotic syndrome between the ages of 5 and 15 years with a median age of 8 years attending the Pediatric Nephrology Clinic were taken up for the study. Patients showing defect in Tc99m-MAA perfusion scintigraphy underwent ventilation scan within 24-48 hours. Scan findings were interpreted by two nuclear medicine physicians independently who were unaware of illness of the patients. The results were interpreted according to Modified Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria. **RESULTS:** The overall incidence of abnormal V/Q scan in our study was 14%. Individually the incidence was 13.9% in group I, 22.22% in group II and 3.6% in group III, which indicates that patients with steroid resistant and steroid sensitive nephrotic syndrome in relapse were prone to develop thromboembolic complications more than those who were in remission. Combined scintigraphic evidence of pulmonary thromboembolism was 18.05% in Groups I and II compared to 3.6% in controls (Group III). **CONCLUSION:** Patients with abnormal ventilation-perfusion scan showed significantly larger ($p<0.05$) duration of illness (mean 69.7±55.3 months) and significantly greater degree ($p<0.001$) of proteinuria as compared to patients with normal ventilation-perfusion scan who had mean duration of illness of 45.5±38.0 months.

KEYWORDS :

INTRODUCTION:

Nephrotic syndrome, characterized by albuminuria, hypoalbuminemia, hyperlipidemia and edema is a common renal disease in children. Its incidence is reported to be 20 to 40 per million population, whereas in the Indian subcontinent the incidence is estimated at 90 to J 00 per million population (1). Venous thrombus formation is an important complication of nephrotic syndrome that arises particularly in the renal veins; but may be in the portal, pelvic or leg veins (2). Clinically silent pulmonary thromboembolism is commoner than symptomatic one in children with nephrotic syndrome. The incidence of symptomatic thrombotic events is greater in adults than in children (3). The cause of this age dependent change in symptoms is unclear (4). Most cases of pulmonary thrombosis occur at the time of massive generalized edema or in the diuretic phase ofnephrotic .syndrome (5). Most children do not have clinical features suggestive of thromboembolic phenomena. As pulmonary thromboembolism is a potentially fatal condition, its early diagnosis isimportant to initiate therapeutic management as early as possible. Ventilation-perfusion lung scintigraphy (V/Q scan) has good sensitivity and specificity for diagnosis of pulmonary thromboembolism in both symptomatic and asymptomatic patients. A high probability lung scan has a specificity of 98% for confirming the diagnosis of pulmonary embolism (6). There are only few studies and sporadic case reports on ventilation-perfusion lung scintigraphy done in children with nephrotic syndrome.

Since there is very less studies on Indian population, the present study was done to look for the occurrence of asymptomatic pulmonary thromboembolism in children with nephrotic syndrome using V IQ scan, which is noninvasive, cost effective and affordable to poor patients of developing countries.

MATERIALS AND METHODS:

This prospective study conducted at a tertiary care centre over a period of one year on one hundred children with nephrotic syndrome between the ages of 5 and 15 years with a median age of 8 years attending the Pediatric Nephrology Clinic were taken up for the study. Of 100 patients, 36 were steroid resistant, 36 were steroid sensitive with relapse and 28 were steroid sensitive in remission.Patient subgroup I. Comprised of 36 patients with steroid resistant nephrotic syndrome and 36 with steroid sensitive nephrotic syndrome in relapse.Patient subgroup II. Comprised of 28 children with steroid sensitive nephrotic syndrome in remission. None of the patients had history of dyspnea, chest pain, cough or hemoptysis and fever.All patirnts underwent physical examination, routine blood investigations and Chest Xray, Tc99m-MAA lung perfusion scintigraphy. Patients showing defect in Tc99m-MAA perfusion scintigraphy underwent ventilation scan within 24-48 hours. Scan findings were interpreted by two nuclear medicine physicians independently who were unaware of illness of the patients.The results were interpreted according to Modified Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria-High Probability > 80 defect.(7) Chi-square test, Student t-test were applied as appropriate. P value<0.05 was considered significant.

RESULTS:

One hundred children (75 boys and 25 girls) between the ages of 5 years and J 5 years with nephrotic syndrome were screened for scintigraphic evidence of pulmonary thromboembolism.

