ORIGINAL PAPER

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Histological diagnosis and risk of renal vein thrombosis, and other thrombotic complications in primitive nephrotic syndrome

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Abstract

Background: The risk of thromboembolic events is increased in patients with nephrotic syndrome (NS) as compared with other medical conditions and is a severe complication associated with significant morbidity and mortality. We aimed to assess the risk of renal vein thrombosis, and other venous thromboembolic events (VTE) in a large cohort of patients with NS and to identify the disease-specific risk for VTE. *Patients and Methods*: We performed a prospective observational study including consecutive adult patients with primitive NS admitted to our department. Clinical and biological data were obtained every six months during follow-up. Occurrence of VTE confirmed by imaging techniques was the primary study outcome. *Results*: We enrolled 191 patients (47±15 years, 53% men) with a median follow-up of 24 [IQR:12,36] months. During follow-up, 23 VTE occurred, of which 65.2% in the first six months. The disease-specific risk of VTE during the follow-up period was different across the histological groups, with the lowest risk in minimal change disease and IgA nephropathy and the highest in membranous nephropathy and membranoproliferative glomerulonephritis patients. In the subgroup of membranous, the severity of the subepithelial electron dense deposits did not correlate with the risk for VTE (p=0.5). *Conclusions*: In this prospective study, the risk of VTE was higher in the first six months of follow-up in NS patients. The histological pattern seems to influence the risk of VTE in this setting.

Keywords: renal vein thrombosis, nephrotic syndrome, membranous nephropathy, thromboembolic events.

Introduction

Venous thromboembolic events, along with infections are the most important cause of morbidity and mortality in nephrotic syndrome patients [1, 2]. Thromboembolic events are complicating the evolution of nephrotic syndrome patients regardless of the fact that gromerular disease has occurred in native or grafted kidney. Venous thromboembolic complications, which occur in nephrotic syndrome, include deep venous thrombosis, pulmonary embolism and especially renal vein thrombosis [1, 3, 4].

There is a large variability regarding the rate of reporting venous thromboembolic complications, including renal vein thrombosis, in patients with nephrotic syndrome, most probably due to methodological limitations, among which retrospective study designs and the lack of standardized and accurate methods for detecting venous thrombosis [2, 3, 5–8].

Renal vein thrombosis (RVT) is rarely met in patients without nephrotic syndrome or a subjacent renal malignancy [9, 10]. The prevalence of RVT in patients with the nephrotic syndrome ranges from 5% to over 60% [1–4].

Although several predictive factors for the risk of developing venous thromboembolic events have been identified in these patients, there is not enough data in the literature to determine the individual risk of each patient with nephrotic syndrome to develop such an event and implicitly, a prophylactic therapeutic indication [11, 12].

Several studies investigated the histological pattern as an independent risk factor for VTE. Data regarding the histological pattern impact on VTE risk in patients with primitive NS are controversial [1, 2].

We sought to prospectively assess the risk of VTE and the predictive value of histological diagnosis for VTE occurrence in patients with primitive NS.

Patients and Methods

Study design

This is a prospective single centre study. Data were obtained at the first admission, and every six months thereafter. Blood tests were also performed in case of an incident VTE.

Patients

All consecutive patients with primitive NS admitted

to our department were considered for inclusion. The diagnosis of NS was confirmed by a persistent protein excretion greater than 3.5 g/24 h and hypoalbuminemia (<3 g/dL).

Exclusion criteria were age under 18 years, an identified condition responsible for glomerulonephritis (for example HBV, HCV infection, SLE, drugs, malignancy, autoimmune diseases, etc.), history of venous or arterial thromboembolic, eGFR ≤40 mL/min./1.73 m^2, and therapy influencing hemostasis (antiplatelet drugs, anticoagulants).

All patients were treated with immunosuppressive therapy and corticosteroids, according to the underlying condition.

Study parameters

The estimated glomerular filtration rate (MDRD formula), proteinuria (24 hours urine collection), serum albumin and blood lipids (cholesterol and triglycerides) were measured at study moments. D-dimers (DDi) were used as markers of intravascular thrombosis.

