Risk Factors of Pulmonary Thrombosis/Embolism in Nephrotic Syndrome

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Abstract: *Background:* Nephrotic syndrome is associated with an increased risk for thromboembolic complications. Until now, few studies have ever specified the risk of pulmonary thrombosis/embolism (PTE) in patients with nephrotic syndrome. In this study, we assessed the risk of PTE in a large cross-sectional study to identify risk factors in this population. *Methods:* Three hundred twelve patients with NS who had screened PTE through lung ventilation-perfusion scan were collected and analyzed. Multivariate Logistic regression was used to detect the independent risk factors for PTE. Logistic regression was used to identify the threshold value of D-dimer. *Results:* Sixty-five patients (20.8%) had PTE in individuals with NS. Elevated level of plasma D-dimer was identified as an independent risk factor of PTE on multivariate analysis (odds ratio = 1.54; 95% confidence interval: 1.27–1.88). While proteinuria at presentation and serum albumin were not associated with PTE after adjusted for D-dimer ($P > 0.05$). The cumulative probability of PTE was in a nearly linear association with the plasma D-dimer level even within the normal range. Based on the plasma D-dimer level, we had developed a concise model to predict the risk of pulmonary embolism using logistic curve. *Conclusions:* In adult patients with NS, high level of plasma D-dimer was closely associated with PTE, whereas proteinuria or serum albumin level was not in this study. Using plasma D-dimer level, we developed a concise model to predict the risk of PTE.

Key Indexing Terms: Risk Factors; Pulmonary Thrombosis; Embolism; Nephrotic Syndrome. **[Am J Med Sci 2014;348(5):394–398.]**

It has long been recognized that nephrotic syndrome (NS) is associated with an increased risk of thromboembolic complications, including deep venous thrombosis, renal vein thrombosis and pulmonary thrombosis/embolism (PTE).[1] It is estimated that the incidence of thromboembolism may be as high as 25% in adult patients.[2] This risk varies with the renal histology and seems to be greater for membranous nephropathy, focal segmental glomerularsclerosis or lupus nephritis.[2–6] Other risk factors, including male gender, cancer history, the level of serum albumin and cholesterol, previous thromboembolic episodes and heavy proteinuria, may be also associated with the thrombosis events.[3,7] Adults with membranous nephropathy seem to be at greatest risk for development of thromboembolism.[2,5,7] Cohort studies have shown that 7.2% to 19.2% of patients with membranous nephropathy would develop clinically apparent thromboembolism complications.[7]

Until now, few studies have ever specified the risk of PTE, one of the most life-threatening complications in NS.[8,9] Additionally, reported risks are mostly based on multiple case reports and small studies. In this study, we assessed the risk of pulmonary embolism or thrombosis in a large, single center, cross-sectional study and attempted to identify risk factors in this population.

MATERIALS AND METHODS

Design

We retrospectively analyzed all the consecutive patients with NS who had received PTE screening using lung ventilation and perfusion scan in the Peking University First Hospital between 2001 and 2011. The prevalence of PTE and its risk factors were investigated in this cross-sectional study.

Participants

All the patients with NS and received lung ventilation and perfusion scan were included in this study. The major inclusion criteria in this study included: age ≥14 years, fulfilled the diagnostic criteria of NS including proteinuria >3.5 g/d and serum albumin <30 g/L with edema and or hyperlipidemia. Major exclusion criteria included: history of PTE before the diagnosis of NS, pneumonia, pulmonary malignancy and chronic obstructive pulmonary disease.

The ethics committee of Peking University First Hospital approved the study.

Data Collection

Clinical assessment of each participant included a review of the medical records with respect to history of NS, blood pressure measurements, history of smoking, hemoglobin, platelet count, serum albumin, serum lipids profile, plasma fibrinogen, D-dimer, urinalysis, quantification of proteinuria, blood urea nitrogen and serum creatinine. Clinical signs and symptoms of pulmonary embolism were recorded, including dyspnea, hemoptysis, chest pain, hemoptysis and syncope. Pathological assessment included the pathological diagnosis of each patient. Medication was also recorded, including the dose and duration of diuretics and corticosteroids.

Lung Ventilation and Perfusion Scintigraphy

In the local practice, patients with NS would receive lung ventilation and perfusion scintigraphy for PTE screening. The results of ventilation and perfusion (V/Q) scintigraphy were interpreted as high, intermediate, low or very low probability

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and normal, using the refined modified prospective investigation of pulmonary embolism diagnosis criteria.[10] The results of V/Q scintigraphy combined with chest radiographs were diagnosed as PTE when they were categorized as high or intermediate probability.

Statistical Analyses

All statistical analyses were performed using SAS 9.2 (Cary, NC). Continuous variables were presented as mean value and SD (mean ± SD) or median and range as appropriate. Categorical variables were summarized as frequency and percentage. Differences among the different groups were tested by using the χ^2 test or Fisher's exact test in qualitative parameters, and the nonparametric Wilcoxon's rank-sum test in quantitative parameters. Differences were considered significant at the 0.05 level.

Univariate analysis followed by multivariate logistic regression analysis with stepwise variable selection procedure was applied to identify independent factors associated with pulmonary embolism event. All baseline variables entered the initial model and were maintained if $P < 0.10$.

