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Coagulation imbalance may not contribute to the development of portal vein thrombosis in patients with cirrhosis

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ABSTRACT

Introduction: The relationship between the imbalance in pro- and anti-coagulant factors and portal vein thrombosis (PVT) in individuals with cirrhosis is unclear. The aim of this study was to determine whether the imbalance in pro- and anti-coagulant factors contributes to the development of PVT in cirrhotic patients.
Materials and methods: Blood samples were collected from 30 consecutive cirrhotic patients with PVT and 30 age-, sex-, and Child-Pugh score-matched cirrhotic patients without PVT (controls), and the plasma levels of coagulation factors II, V, VII, VIII, IX, X, XI and XII and of protein C (PC), protein S (PS) and antithrombin (AT) were analyzed. The ratios of pro- vs. anti-coagulant factors were further investigated.
Results: The levels of pro- and anti-coagulant factors were not statistically different between the PVT and control groups. Similar results were obtained when the patients were divided according to Child-Pugh classification. No difference was observed for the ratios of pro- vs. anti-coagulant factors between the two groups but the ratios of factor II-to-PC and factor VII-to-PC which were significantly decreased in the PVT group. Most of the ratios did not reach statistical significance in each Child-Pugh category except the followings: factor VIII-to-PS, factor XII–to-PC and factor XII-to-PS in class A patients; factor II-to-PS, factor VII-to-PC and factor VII-to-PS in class B patients. But the difference might not be so convincing.
Conclusions: PVT in cirrhotic patients may not result from coagulation imbalance.

Introduction

Coagulation is a highly integrated cellular and humoral process that is balanced by two opposing drivers [1]. The pro-coagulant driver is triggered by the complex of factor VII and its specific receptor tissue factor, which in turn activates a series of events in the coagulation cascade, ultimately leading to thrombin generation and fibrin clot formation [2]. The primary anti-coagulant drivers include proteins C (PC), its cofactor protein S (PS) and antithrombin (AT). The ratios of pro- to anti-coagulant factors can be considered indexes of the coagulation imbalance [3].

Patients with liver cirrhosis are characterized by decreased levels of most pro- and anti-coagulant factors, with the exception of factor VIII, which is markedly elevated [4–6]. For decades, it has been believed that patients with cirrhosis are prone to hypocoagulation and autoanticoagulation, and are thus protected from thrombotic episodes [7]. However, accumulating evidence from both clinical [8–11] and laboratory studies [3,12] indicates that patients with cirrhosis have an increased tendency to develop thrombosis. Thus, the prevailing paradigm has been challenged by the concept of rebalanced hemostasis in patients with liver disease [7,13]. This balance may not be as stable as in healthy individuals, and only slight alterations may tip the balance to either bleeding or thrombosis [7].

Portal vein thrombosis (PVT) is a common complication of liver cirrhosis and is associated with decreased liver function and aggravated portal hypertension [14]. The prevalence of PVT in individuals with liver cirrhosis varies from 10% to 25% [15]. It is generally accepted that decreased portal vein velocity is the primary factor underlying PVT in cirrhosis [16]. The role played by coagulation imbalance in PVT is still unclear. Tripodi et al. hypothesized that hypercoagulability due to high factor VIII combined with low PC is an additional risk factor for PVT, but this has never been demonstrated conclusively [3,17].

The aim of our study was to investigate the relationship between coagulation imbalance and PVT in patients with liver cirrhosis by comprehensively analyzing the plasma levels of pro- and anti-coagulant factors.

Materials and Methods

A total of 30 consecutive adult patients (19 males and 11 females; median age, 52 years) with decompensated cirrhosis and PVT who

Abbreviations: AT, antithrombin; ETP, endogenous thrombin potential; PC, protein C; PH, portal hypertension; PS, protein S; PT, prothrombin time; PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt.

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were evaluated between August 2011 and June 2012 were enrolled in this study. The study protocol was approved by the ethics committee of our hospital, and informed consent was obtained from all patients. Criteria for exclusion were hepatocellular carcinoma or other cancer, Budd–Chiari syndrome, splenectomy, previous shunt procedures (e.g., TIPS insertion or shunt surgery), known hemostatic disorders other than cirrhosis and blood transfusion within 3 days. No patient was receiving antiaggregants or anti-coagulants.

The severity of the disease was estimated using the Child–Pugh Score [18] and the Model for End-stage Liver Disease (MELD) scoring system [19].

30 age-, sex- and Child-Pugh score-matched cirrhotic patients without PVT also evaluated from August 2011 to June 2012 in the same center were enrolled in this study as controls.

Measurements

Blood samples were taken from the antecubital vein in a standardized manner from patients who had fasted for at least 12 hours. After discarding the first 1 to 3 mL of blood, 3 mL of blood was drawn into vacuum tubes (Improve Medical, Guangzhou, China) containing 3.8% sodium citrate (ratio 9:1) as an anti-coagulant. Blood was centrifuged at 3000 *g* for 25 minutes at 18 °C within 30 minutes after collection. Fresh platelet-poor plasma was then harvested and all coagulation tests were performed within 4 hours after drawing the blood. All hemostasis tests were performed in an automated blood coagulation analyzer (CA-7000, Sysmex, Hyogo, Japan) using standard reagents.