All the assays were performed in "Fundeni" Clinical Institute laboratories, Bucharest, Romania, on the day the specimens were obtained. DDi were assessed using coagulation analyzer CS-2100i (Sysmex Corporation) and commercial kits (Siemens AG).

Protocol for pathological examination

Kidney histological samples obtained through ultrasound-guided biopsy or during surgery were analyzed by optical microscopy (OM), immunofluorescence (IF) and electronic microscopy (EM) at the Ultrastructural Pathology Lab, "Victor Babeş" National Institute of Pathology, Bucharest, Romania.

The samples have been harvested with GBL 16G guillotine needles, rapidly placed in saline, and divided as follows: 2 mm of tissue ends were separated with a sharp razor blade and placed in 4% buffered glutaraldehyde, while the middle part was placed in a cryostat for frozen sections after being checked for glomeruli with a stereomicroscope. The frozen sections have been stained with FITC-conjugated antibodies for routine diagnostic. The 1-mm^3 fragments fixed in glutaraldehyde for over four hours, have been later washed overnight in cacodylate buffer, and post-fixed for one hour in 1% osmium tetroxide. This procedure was followed by the classical technique of dehydration in alcohols and embedding in Epon.

The semithin Toluidine Blue stained sections have been used for light microscopy examination, and next oriented thin sections were prepared for electron microscopy. The ultrathin (60 nm thick) have been double stained with uranyl acetate and lead citrate (Raynolds solution). The examination was performed with a JEM-1011 electron microscope. The images were captured with a Megaview G2 CCD camera, and the resolution was enhanced through the iTEM multiple image alignment.

Membranous nephropathy (MN) stadialization was performed according to Ehrenreich and Churg criteria [13].

Protocol for diagnosis of thromboembolic events: thromboembolic events were suspected in the presence of serum D-dimer levels higher than 2 mcg/mL at any time during the study and/or the presence of clinical signs. Moreover, patients were educated to recognize signs and symptoms of thromboembolic events (for example asymmetric tumefaction of limbs, unilateral pain in the limbs, thoracic pain, cough, dyspnea, hemoptysis, etc.).

The diagnosis of venous thromboembolic events was established by color Doppler vascular examination for deep venous thrombosis of the lower limbs, color Doppler vascular examination and spiral computed tomography for thrombosis of the renal vein and/or cava vein, and thoracic spiral CT scan in patients with suspicion of pulmonary embolism.

Statistical analysis

Data distribution was evaluated with Jarque–Bera test. Normally distributed variables were expressed as mean and standard deviation. Non-parametric variables were described as median (lower quartile and upper quartile). For continuous variables, differences between groups were assessed with Student's *t*-test or Mann–Whitney *U*-test, according to their distribution. Categorical variables were compared with the χ^2-test. All *p*-values are two-tailed, and a $p<0.05$ considered statistically significant. The time to event was measured from baseline to the moment of a documented VTE. Kaplan–Meier survival free of event (VTE) curves were drawn. Statistical analysis was performed with SPSS for Windows version 17.0 (SPSS, Inc., Chicago, IL, USA).

Results

The study population included 191 patients with primitive NS. The mean age was 47±15 years and 53% were male.

Membranous nephropathy (29%), focal segmental glomerulosclerosis (25%), IgA nephropathy (18%), membranoproliferative glomerulonephritis (15%) and minimal change disease (13%) were found at kidney biopsy.

The baseline proteinuria and serum albumin were 7.9±1.9 g/day and 2.34±0.74 g/dL, respectively. The renal function was only marginally impaired (eGFR 74± 19.4 mL/min./1.73m^2). Hypercholesterolemia and hyper-triglyceridemia (304±52 mg/dL and 239±46 mg/dL) were also noted.

The median follow-up was 24 [IQR:12,36] months per patient (Table 1).

