Research Article

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Central obesity is associated with non-cirrhotic portal vein thrombosis

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Background & Aims: 30–40% of portal vein thrombosis (PVT) remains of unknown origin. An association between metabolic syndrome (MetS) and peripheral vein thrombosis has been reported but not with PVT, to date. The aim of this study was to investigate the association between MetS and PVT.

Methods: Between 2003 and 2014, all consecutive patients with non-cirrhotic PVT were prospectively included. Patient's characteristics and risks factors were recorded at the time of inclusion. Controls were selected by random in the general population and were matched 1/1 according to age and sex.

Results: Seventy-nine patients with PVT were included: 40 present with at least one risk factor for PVT (SPVT) and 39 were found to be idiopathic (IPVT). The prevalence of MetS was 25.6% in SPVT group *vs.* 47.4% in IPVT group and 17.9% in controls from the general population (C-IPVT: $p = 0.01$). The waist circumference and body mass index were higher in the IPVT group than in the SPVT group (105 *vs.* 93 cm, $p = 0.004$ and 29.4 *vs.* 25.0 kg/m^2, $p = 0.004$) and in the C-IPVT group (105 *vs.* 92 cm, $p = 0.001$ and 29.4 *vs.* 25.8 kg/m^2, $p = 0.003$). Overweight was observed in 82.0% of patients in the IPVT group *vs.* 44% in the SPVT group ($p = 0.002$) and 51% in the C-IPVT group ($p = 0.01$). The mean visceral fat area was higher in IPVT than in SPVT (18,223 mm^2 *vs.* 12,690 mm^2, $p = 0.02$). In multivariate analyses, an increase in waist circumference was the strongest parameter associated with idiopathic PVT.

Conclusion: Central obesity is associated with PVT and could become one of the main risk factors for digestive thromboses.

Keywords: Portal vein thrombosis; Obesity; Metabolic syndrome; Risk factor.
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Abbreviations: PVT, portal vein thombosis; SPVT, secondary portal vein thrombosis group; IPVT, idiopathic portal vein thrombosis group; C-SPVT, control group for secondary portal vein thrombosis group; C-IPVT, control group for idiopathic portal vein thrombosis; VTE, venous thromboembolism; MetS, Metabolic syndrome; BMI, body mass index; INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipids; γGT, Gamma glutamyl transpeptidase; CRP, C-reactive protein.

Introduction

Non-tumorous, non-cirrhotic, portal vein thrombosis (PVT) is rare but can cause severe complications. Acute PVT can lead to intestinal infarction with a reported mortality of up to 50% [1]. Chronic PVT with a transformation to cavernoma is the first cause of non-cirrhotic portal hypertension (PHT) in developed countries [2–4]. These patients are at risk of PHT-related bleeding, recurrent thrombosis and biliary complications. When a precipitating factor is identified, a local and/or a systemic factor is found in 30% and 70% of cases of PVT, respectively [5–7]. Because 30% of PVT cases are multifactorial [8], a complete investigation is needed at the time of diagnosis. Despite this, 30–40% of cases of PVT remain of unknown origin [5,9].

In the last decades, the prevalence of metabolic syndrome (MetS) and obesity have increased dramatically and are now a public health challenge. In Western Europe, the obesity rate is about 20.5% in men and 21% in women [10]. In France close to 50% of the adult population are overweight [10].

MetS is associated with the risk of developing cardiovascular disease through atherosclerosis [11,12]. Other studies have observed an association between MetS and venous thromboembolism (VTE) [13–15]. Among the components of MetS, increased waist circumference has been shown to be the strongest risk factor. Obesity, per se, is also a risk factor for VTE [16,17]. Among the anthropometric parameters used to assess obesity (body mass index, waist and hip circumferences, waist–hip ratio), studies show that a large waist circumference is key to the association between obesity and VTE [18–20]. Thus, abdominal obesity, due to visceral fat accumulation, seems to be the main risk factor for VTE. Ayala *et al.* [21] showed that obesity is an independent risk factor for PVT in patients with cirrhosis. However, to date, the association between MetS or obesity and PVT has not been reported in patients with non-cirrhotic PVT.

The aim of this study was to investigate the prevalence of MetS and its different criteria in patients suffering from idiopathic PVT, and to compare this rate with those of two other groups: PVT with a recognized origin and controls from the general population.

Patients and methods

Eligible patients and controls

Between July 2003 and January 2014, all consecutive patients suffering from PVT were prospectively recruited from our liver unit (belonging to the French network for vascular liver diseases). All participants signed an informed consent and the study protocol was conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in approval by the institutional review committee.

Inclusion criteria were adults aged >18 years, with acute or chronic PVT that involved the main portal vein or its branches, and diagnosed by radiological imaging (CT scan, MRI or ultrasound). Patients were excluded if they presented with one of the following criteria: cancer-related PVT, previously known cirrhosis or cirrhosis diagnosed at the time of inclusion. According to European guidelines, a complete etiological investigation (see below) was done. If a PVT risk factor was found, patients were included in the SPVT group. In other cases, patients were included in the idiopathic (IPVT) group.