The activities of coagulation factors II, V, VII, VIII, IX, X, XI, and XII were determined by one-stage clotting assays using factor-deficient plasmas (Siemens, Marburg, Germany). PS activity was also measured by a clotting assay (PS Ac, Siemens, Marburg, Germany). The activities of PC and AT were measured using chromogenic assays (Berichrom PC, Berichrom AT, Siemens, Marburg, Germany). The results were expressed as percent protein activity. Normal ranges for these tests are 70–120% for factor II, V, VII, IX, X, and XI; 70–150% for factor VIII and XII; 70–140% for PC; 75–130% for protein S; and 75–125% for AT.

Definitions

Cirrhosis was diagnosed based on the history of liver disease, clinical presentation such as variceal haemorrhage, ascites, spontaneous bacterial peritonitis, or hepatic encephalopathy, laboratory testing indicating decreased liver function and imaging studies which included color Doppler ultrasound, computed tomography, and MRI. Confirmation with a liver biopsy was obtained if a diagnosis of cirrhosis was inconclusive [20–22]. The decompensated stage was defined by the presence of ascites, variceal bleeding, jaundice, or encephalopathy [23].

The diagnostic criteria for PVT were imaging evidence of solid material in part or all the lumen of the portal vein trunk, portal vein branches, splenic vein or superior mesenteric vein based on color Doppler ultrasound, computed tomography, and/or angiography with a reduction or absence of portal flow.

Statistical Analysis

Continuous variables were expressed as medians and ranges, and categorical variables were displayed as frequencies. Statistical analysis was performed using the appropriate parametric or nonparametric tests (t test or Wilcoxon signed ranks test for comparisons of continuous variables between paired groups, χ^2 test or Kruskal-Wallis *H* test for categorical data). Two-tailed p values less than 0.05 were considered significant. All data were analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL).

Results

The demographic characteristics of the thirty matched cirrhotic patients with and without PVT are presented in Table 1. The two groups are comparable. The diagnosis of liver cirrhosis was well-established in 57 patients by the combination of history of liver disease, clinical presentations and images and three by liver biopsy, respectively. All patients with cirrhosis were decompensated.

Pro- and Anti-Coagulant Factors Between PVT and Control Groups

The pro- and anti-coagulant factors are reported in Table 2. In comparison with controls, no difference in plasma levels of pro- and anti-coagulant factors was detected. Factor VIII was elevated and other pro- and anti-coagulant factors were below the lower limits of the normal ranges.

Ratios of Pro- vs. Anti-Coagulant Factors Between PVT and Control Groups

The ratios between pro- and anti-coagulant factors were shown in Table 3. Among these ratios, the factor II-to-PC ratio was slightly lower in the PVT group than in the paired control group (P = 0.017), as were the factor VII-to-PC ratio (P = 0.005).

The ratios of factor VIII-to-PC, factor VIII-to-PS and factor VIII-to-AT were higher than other ratios in both group, but no difference was observed between the two groups (Fig. 1).

Pro- vs. Anti-Coagulant Factors and Their Ratios According to Child-Pugh Classification

Further, the patients were stratified according to Child-Pugh classification. The plasma levels of pro- and anti-coagulant factors were similar between the two groups in all the subgroups (Data not shown).

Most of the ratios did not reach statistical significance in each subgroup between PVT and controls, including the ratios of factor VIII-to-PC (Fig. 2). Marginal significance was observed for ratios of factor VIII–to-PS (P = 0.046), factor XII-to-PC (P = 0.043) and factor XII-to-PS (P = 0.046) in class A patients. The ratios of factor II-to-PS (P = 0.044), factor VII-to-PC and factor VII-to-PS (P = 0.02 and 0.022,

Table 1
Demographic characteristics of 30 paired cirrhotic patients with and without PVT.

Parameters	PVT	Controls	P value
Age, years	52(31–76)	52(34–76)	0.583
Gender, male/female, n	19/11	19/11	1
Etiology			0.772
HBV, n	19	20	
HCV, n	2	2	
Alcoholic, n	1	1	
Other, n	8	7	
PH-related bleeding, n (%)	22 (73.3)	26 (86.7)	0.2
Ascites, n (%)	24(80)	24(80)	1
Child-Pugh score	8(5–11)	8(5–11)	0.102
Child-Pugh class, A/B/C, n	7/19/4	7/19/4	1
MELD score	8.86(3.25–22.03)	9.33(0.36–14.28)	0.943
Albumin, mg/dl	31.8(19–41.2)	32.8 (22.3–47.6)	0.399
Bilirubin, μmol/L	26.8 (7.7–133.1)	23.4(5.4–55.7)	0.213
Creatinine, mg/dl	82 (52–307)	85 (41–240)	0.658
Leukocytes, $x10^9$/L	2.71(0.72–29.55)	2.94(1–17.9)	0.951
Hemoglobin, g/L	82(42–141)	83(47–116)	0.611
Platelets, $x10^9$/L	45 (10–563)	57.5 (23–160)	0.213
PT, s	15.1(12.6–18)	14.5(11.9–18.4)	0.64
INR	1.27(1.05–1.52)	1.21(0.99–1.53)	0.58

NOTE. Values are expressed as median (range); n indicates number of cases. Bold values indicate P values<0.05.
HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; PH, Portal hypertension; PT, prothrombin time; PVT, portal vein thrombosis.