Table 1 – ***Patients characteristics at baseline***

Parameter	All	With VTE	Without VTE	*P**
No. of patients	191	23	168	
Age [years]	47.2±14.6	48.6±14.1	46.8±13.4	0.57
Gender [% male]	53.4	56.5	53.6	0.65
Median time to VTE or end of the study [months]	24 [IQR:12,36]	4 [IQR:2,9]	24 [IQR:12,36]	<0.001
eGFR [mL/min./1.73m^2]	74±19	78±19	73±19	0.28
PLT [×10^3/mm^3]	273±56	281±54	272±59	0.45
Proteinuria [g/24 h]	7.86±1.9	9.36±1.8	7.7±1.8	<0.001
Serum albumin [g/dL]	2.34±0.74	1.3±0.5	2.50±0.67	<0.001

Parameter	All	With VTE	Without VTE	*P**
Duration of hypoalbuminemia [months with serum albumin <2 g/dL]	12 [IQR:6,16.5]	12 [IQR:12,12]	12 [IQR:6,18]	0.6
Serum cholesterol [mg/dL]	304±52	314±63	303±51	0.4
Serum triglycerides [mg/dL]	239±46	242±52	239±45	0.77

*Patients with VTE *vs.* without VTE. eGFR – Estimated glomerular filtration rate; PLT – Platelets; VTE – Venous thromboembolic event.

During follow-up, a VTE occurred in 23 (12%) patients with an incidence of five events per 100 patients-year (Table 1). Membranous nephropathy was the most frequent associated condition with thromboembolic complications (20%, incidence rate 11.5% patients-year), followed by membranoproliferative glomerulonephritis (14%, incidence rate 5% patient-year).

The median time from baseline to VTE for the entire study population was four months [IQR:2,9]; 65% of VTE occurred in the first six months and 96% in the first year. The cumulative probability of event-free survival abruptly decreased to 93% and 89% at six and 12 months, and remained stable thereafter.

In the group of patients with MN, the median time from baseline to VTE was three months [IQR:1,4]; 91% of the VTE registered during follow-up period occurred in the first six months from study enrolment and 100% during the first year. In the group of patients diagnosed with membranoproliferative glomerulonephritis, the median time to VTE was 9.5 months [IQR:6,11.5]; 25% of the VTE occurred in the six months of the follow-up period and 100% during the first year (Figure 1).

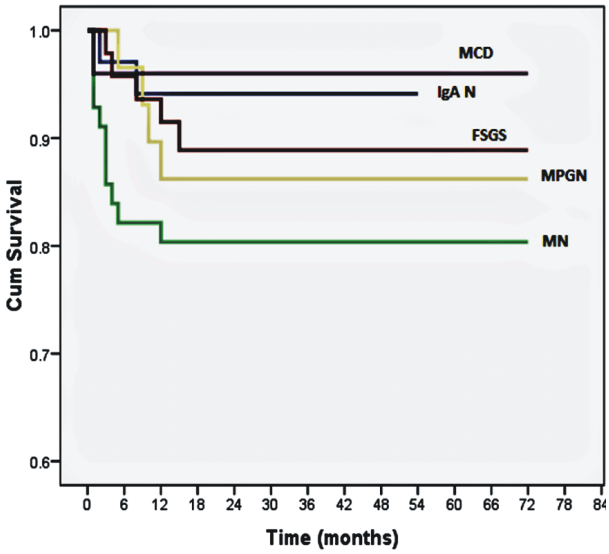

Figure 1 – ***The risk of VTE in the follow-up period by underlying nephropathy (across groups). VTE – Thromboembolic events; MN – Membranous nephropathy; FSGS – Focal segmental glomerulosclerosis; IgAN – IgA nephropathy; MPGN – Membranoproliferative glomerulonephritis; MCD – Minimal change disease. Kaplan–Meier analysis.***

Renal vein thrombosis was identified in 13% of cases. In one patient diagnosed with MN, renal vein thrombosis was bilateral and was followed by acute renal failure and pulmonary embolism. DVT (34.8%) and pulmonary embolism (26.1%) were the most common VTE, followed by other vein thrombosis (Table 2).

