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Unprovoked proximal venous thrombosis is associated with an increased risk of asymptomatic pulmonary embolism

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ABSTRACT

Introduction: Pulmonary embolism (PE) is common in patients with deep venous thrombosis (DVT). The outcome of DVT with concomitant symptomatic PE is worse than the outcome of isolated DVT. The risk factors for DVT and simultaneous asymptomatic PE have not been systematically studied yet.
Aim: To evaluate the frequency and risk factors for asymptomatic PE in patients with DVT.
Patients/methods: In 155 consecutive patients with a first episode of DVT and no PE symptoms, a ventilation-perfusion lung scan was performed. Body mass index (BMI) and waist-to-hip ratio (WHR) were calculated and concentrations of D-dimer, high-sensitivity CRP (hsCRP), tissue plasminogen activator (t-PA) and troponin were measured. Laboratory tests for thrombophilia were performed.
Results: Asymptomatic PE was present in 36% of patients. No differences in gender, age, BMI and WHR were found between the patients with and without PE. PE was more common in patients with proximal DVT than in those with distal DVT (42% vs. 17%, $p < 0.01$), and in patients with unprovoked DVT compared to patients with provoked DVT (51% vs. 28%, $p < 0.01$). The risk of silent PE was the highest in patients with unprovoked proximal DVT (OR, 6.9; 95% CI, 2.3–21.0). Patients with asymptomatic PE had significantly higher values of D-dimer, hsCRP, t-PA and troponin than patients with isolated DVT.
Conclusions: Asymptomatic PE affected more than one third of patients with a first DVT. Unprovoked proximal DVT is the most important risk factor for the occurrence of silent PE.

Introduction

Venous thromboembolism, the collective term used for deep venous thrombosis (DVT) and pulmonary embolism (PE), is the most common vascular disease after myocardial infarction and ischemic stroke. The incidence of venous thromboembolism is 2 to 3 per 1000 persons per year and increases with age. Approximately one third of patients with symptomatic venous thromboembolism manifest PE, whereas two thirds manifest DVT [1]. The signs and symptoms of DVT and PE are non-specific and some patients may have clinically silent PE [2]. A systematic review of the literature showed that an asymptomatic PE occurs in at least one third of the patients with acute DVT [3]. Those patients are at higher risk of recurrent PE [4–7]. It was shown recently that the risk of symptomatic PE is increased almost 5-fold in patients with silent PE in the first 2 weeks of anticoagulant therapy [8]. Although DVT and PE are generally considered as manifestations of the same disease, it is well established that patients presenting with symptomatic PE are at higher risk of fatal recurrent PE than patients presenting with DVT alone [9]. Although routine screening for asymptomatic PE in patients with DVT is not performed in clinical practice, it seems possible that if patients with a high probability of asymptomatic PE could be identified, they might benefit from screening.

So far it has been demonstrated that the prevalence of silent PE in patients with proximal DVT is higher than in those with distal DVT, and it was shown recently that the silent PE occurred frequently in patients with unprovoked DVT and in patients with coexisting heart disease [10]. In patients with symptomatic venous thromboembolism also, the role of some biomarkers in the risk stratification was studied. Increased levels of troponin, D-dimer and white blood cell count were associated with the clot burden or mortality [11–13]. However, the role of biomarkers in asymptomatic PE has not been established yet. Therefore, the purpose of this clinical study was to evaluate the

Abbreviations: aCL, anticardiolipin antibodies; anti-beta2 GPI, antibodies against beta2-glycoprotein I; BMI, body mass index; CT, computed tomography; DVT, deep venous thrombosis; hsCRP, high-sensitivity C-reactive protein; LA, lupus anticoagulants; OR, odds ratio; PE, pulmonary embolism; t-PA, tissue type plasminogen activator; WHR, waist-to-hip ratio.

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frequency of silent PE and to find any association between clinical and laboratory factors and occurrence of asymptomatic PE.

Patients and methods

Patients

From September 2008 to May 2010, 155 consecutive adult patients who were admitted to our outpatient clinic with a first episode of DVT of a lower limb were included in the study. Exclusion criteria were symptoms of PE at the time of enrolment, which was assessed by a standardized questionnaire, (presence of dyspnea, cough, pleuritic pain, haemoptysis, and collapse), or a previous episode of venous thromboembolism, pregnancy or cancer. With patients who entered the study, a detailed medical history was obtained, risk factors for DVT were assessed (injury, immobilisation, surgery, puerperium, estrogen intake, acute or chronic illness, leg varicosities, family history of venous thromboembolism in 1st degree relatives), a physical examination was performed, and body mass index (BMI) and waist-to-hip ratio (WHR) were calculated.

Blood sampling was performed within 24 hours after confirmation of DVT. Venous blood was collected into siliconised glass vacuum tubes, 1:10 volume of 0.11 mol/L trisodium citrate, or into vacuum tubes without anticoagulant, and centrifuged. Aliquots of plasma and serum were stored at −70 ° C until analysed. In plasma samples, tissue type plasminogen activator (t-PA) antigen was determined by an enzyme-linked immunosorbent assay (Imulyse^{TM}t-PA, Biopool, Sweden), D-dimer was determined by an immunoturbidimetric assay Auto-Dimer (Axis-Shield, Sweden). In serum samples, high-sensitivity C-reactive protein (hsCRP) was determined by an immunoturbidimetric assay (Vitros® Fusion 5.1, Ortho-Clinical Diagnostics, USA), troponin I was determined by three-site sandwich chemiluminescence immunoassay (ADVIA Centaur XP, Siemens, USA). Anticardiolipin antibodies (aCL) were determined by standard enzyme-linked immunosorbent assay (Medium Costar, USA), and antibodies against beta2-glycoprotein I (anti-beta2 GPI) were determined by the home modified ELISA method. If they were present in medium or high titre, they were considered as positive and repeated after 12 weeks.