The mean and median age of these patients were 8.74±3.17 years (range 5-15) and 8.00 years respectively. Sex ratio was 3: 1 (M: F). Their mean and median duration of illness were 48.91±41.45 months (range 1-168) and 36 months respectively. Of these 100 patients, 36 were steroid resistant (Group I), 36 steroid sensitive in relapse (Group II) and 28 steroid sensitive in remission (Group III). The sex ratio was similar (M: F 3:1) in all groups.

Group I comprised of27 boys, 9 girls; Group II 27 boys, 9 girls and Group III of 21 boys, 7 girls. Groups I and II together were considered as patients and Group III as controls. Of 67 patients who underwent a D-dimer test, the test was positive in 61 patients.In Group I, 16 patients had positive, 1 had negative result; in Group II, 25 patients were positive, 1 was negative and in Group III, 20 showed positive and 4 showed negative result. Of 5 abnormal ventilation-perfusion scans in Group I, 2 patients had D-dimer positive and in rest 3 patients the test was not done. In other words, out of 16 patients with positive D-dimer result, 2 had abnormal ventilation-perfusion scan and rest 14 had normal scan.In Group II, out of 8 patients with abnormal scan 6 had positive result, 1 had negative result and in 1 patient test was not done. Out of 25 positive cases, 6 had abnormal scan whereas rest 19 had normal scan finding.In Group III, of 20 D-dimer positive cases only 1 had abnormal scan finding. D-dimer test showed a sensitivity of 90% (95% CI 54.1-99.5), specificity of 8.8% (95% CI 3.3-20), positive predictive value 14.8% (95% CI 7.4-26.7) and a negative predictive value of 83.3% (95% CI 36.5-99.1). Of 100 patients, 14 showed

ventilation-perfusion mismatch defects and normal chest X-ray. Therefore, overall incidence of significant abnormality on ventilation-perfusion scan was 14% . Of these, 5 out of 36 patients of Group I, 8 out of 36 in Group II and 1 out of 28 patients in Group III had ventilation-perfusion mismatch defects. Therefore, the incidence of ventilation-perfusion mismatch in Group I was 13.9%, in Group II 22.2% and in Group III it was 3.6% . Chi-square test applied to examine for any association of abnormal V/Q scan findings in different groups, did not show any difference (Pearson Chi-square value=4.551,P=0.103). Overall, the incidence was 18.1% (13 among 72) in cases as compared to 3.6% in controls. The Chi-square test applied to see the association of abnormality between cases (Group I + Group II) and controls (Group III), did not show significant differences (Pearson Chi-square value=2.4,P=0.12).(Table-1)Clinical, hematological and biochemical parameters of patients with abnormal ventilation-perfusion scan are displayed in.(Table-2) Patients with abnormal ventilation-perfusion scan showed significantly higher (P <0.05) duration of illness (mean 69.71±55.34 months) and significantly greater (P=0.001) proteinuria as compared to patients with normal ventilation-perfusion scan who had mean duration of illness of 45.45±37.99 months.Considering different hematological and biochemical parameters between cases (n=72) and controls (n=28), cases showed significantly higher (P=0.003) levels of blood urea (mean 24.59 ±10.10 mg/dL), significantly higher (P<0.008) nephrotic range of proteinuria, significantly lower (p=0.001) levels of serum albumin (mean2.25±0.95g/dL), significantly lower (p=0.001) levels of total serum protein (mean 4.89±1.10 g/dL) and significantly higher (p=<0.001) levels of serum cholesterol (mean 346.38±158.29 mg/dL) as compared to controls who showed mean value of 21.17±5.63 mg /dL,3.97±0.59 g/dL, 6.53±0.63 g/dL and 173.03±53.11 mg/dL respectively.(Table-2)

Table 1: Values (Mean ±SD) Of Different Parameters In Patients With Normal & Abnormal V/Q Scans