Table 2 – ***Frequency and type of venous thromboembolic events according to the underlying glomerulonephritis***

VTE, *n*	All (*n*=191)	MN (*n*=56)	FSGS (*n*=47)	IgAN (*n*=34)	MPGN (*n*=29)	MCD (*n*=25)
DVT	8	4 (36.4%)	1 (20%)	1 (50%)	1 (25%)	1 (100%)
PE	6	2 (18.2%)	1 (20%)	1 (50%)	2 (50%)	0
RVT	2	1 (9.1%)	1 (20%)	0	0	0
PE + RVT	1	1 (9.1%)	0	0	0	0
PE + DVT	3	1 (9.1%)	1 (20%)	0	1 (25%)	0
Other	3	2 (18.2%)	1 (20%)	0	0	0
All	23	11	5	2	4	1
Prevalence of VTE [%]	12	20	11	5.9	13.8	4

VTE – Thromboembolic events; DVT – Deep vein thrombosis; PE – Pulmonary embolism; RVT – Renal vein thrombosis; MN – Membranous nephropathy; FSGS – Focal segmental glomerulosclerosis; IgAN – IgA nephropathy; MPGN – Membranoproliferative glomerulonephritis; MCD – Minimal change disease.

Although VTE seemed to occur more frequently in membranous nephropathy (20%) and membranoproliferative glomerulonephritis (13.8%) than in focal segmental glomerulosclerosis (11%), IgA nephropathy (6%) and minimal change disease (4%) the difference was not statistically significant (p=0.2). Even though there was no statistically significant difference in terms of frequency, the incidence rate of VTE was significantly higher in patients having MG (11.5% patients-year), MPGN (5% patients-year) and FSGS (3.8% patients-year) compared with MCD (1.4% patients-year) and IgAN (2.3% patients-year) (Figure 2).

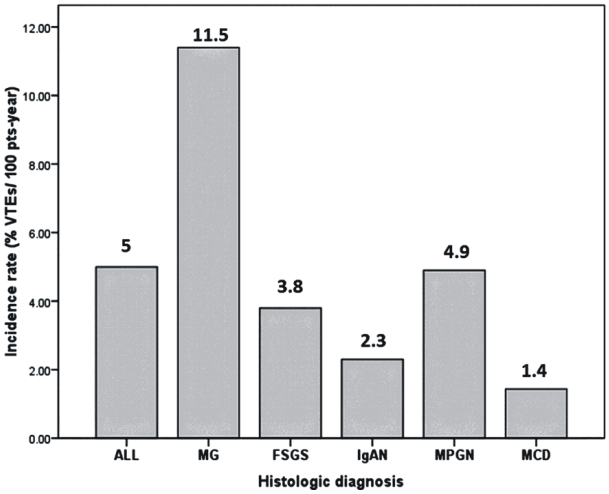

Figure 2 – ***Incidence rate of VTEs. VTE – Thromboembolic events; MG – Membranous glomerulopathy; FSGS – Focal segmental glomerulosclerosis; IgAN – IgA nephropathy; MPGN – Membranoproliferative glomerulonephritis; MCD – Minimal change disease.***

The maximum incidence of VTE was registered in the group of patients diagnosed with MN, this being the reason why we have analyzed the relationship between the severity of lesions in glomerular basement membrane (GMB) and the risk for VTE in this group (Figure 3).