The cumulative probability of pulmonary embolism was calculated by logistic regression. The function to calculate the probability of event was:

$$P = \frac{e^{-a+bx}}{1 + e^{-a+bx}}$$

P denoted the probability of pulmonary embolism; x denoted independent risk factor, that is, D-dimer at baseline. Thus, we calculated the values of D-dimer to make the probability were 10% and 90%. The high-risk threshold of D-dimer was that made the cumulative probability of pulmonary embolism reached 90%. The low-risk threshold of initial D-dimer was which made the cumulative probability of pulmonary embolism less than 10%.[11]

RESULTS

Baseline Characteristics

A total of 312 patients with NS who underwent evaluation at the Peking University First Hospital from 2001 to 2011 were included in the analysis. Baseline characteristic of all patients with NS with and without PTE were listed in Table 1. Overall, 65 (20.8%) patients were found PTE by means of lung ventilation and perfusion scintigraphy. In patients with PTE, 49 (75.4%) were male with a mean age of 43.6 ± 17.7 years at diagnosis. The mean duration of NS was 17.7 ± 37.7 months. Serum creatinine was 128.0 ± 124.5 μmol/L and mean artery blood pressure 93.0 ± 10.9 mm Hg. The serum albumin was 21.1 ± 4.2 g/L and proteinuria 7.93 ± 4.23 g/d. The level of serum fibrinogen was 5.42 ± 8.53 g/L and D-dimer 2.05 ± 1.91 mg/L. Only 16 (24.6%) of these patients had symptoms or signs of pulmonary embolism, including dyspnea in 12 (18.5%), hemoptysis in 3 (4.6%), chest pain in 3 (4.6%) and syncope in 3 (4.6%) patients. As shown in Table 1, patients with NS with PTE had higher platelet count, serum cholesterol, urine protein and D-dimer than those without PTE ($P < 0.05$).

Pathological characteristics of patients with and without PTE were shown in Table 2. Membranous nephropathy was strongly associated with the development of PTE. Among the 42 patients with PTE who had received kidney biopsy, 35.4% (n = 17) attributed to membranous nephropathy compared with 20.3% among those without PTE ($P = 0.027$).

Risk Factors of Pulmonary Embolism

Results of the univariate and multivariate logistic regression analyzing risk factors of PTE in NS were shown in Table 3. On the univariate logistic regression, sign of pulmonary embolism (odds ratio [OR] = 2.24; 95% confidence interval [CI]: 1.14–4.40), hemoptysis (OR = 6.34; 95% CI: 1.04–38.84), heart rate (OR = 1.04; 95% CI: 1.01–1.06), proteinuria (OR = 0.93; 95% CI: 0.87–0.99) and plasma level of D-dimer (OR = 1.61; 95% CI: 1.34–1.95) were associated with the development of PTE. As shown in Table 3, on multivariate logistic regression, only D-dimer was independent risk factor of PTE (OR = 1.54; 95% CI: 1.27–1.88).

Using D-dimer as the independent variant, we could calculate the cumulative probability of PTE of each patient by multivariate logistic regression. The cumulative probability function was as follows:

$$P = \frac{e^{-2.057+0.477\text{D-dimer}}}{1 + e^{-2.057+0.477\text{D-dimer}}}$$

P denotes the probability of PTE. D-dimer denotes the value of D-dimer (mg/L). The logistic curve was shown in Figure 1. The risk of PTE was almost linear calculated by the value of plasma D-dimer. When D-dimer was lower than 0.5 mg/L, the cumulative risk of PTE was lower than 10%. Then, the risk grew rapidly with the increase of D-dimer. When D-dimer was higher than 8.9 mg/L, the probability of PTE was higher than 90%. Thus, we identified 0.5 mg/L as the threshold value of plasma D-dimer in patients with NS associated with increased risk of PTE. "Sensitivity" of this threshold in predicting PTE (using pulmonary V/Q scan to diagnose PTE) was 75.4%; "specificity" was 42.5%. The false-positive rate, false-negative rate, positive predictive value and negative predictive value were 73.5%, 9.5%, 26.5% and 90.5%, respectively.

The plasma D-dimer level may be influenced by antithrombotic agents used. We also perform a sensitivity analysis among the 286 patients without antithrombotic therapy. The results were consistent with the whole population (see **Tables S1–S3**, **Figure S1**, **Supplemental Digital Content**, http://links.lww.com/MAJ/A58).

DISCUSSION

In this large observational study, we had firmly confirmed that NS was a high-risk factor for PTE. More than 20% of this population had symptomatic or asymptomatic PTE. Interestingly, we did not found urine protein or serum albumin level was associated with the development of PTE, which had been found risk factors for renal vein thrombosis in other reports. We had identified plasma D-dimer level was closely associated with the risk of PTE in NS. Additionally, we have developed a concise model to predict probability of PTE based on plasma D-dimer. The risk of PTE increased rapidly in a linear association when plasma D-dimer was more than 0.5 mg/L. When plasma D-dimer was reaching 8.9 mg/L, the cumulative probability of PTE was about 90%. Thus, our study provided an easy way to predict the PTE risk in NS. This finding will be of importance for the kidney clinical practice.

Thrombosis was one of the most important complications in NS,[2,12] as shown in our study, especially in patients with membranous nephropathy. Several mechanisms have been suggested for the development of thrombosis in NS, including imbalance between prothrombotic and antithrombotic factors, hyperviscosity and increased platelet aggregation.[2,9,12–15] Recent guidelines have suggested prophylactic anticoagulation in patients with risk of thrombosis including serum albumin drops