Findings on V/Q scan	Abnormal V/Q scan n=14	Normal V/Q scan n=86	p value
Age (years)	10.00±3.30	8.53±3.12	0.109
Duration of illness (months)	69.71±55.34	45.45±37.99	0.135
Duration of relapse/remission (months)	5.21±7.31	7.87±12.93	0.749
Hemoglobin (g/dL)	10.77±2.42	11.83±1.98	0.086
Total leukocyte count (/mm^3)	10254.28±3340.70	10218.29±5145.51	0.980
Serum Albumin (g/dL)	2.51±1.03	2.78±1.18	0.428
Total protein (g/dL)	5.23±1.20	5.37±1.25	0.699
Cholesterol (mg/dL)	306.21±145.25	295.89±160.27	0.822
Urea (mg/dL)	24.50±10.08	23.48±9.06	0.704
Creatinine (mg/dL)	0.58±0.15	0.66±0.23	0.215
Uric acid (mg/dL)	5.11±1.68	5.06±1.65	0.918
Nephrotic range proteinuria	0.92±0.26	0.63±0.48	0.003

Table 2: Values (Mean ± SD) Of Different Parameters Of Cases And Controls

	Group I+Group II n=(36+36) =72	Group III n=28	p value
Age (years)	9.12±3.17	7.75±2.99	0.051
Duration of illness (months)	50.51±42.61	44.50±38.51	0.529
Duration of relapse /remission (months)	7.17±12.92	8.32±10.74	0.679
Hemoglobin (g/dL)	11.49±2.11	12.19±1.88	0.139
Total leukocyte count /mm3	10496.52±5126.52	9525.92±4315.76	0.387
Serum Albumin (g/dL)	2.25±0.95	3.97±0.59	0.001
Total protein (g/dL)	4.89±1.10	6.53±0.63	0.001
Cholesterol (mg/dL)	346.38±158.29	173.03±53.1	0.001
Urea (mg/dL)	24.59±10.10	21.17±5.63	0.036
Creatinine (mg/dL)	0.63±0.24	0.69±0.15	0.286
Uric acid (mg/dL)	5.33±1.71	4.39±1.28	0.010
Nephrotic range proteinuria	0.9444±0.23	000.00	0.001

DISCUSSION:

On reviewing literatures, it was found that the most frequent site of thrombosis in nephrotic syndrome is the renal vein, with a reported incidence varying from 2-42% (8).Venous thromboses are frequently asymptomatic particularly in children and are only manifested by pulmonary embolism Pulmonary thromboembolism may often be asymptomatic in children with nephrotic syndrome (4). In children the reported rate of symptomatic thromboembolic complication varies from 1.8% by Egli et al (9) to 5.3% by Mehls et al (3). Hoyer et al investigated 26 asymptomatic children and found pulmonary embolism in 26.9% cases (10).

We conducted the study primarily to evaluate the role of ventilation-perfusion lung scan for screening asymptomatic pulmonary thromboembolism in children with nephrotic syndrome. We attempted to find out if there was any relation between age, duration of illness, serum albumin, total protein, cholesterol, urea, creatinine, uric acid, hemoglobin, total leukocyte count and D-dimer with the occurrence of abnormal V/Q scan, which is consistent with pulmonary thromboembolism. The most obvious benefit of post-perfusion ventilation imaging is the ability to tailor the study to the findings on the perfusion scan, performing the study in the same projection that best demonstrated the most significant perfusion abnormality. If the perfusion images are normal, the ventilation study can be obviated altogether (11).

Of 100 patients, 14 showed abnormal V/Q scan consistent with pulmonary thromboembolism and 86 normal V/Q scan findings. The overall incidence of V/Q scan abnormality consistent with pulmonary embolism in our study was 14%. The incidence was 13.9% in steroid resistant nephrotic syndrome (Group I), 22.2% in steroid sensitive nephrotic syndrome with relapse (Group II) and 3.6% in steroid sensitive nephrotic syndrome in remission (Group III). Though there was a trend towards occurrence of more V/Q scans abnormalities in children with steroid resistant and relapsing steroid sensitive nephrotic syndrome, differences between these groups were not significantly different from the controls (p=0.1). Only a prolonged duration of nephrotic syndrome and presence of nephrotic range proteinuria were found to be significantly associated with abnormal V/Q scan findings. We examined the blood for D-dimer in 67 children with nephrotic syndrome. Only a few authors have applied this test in this group of patients in the past. Mattia et al (12) found no change in levels of plasma D-dimer at any stage of the period of illness in children with nephrotic syndrome. We found that presence of D-dimer of more than 250ng /ml in blood has a sensitivity of 90% (95% CI 54.1-99.5), specificity 8.8% (95% CI 3.3-20), positive predictive value 14.8% (95% CI 7.4-26.7) and negative predictive value of 83.3% (95% CI 36.5-99.1) for detecting a V/Q scan abnormality. Positive D-dimer results in the present study indicate an enhanced fibrin formation and degradation in patients with nephrotic syndrome. The patients who show a positive D-dimer result but normal findings on V/Q scan may indicate ongoing production and lysis of microthrombi, the significance of which is uncertain.