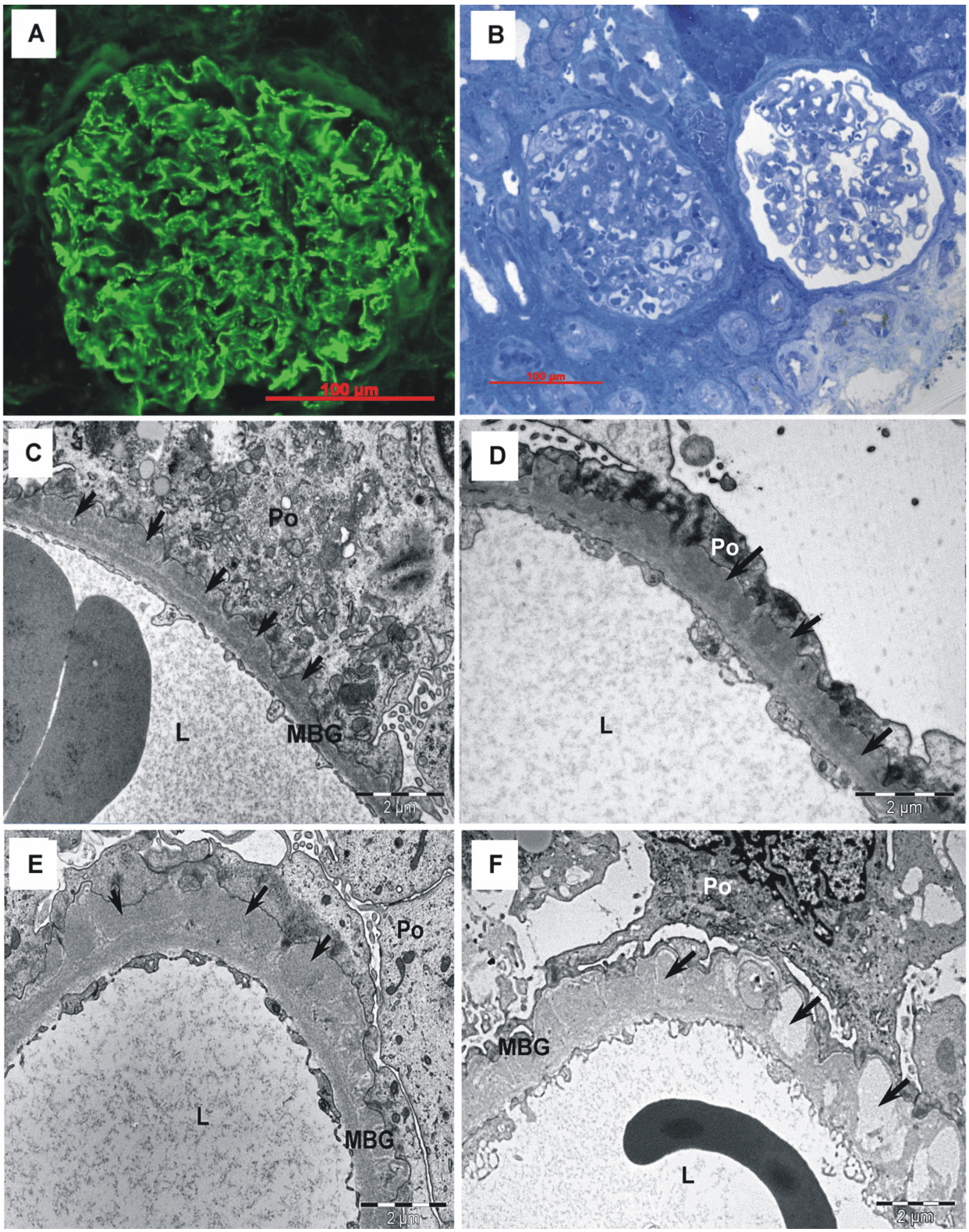

Figure 3 – ***Membranous glomerulonephritis. Direct immunofluorescence (A) proves the IgG granular deposits on the glomerular capillaries walls (FITC conjugated antibody). Light microscopy (B) on semithin section (Toluidine Blue) shows the increase of glomerular capillaries walls thickness. Electron microscopy shows differences between stage I (C), stage II (D), stage III (E) and stage IV (F) of membranous glomerulonephritis. The arrows in both electron microscopy pictures (C–F) are pointing out dense deposits on the subepithelial face of the glomerular basement membrane (GBM). Note the diffuse effacement of the foot processes of podocytes (Po) covering dense deposits. L – Glomerular capillary lumens.***

The prevalence of VTE was 13% in the subgroup of patients with stage 1 MN *vs.* 20% in the subgroup of patients with stage 2 MN *vs.* 23.5% in the subgroup of patients with stage 3 MN *vs.* 22% in the subgroup of patients with stage 4 MN (p=0.5) (Table 3).