All patients were initially treated with subcutaneous body-weight adjusted therapeutic doses of low molecular weight heparin, followed by warfarin, aiming for an international normalized ratio (INR) of 2.0 to 3.0, for at least 3 months. Four weeks after the discontinuation of warfarin treatment, tests for thrombophilia were performed. Antithrombin and protein C activity (Berichrom AT III and Berichrom Protein C, respectively, Siemens Healthcare Diagnostics, USA), and protein S free antigen (STA-Liatest® Free Protein S, Diagnostica Stago, France) were measured on an automated coagulation analyzer (Behring Coagulation Timer, Siemens Healthcare Diagnostics, USA), according to the instructions of the manufacturers. Polymorphisms of factor V Leiden and prothrombin G20210A were searched for by the real-time polymerase chain reaction (Custom TaqMan® SNP Genotyping Assays, Applied Biosystems, USA). Lupus anticoagulants (LA) were determined with LA-Screen and LA-Confirm reagents (Life Diagnostics Inc., USA). The test was repeated after 12 weeks in patients with present LA. As all recruited patients had suffered DVT, the patients with positive aCL, anti-beta2 GPI or LA on two occasions fulfilled the diagnostic criteria of antiphospholipid syndrome [14].

All the patients were Caucasians of Slovenian nationality. They signed an informed consent form to participate in the study. The study was approved by the Medical Ethical Committee of the Slovenian Ministry of Health.

Diagnostic Methods

The presence of DVT was confirmed with a venous ultrasound examination on an ATL Ultrasound, HDI 5000 duplex scanner (Bothell, USA), with a linear 10 MHz probe. Iliac, common femoral, femoral, popliteal, and calf veins were examined, with the patient in a supine position. DVT affecting the iliac, common femoral, femoral and/or popliteal vein was defined as proximal, whereas DVT confined to the veins of the calf was defined as distal.

Ventilation-perfusion scintigraphy of the lungs was performed within the first 48 hours after diagnosis of DVT. At least four views (anterior, posterior, left and right posterior oblique) were obtained on the standard gamma camera (Siemens Basicam or Siemens Symbia T2, Siemens, USA). Ventilation scintigraphy was performed with ultra fine dispersion of 99mTc-labelled carbon in inert gas (Technegas®, Cyclomedica, Australia), containing 400 MBq of 99mTc radioisotope (approximately 20–40 MBq accumulated in the lung). Perfusion scintigraphy was performed with 160 MBq of 99Tc-labelled microaggregated albumin (Macrotec, Mallinckrodt, Netherland), injected intravenously. In the presence of DVT, PE was confirmed if there were 1 or more segmental perfusion defects with normal ventilation, or 2 or more large subsegmental perfusion defects with normal ventilation [15]. Lung scans were categorised as normal if there were no perfusion defects. All scans were interpreted by experienced nuclear medicine physicians. Patients with non-diagnostic scans underwent chest computed tomography (CT) angiography. CT scans were performed on 128-row multidetector CT (Dual Source CT, SOMATOM® Definition, Siemens, Germany) using the spiral technique, during a single breath-hold period. In all patients, 80 ml of iodinated contrast agent (Ultravist 370 mg/ml, Bayer Health Care, Germany) were administered into the cubital vein. PE was confirmed if one or more intraluminal filling defects were present in the pulmonary arteries.

Statistical Analysis

Distribution of variables was tested with the Kolmogorov-Smirnov test. Variables with normal distribution were expressed as mean and standard deviation, and variables with asymmetric distribution as median and range between 1st and 3rd quartile. Differences between the groups were tested with the Student t-test for normally distributed data, and with the Mann–Whitney U test for asymmetrically distributed data. Categorical data were compared with the χ^2 test. Predictive factors for PE were assessed with logistic regression; the univariate approach was followed by the multivariate approach. Data were analysed using the SPSS statistical package (IBM SPSS Statistics, USA) and program R version 3.0.2 [16].

Results

One hundred and fifty-five consecutive patients with a first episode of acute lower limb DVT were included. Baseline characteristics are

Table 1
Baseline characteristics of the study participants.

Characteristic	
Age (years)	55 ± 16
Gender male/female (N)	91/64
BMI (kg/m^2)	29.0 ± 4.9
WHR: men	0.99 ± 0.05
WHR: women	0.86 ± 0.06
DVT location proximal/distal (N)	119/36
Risk factors for DVT, N (%)	
Injury with or without immobilisation	35 (22.6)
Surgery	18 (11.6)
Estrogen use and puerperium	27 (17.4)
Acute or chronic illness	19 (12.3)
Varicose veins	15 (9.7)
Family history of venous thromboembolism	21 (13.6)
Non identified	53 (34.2)

Data are expressed as mean ± SD. BMI, body mass index; WHR, waist-to-hip ratio; DVT, deep venous thrombosis.