Controls were randomly selected using a local electoral list between 2006 and 2007 [22]. For each case group, we also defined a "healthy" control group (groups C-SPVT and C-IPVT). The controls were matched (1:1) from the general population with the cases according to age and gender [22].

Data collection

Clinical, laboratory and radiological data were collected at the time of diagnosis. Data from controls were extracted from a database, previously established by the epidemiological and community-health laboratory at our center [22].

The following data were collected from both the cases and control groups.

- Age, gender
- Tobacco use
- Contraception use
- Weight, height, calculated body mass index (BMI), waist circumference
- Previous high blood pressure, diabetes, dyslipidemia or ongoing treatment
- Blood-cell counts
- Gamma glutamyl transpeptidase (γGT)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Serum creatinin
- C-reactive protein (CRP)
- Fasting plasma insulin; fasting plasma glucose; HOMA score; hemoglobin A1c
- Total cholesterol, high-density lipids (HDL), triglycerides
- Presence of MetS according to the National Cholesterol Education Program (NCEP) ATP III [23] definition.

The following supplementary data were also collected for each case.

- Serum sodium, liver-function tests, international normalized ratio
- Platelet counts
- Presence of hepatic steatosis
- Visceral fat area, measured on a CT scan at navel level, as previously described [24]
- For each case of PVT, the date of diagnosis corresponded to the date of the imaging study. Clinical history, symptoms, personal and family history of deep vein thrombosis, and radiological characteristics (acute thrombosis or cavernoma, extension of thrombosis, complete or partial obstruction, porto-systemic collaterals) were collected
- An etiological investigation was done for all patients including myeloproliferative disorders, antiphospholipid syndrome, protein C, S and antithrombin III deficiency, prothrombin gene mutation, factor V Leiden, paroxysmal nocturnal hemoglobinuria, connective-tissue diseases, underlying liver disease, and local risk factors. Data about hormonal contraception or replacement therapy and pregnancy were also collected

Statistical analyses

In bivariate analysis, categorical variables were compared using a chi-squared test or Fischer's exact test, as appropriate. Student's t test was used to compare differences of the continuous variables between the case groups and control groups. When the normality of continuous variables was not assumed or when the equality of variances was not observed, logarithmic transformation or a Wilcoxon–Mann–Whitney test was completed. Multivariate logistic-regression models were constructed by introducing explanatory variables using an ascendant step-by-step method. Only variables with a statistical p value of <0.20 in bivariate analyses were included in the multivariate analysis. They were standardized; the odds ratios express a variation of one standard deviation. Only variables significantly associated (p <0.05) with the dependant variables after stepwise selection were maintained in the final model. The linearity of the association between the dependant variable with each of the continuous explicative variables was checked. Three different models were established. The first model forced the "metabolic syndrome" variable in the model, the second one was computed excluding this variable, and the third model introduced only the components of MetS. The primary analyses included a complete-case analysis. All the variables found to be associated with the variable "metabolic syndrome" were used for multiple imputations. As a whole, ten multiple imputations were performed. An adjustment for multiple comparisons using the false discovery rate procedure was used. Statistical analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC), and $p \leqslant 0.05$ was considered statistically significant unless otherwise specified.

Results

Characteristics of the whole PVT cohort

The main characteristics of patients included in the study are listed in Table 1. Seventy-nine patients with PVT were included. Two-thirds of cases were men, mainly of Caucasian origin, with a mean age of 50.8 ± 14.0 years [20–83]. The most common presentation of PVT was abdominal pain. The main radiological characteristics of PVT are presented in Table 2. Most cases were acute PVT (64.5%) with occlusion of the portal stem in 61.7%. Extension to the portal branches was observed in half of the patients. An isolated occlusion of portal branches was observed in 36.7% of patients. Fourteen percent of cases were isolated cavernoma. The risk factors for PVT are detailed in Table 3. Oral contraception and pregnancy were not considered risk factors for PVT in this study. According to the etiological investigation, 40 cases of PVT were found to be secondary to at least one risk factor, and 39 cases of PVT were classified idiopathic.

Comparison between idiopathic PVT, secondary PVT, and their respective controls

Comparisons of the characteristics between the groups are presented in Table 4. Clinical characteristics did not differ between the SPVT and IPVT groups. The number of cavernoma was found to be similar between both PVT groups. The main biological characteristics were also comparable. A comparison of both groups with PVT and controls showed no differences for the main clinical characteristics. Leukocyte levels were higher in the SPVT group. γGT, AST, ALT and CRP were higher in both PVT groups (groups SPVT and IPVT) compared to their control groups from the general population (groups C-SPVT and C-IPVT).

The clinical metabolic characteristics are summarized in Table 4. Patients with IPVT had a higher weight (86.8 *vs.* 73.1 kg, p <0.001), BMI (29.4 *vs.* 25.0 kg/m^2, p = 0.004), and waist circumference (104.6 cm *vs.* 93.2 cm, p = 0.004) than patients with SPVT. There were also more overweight and obese patients