Table 3 – ***Frequency of venous thromboembolic events according to the membranous nephropathy stages***

	MN (*n*=56)	MN 1 (*n*=15)	MN 2 (*n*=15)	MN 3 (*n*=17)	MN 4 (*n*=9)	*P*
VTE, n	11	2	3	4	2	
Prevalence of VTE [%]	20	13	20	23.5	22	0.5

VTE – Thromboembolic events; MN – Membranous nephropathy; MN 1 – Stage 1 membranous nephropathy; MN 2 – Stage 2 membranous nephropathy; MN 3 – Stage 3 membranous nephropathy; MN 4 – Stage 4 membranous nephropathy.

Discussion

The study group enlisted 191 patients with primary NS, with a mean age of 47 years, 53% of which were male. The severity of NS requires emphasis, since baseline mean proteinuria for the entire group was 7.8 g/day, while serum albumin concentration was 2.4 g/dL. Baseline renal function, assessed by eGFR, was 74 mL/min./1.73 m^2. In contrast, the largest study published so far which prospectively investigated hypercoagulability in patients with nephrotic syndrome enrolled 151 such patients, with a mean serum albumin concentration of 2.4 g/dL and proteinuria of 5.8 g/day, the majority of which (69 patients) had membranous glomerulopathy [1]. Among our study group, 29% had membranous glomerulopathy, 25% focal segmental glomerulosclerosis, 18% IgA nephropathy, 15% membranoproliferative glomerulonephritis, and 13% had minimal change nephropathy respectively. Although our study enrolled consecutive adults with NS, there was a remarkably increased proportion of patients with membranoproliferative glomerulonephritis and IgA nephropathy, relative to reports of other consecutive series of renal biopsy in such patients.

Unlike other studies, we used DDi level assessment as a screening method for VTE. The VTE incidence confirmed by imaging techniques was 12% and 69% of these events were asymptomatic. This higher incidence, as compared with other reports, could result from using a VTE screening method in our study [5]. Median follow-up time in our study was 24 [IQR:12,36] months. Median time to first VTE was four months [IQR:2,9], and 65% of the events occurred in the first six months and 96% in the first year.

Although the risk of venous thromboembolism (VTE) in patients with nephrotic syndrome is universally acknowledged, the actual incidence of VTE in such patients has not been established to date. The reported cumulative incidence rates range between 3% and 60%, while different study designs, diagnosis protocols and therapies which have been used prevent comparisons. Moreover, the matter has been investigated in very few prospective studies. In a recent study based on prospectively collected data, which enrolled patients with nephrotic syndrome due to a substrate of membranous glomerulopathy, Kumar S *et al.* [14] reported a 19% cumulative incidence rate of VTE, considerably higher than our results for the overall patient population (12%) but similar to our findings in the subgroup of patients with nephrotic syndrome and membranous glomerulopathy (20%). The incidence rate of VTE was higher in our study, namely five (95% CI 3.2–5.7) cases per 100 patients-year, comparable with data from the study conducted by Kumar S *et al.*, of 7.7% (95% CI 2.5–17) at six months. Although the severity of the nephrotic syndrome was similar, Kumar S *et al.* investigated only patients with membranous nephropathy, while in our study patients had different types of glomerulonephritis as a histological substrate of the nephrotic syndrome, which may account for these differences [12]. Our data indicate a 30-fold higher incidence of VTE patients with NS during the first year, comparable to those reported in the general population (0.12 cases per 100 patient-years), 5-fold higher than the incidence rate of VTE in SLE patients (one case per 100 patient-years) and 15-fold higher than in pregnancy (0.3 cases per 100 patient-years) [14, 15]. The analysis of VTE incidence rate based on the histological substrate of the nephrotic syndrome in our study patients indicates a rate of 11.5% patients-year in the group of patients with membranous glomerulopathy, significantly higher than the incidence reported in other studies [14]. In patients with membranoproliferative glomerulonephritis, the incidence rate reached 5% patients-year. It is important to note that most VTE events occurred within six months from diagnosis, which holds clinical relevance and confirms results from other studies [12, 14].