Three of our patients developed symptomatic thrombotic episodes, involving large vessels on follow-up. The diagnosis of thrombotic event was suspected clinically and confirmed by Doppler ultrasound. Among them one was 5-yr-old boy with steroid resistant nephrotic syndrome, who developed thrombosis of axillary vein and subclavian vein on right side (diagnosed on Doppler ultrasound). A 10-yr-old girl with steroid resistant nephrotic syndrome child showed thrombosis of left femoral vein (Doppler ultrasound). The third patient had steroid sensitive nephrotic syndrome in relapse, who had thrombosis of femoral vein and saphenous vein on right side (diagnosed on Doppler ultraultrasound). All the three patients had serum albumin level < 2.5g/dL (1.7g/dL, 1.8g/dL and 2.2g/dL respectively) and they showed scintigraphic evidence of high probability for pulmonary embolism. They were managed with subcutaneous heparin and oral warfarin. This shows the importance of screening for asymptomatic pulmonary thromboembolism by lung scintigraphy which otherwise might lead to serious complications in 3-5% cases.Only 14% of our patients with nephrotic syndrome showed scintigraphic abnormalities. This occurrence is less than the figure of 27.9% reported by Hoyer et al (10). The incidence rate in remission of our study population was much less than the incidence rate in remission group conducted by P.F. Hoyer et al (10), which was 27.9%.

The incidence of thromboembolism and coagulation profiles in nephrotic children and adults were compared by Mehls et al (3). The incidence of thromboembolism was 5.3% in children and 43.9% in adults. In children 5 had arterial thrombosis, 4 had venous thrombosis

and 2 had pulmonary embolism. The incidence was more (14%) in our study population. There was no significant correlation between proteinuria (g/24 h/1.73 m^2) and serum albumin concentration (g/dL) in either children (r=0.41) or adults (r=0.017). They have described that despite the lower incidence, thromboembolic complications tended to be more severe in children. There was no correlation between the occurrence of pulmonary embolism and biochemical parameters. They also evaluated cases of nephrotic syndrome with asymptomatic thromboembolism that was consistent with our study objective, the exception being age of patients. There was no correlation between the occurrence of pulmonary embolism and severity of hematological and biochemical abnormalities, except for the association with elevated levels of fibrinogen and reduced levels of AT-III. We found serum albumin levels ≤2g/dl in 3 patients with steroid resistance, 5 steroid sensitive of steroid resistant and 5 with steroid sensitive nephrotic syndrome in relapse who had scintigraphic evidence of pulmonary thromboembolism. Serum albumin <2g/dL is found to be an important factor favoring thrombosis in patients with nephrotic syndrome (8,13,14,15,16).

CONCLUSION:

Children with nephrotic syndrome are at considerable risk for developing pulmonary thromboembolism, which may be asymptomatic.There was no significant difference in the occurrence of scintigraphic evidence of thromboembolic events between patients with steroid resistant and steroid sensitive nephrotic syndrome in relapse.Patients with abnormal ventilation-perfusion scan showed significantly larger ($p<0.05$) duration of illness (mean 69.7±55.3 months) and significantly greater degree ($p<0.001$) of proteinuria as compared to patients with normal ventilation-perfusion scan who had mean duration of illness of 45.5±38.0 months.As a screening test, D-dimer test was found to have a good sensitivity to detect a thromboembolic event, but poor specificity to rule out the same.

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