Renal vein thrombosis is seldomly encountered in patients without nephrotic syndrome or a subjacent renal malignancy. Of 218 patients enrolled in a single center study, who presented with RVT, 143 were diagnosed with malignancy (111 with renal carcinoma) and 43 patients were diagnosed with nephrotic syndrome [9].

Unlike studies conducted in the 80's–90's which indicated renal vein thrombosis to be the most frequent thromboembolic event in patients with nephrotic syndrome, a recent analysis of a large cohort of such patients showed that deep vein thrombosis of the legs was the most frequently occurring thrombotic complication, followed by pulmonary embolism and renal vein thrombosis [14]. In our study, the most frequent thromboembolic events were venous thrombosis of the legs (34.8%) and pulmonary embolism (26%), followed by renal vein thrombosis (13%). Concomitant occurrence of deep venous thrombosis of the legs and pulmonary embolism was seen in three (13%) patients, while there was only one (4.3%) case of renal vein thrombosis and pulmonary embolism co-occurrence.

Several studies investigated the histological pattern as an independent risk factor for VTE [16, 17]. Data regarding the histological pattern impact on VTE risk in patients with primitive NS are controversial. In one study including 298 NS patients, of whom 157 had primitive nephropathy, there were no differences in VTE incidence according to histological pattern [17]. Another study showed in a cohort of more than 1313 patients with primitive NS that histological pattern is a predictive factor for VTE independent of the proteinuria and serum albumin level [8]. In our study, the analysis of thromboembolic events frequency based on the histo-pathological substrate of the nephrotic syndrome identified a maximum frequency in the subgroup of membranous nephropathy (20%) and membranoproliferative glomerulo-nephritis (14%), followed by focal segmental glomerulo-sclerosis (11%), and IgA nephropathy (6%) respectively. However, these differences in frequency were not

significant, probably due to the low number of observed cases.

The hallmark of membranous nephropathy is the presence of subepithelial electron dense deposits. These deposits go through a series of stages of incorporation into the GBM, as originally described by Ehrenreich T and Churg J [13]. Ehrenreich and Churg stages of MN did not correlate in some studies, but not in all studies, with the severity of the nephrotic syndrome [18, 19]. Furthermore, transformation between MN stages may be associated with either an increase or decrease in proteinuria. In our study, the severity of the subepithelial electron dense deposits, evaluated by Ehrenreich and Churg stages, did not correlate with the risk for VTE (p=0.5).

Conclusions

The rate of VTE incidence of five per 100 patients-year found in this prospective study confirms the primitive nephrotic syndrome as a thromboembolism generating condition and underlines the higher VTE risk in the first six months following diagnosis. The maximum incidence of VTE was registered in the group of patients diagnosed with MN but the stages of MN did not correlate with the risk for VTE.

References

[1] Llach F, *Hypercoagulability, renal vein thrombosis, and other thrombotic complications of nephrotic syndrome*, Kidney Int, 1985, 28(3):429–439.

[2] Singhal R, Brimble KS, *Thromboembolic complications in the nephrotic syndrome: pathophysiology and clinical management*, Thromb Res, 2006, 118(3):397–407.

[3] Wei LQ, Rong ZK, Gui L, Shan RD, *CT diagnosis of renal vein thrombosis in nephrotic syndrome*, J Comput Assist Tomogr, 1991, 15(3):454–457.

[4] Llach F, Papper S, Massry SG, *The clinical spectrum of renal vein thrombosis: acute and chronic*, Am J Med, 1980, 69(6):819–827.

[5] Wagoner RD, Stanson AW, Holley KE, Winter CS, *Renal vein thrombosis in idiopathic membranous glomerulopathy and nephrotic syndrome: incidence and significance*, Kidney Int, 1983, 23(2):368–374.

[6] Sarasin FP, Schifferli JA, *Prophylactic oral anticoagulation in nephrotic patients with idiopathic membranous nephropathy*, Kidney Int, 1994, 45(2):578–585.

[7] Robert A, Olmer M, Sampol J, Gugliotta JE, Casanova P, *Clinical correlation between hypercoagulability and thrombo-embolic phenomena*, Kidney Int, 1987, 31(3):830–835.

[8] Barbour SJ, Greenwald A, Djurdjev O, Levin A, Hladunewich MA, Nachman PH, Hogan SL, Cattran DC, Reich HN, *Disease-specific risk of venous thromboembolic events is increased in idiopathic glomerulonephritis*, Kidney Int, 2012, 81(2):190–195.

[9] Wysokinski WE, Gosk-Bierska I, Greene EL, Grill D, Wiste H, McBane RD 2nd, *Clinical characteristics and long-term follow-up of patients with renal vein thrombosis*, Am J Kidney Dis, 2008, 51(2):224–232.

[10] Wolak T, Rogachev B, Tovbin D, Hertzanu Y, Zlotnik M, Lugassy G, *Renal vein thrombosis as a presenting symptom of multiple genetic pro-coagulant defects*, Nephrol Dial Transplant, 2005, 20(4):827–830.

[11] Lionaki S, Derebail VK, Hogan SL, Barbour S, Lee T, Hladunewich M, Greenwald A, Hu Y, Jennette CE, Jennette JC, Falk RJ, Cattran DC, Nachman PH, Reich HN, *Venous thrombo-embolism in patients with membranous nephropathy*, Clin J Am Soc Nephrol, 2012, 7(1):43–51.

[12] Glassock RJ, *Prophylactic anticoagulation in nephrotic syndrome: a clinical conundrum*, J Am Soc Nephrol, 2007, 18(8):2221–2225.

[13] Ehrenreich T, Churg J, Pathology of membranous nephropathy. In: Sommers SC (ed), *Pathology Annual*, Appleton-Century-Crofts, New York, 1968, 107–120.

[14] Kumar S, Chapagain A, Nitsch D, Yaqoob MM, *Proteinuria and hypoalbuminemia are risk factors for thromboembolic events in patients with idiopathic membranous nephropathy: an observational study*, BMC Nephrol, 2012, 13:107.

[15] Li SJ, Guo JZ, Zuo K, Zhang J, Wu Y, Zhou CS, Lu GM, Liu ZH, *Thromboembolic complications in membranous nephropathy patients with nephrotic syndrome – a prospective study*, Thromb Res, 2012,130(3):501–505.

[16] Cameron JS, *The nephrotic syndrome and its complications*, Am J Kidney Dis, 1987, 10(3):157–171.

[17] Mahmoodi BK, ten Kate MK, Waanders F, Veeger NJ, Brouwer JL, Vogt L, Navis G, van der Meer J, *High absolute risks and predictors of venous and arterial thromboembolic events in patients with nephrotic syndrome: results from a large retrospective cohort study*, Circulation, 2008, 117(2): 224–230.

[18] Yoshimoto K, Yokoyama H, Wada T, Furuichi K, Sakai N, Iwata Y, Goshima S, Kida H, *Pathologic findings of initial biopsies reflect the outcomes of membranous nephropathy*, Kidney Int, 2004, 65(1):148–153.

[19] Yokoyama H, Yoshimoto K, Wada T, Furuichi K, Goshima S, Kida H, Kobayashi K, *Electron-dense deposition patterns and the outcomes of idiopathic membranous nephropathy in Japanese*, Med Electron Microsc, 2002, 35(2):81–86.

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Received: April 29, 2013

Accepted: August 12, 2013