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Thrombotic risk factors in patients with liver cirrhosis: Correlation with MELD scoring system and portal vein thrombosis development☆

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***Background/Aims*: Prognostic scores currently used in cirrhotic patients do not include thrombotic risk factors (TRFs). Predicting factors of portal vein thrombosis (PVT) development are still unknown. We wanted to describe TRFs as a function of liver disease severity using the MELD score and assess the role of local and systemic TRFs as predictors of PVT development in cirrhotic patients.**

***Methods*: One hundred consecutive patients with liver cirrhosis were included in the study. TRFs, D-dimers, MELD score, portal vein patency and flow velocity were evaluated in all subjects at baseline and every 6 months thereafter. Variables able to predict PVT development within 1 year were identified by means of multiple logistic regression.**

***Results*: The plasma levels of protein C and antithrombin were lower and the concentration of D-dimers was higher in patients with advanced disease. Plasma levels of antithrombin, protein C and protein S resulted significantly lower in PVT group at univariate analysis, but reduced portal vein flow velocity was the only variable independently associated with PVT development.**

***Conclusions*: Lower concentrations of natural coagulation inhibitors are frequently detected in patients with liver cirrhosis. A reduced portal flow velocity seems to be the most important predictive variable for PVT development in patients with cirrhosis.**

***Keywords*: Thrombotic risk factors; Liver cirrhosis; MELD score; Portal vein thrombosis; Portal flow velocity**

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Abbreviations: TRFs, thrombotic risk factors; PVT, portal vein thrombosis; AT, antithrombin; APA, antiphospholipid antibodies; MELD, Model for End-stage Liver Disease; LAC, lupus anticoagulant; INR, international normalized ratio; APTT, activated partial thromboplastin time; ELISA, enzyme-linked immunosorbent assay; PT, prothrombin time.

1. Introduction

The liver has many haemostatic functions, including the synthesis of most coagulation factors and inhibitors as well as fibrinolytic factors [1,2]. The balance between procoagulant and anticoagulant factors is essential to avoid excessive thrombin generation under physiological conditions [3]. Therefore, it is not surprising that advanced liver disease results in a complex pattern of defects in haemostatic functions in the form of reduced synthesis of coagulation factors, inhibitors, and abnormal clotting factors, abnormalities of fibrinolytic

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activity, disseminated intravascular coagulation and platelet function defects [4–7].

Moreover, thrombosis of the intrahepatic veins is frequently observed in cirrhosis and has been associated with its progression [8], while occlusion of small sized intrahepatic veins and sinusoids has been considered a potential triggering factor of liver tissue remodelling [9].

Recently, the prevalence of several genetic and acquired thrombotic risk factors in patients with chronic hepatitis B or C as well as their possible association with necroinflammatory activity and extent of fibrosis has been evaluated [10,11]. It is well known that protein C, protein S and antithrombin (AT) serum levels are decreased in patients with liver disease [12,13] but, to date, few reports are available about the association between the above mentioned and other natural anticoagulant factors produced by the liver and different stages of liver cirrhosis.

Portal vein thrombosis (PVT) is an important complication of cirrhosis, and is mostly associated with the occurrence of hepatocellular carcinoma [14]. The incidence of non-neoplastic PVT in cirrhotic patients is unknown, while its prevalence ranges from 0.6% to 16% [15–17]. Since PVT can be an important source of morbidity and mortality, early detection and treatment for *de novo* thrombosis is an important issue, especially in patients on the waiting list for liver transplantation [18]. Over the last few years the etiology of PVT has been better defined and large case series have improved our understanding of the natural history of this condition [19]. Male sex, previous abdominal surgery including splenectomy and portocaval shunts, encephalopathy, ascites, past history of bleeding varices, low platelet count, and Child–Pugh class C have been considered predisposing factors to PVT in liver cirrhosis [18,20,21]. Previous sclerotherapy of varices has been shown to be a risk factor in some studies [22,23]; other authors did not confirm this datum [16,24] or have shown that sclerotherapy may only be a trigger factor for PVT in patients with genetic thrombophilia [25,26]. Two studies found antiphospholipid antibodies (APA) in more than half of cirrhotic patients with PVT [27,28] but no relationship was found between anticardiolipin antibodies and PVT in another study [29]. Moreover, inherited (such as the factor V Leiden 1691 G–A mutation and the prothrombin 20210 G–A mutation), or acquired (such as the reduced levels of natural inhibitors of coagulation like protein C, protein S and antithrombin) coagulative defects leading to a hypercoagulable state, have been found in cirrhotic patients with PVT [16,30–34].

On the whole, the occurrence of PVT in liver cirrhosis appears to be a multifactorial complication, in which the involvement of inherited and acquired thrombotic risk factors as well as local anatomical and hemodynamic factors may be involved.

This study was designed to determine whether acquired systemic thrombogenic factors and local factors related to hepatic haemodynamics and portal hypertension might be related to liver disease progression and to the development of PVT.

2. Patients and methods

2.1. Patient population and study design

One hundred consecutive adult patients with cirrhosis (76 men, 24 women) with a median age of 60 years (range 31–81 yrs) were enrolled in the study, which conformed to the ethical standards of the Declaration of Helsinki and was approved by the local ethics committee. Liver cirrhosis was diagnosed by histological examination of liver biopsy or by unequivocal hematochemical, ultrasound (US) or endoscopic findings suggesting advanced liver disease with portal hypertension. The severity of liver disease was estimated according to Model for End-stage Liver Disease (MELD) scoring system [35].

Patients with patent paraumbilical vein, reversed portal blood flow, known hepatocellular carcinoma or any other malignancy, known hemostatic disorders other than liver disease, bacterial infection, a clinical history of peripheral venous thrombosis, or those who had received any form of antiviral and/or immunomodulatory therapy within the last 6 months were excluded from the study. No patient was taking oral contraceptives, anticoagulation or anti-platelet drugs.

Exclusion criteria were also the presence of the most common inherited coagulation abnormalities (Factor V Leiden and prothrombin (G20210A) genes mutation), as well as, based on familiar screening, antithrombotic protein deficiency (protein C, protein S, antithrombin (AT)). Only 2 patients of the initial population evaluated were affected by Factor V Leiden (heterozygote state) or prothrombin (G20210A – heterozygote state) mutation. Based on this finding, we decided to exclude these patients from further analysis.

The demographic, clinical and laboratory data of the patients enrolled in the study are summarized in Table 1. The following parameters were considered as thrombotic risk factors (TRFs): deficiency in AT, protein S, protein C, presence of lupus anticoagulant (LAC) antibodies, elevated homocysteine and, cryoglobulinemia. TRFs and D-dimer levels were evaluated as functions of a stratified MELD score; an arbitrary cut-of value was set at 13 (usually applied in our institution to select patients for liver transplantation).

The patients were followed up for one year and were evaluated at baseline and every 6 months by liver function tests, D-dimer, TRFs and abdominal Doppler US.

Concerning the development of PVT during follow-up, we evaluated, for their prognostic significance, the clinical and demographic characteristics of patients at baseline. In particular previously described TRFs were analyzed in addition to age, gender, platelet cell count, international normalized ratio (INR), activated partial thromboplastin time (APTT), D-dimer levels, grading of oesophageal varices and MELD score.

PVT was suspected by the occurrence of endoluminal material in the main trunk of portal vein and/or its branches at grey-scale ultrasonography or by the presence of a filling defect at color or power Doppler ultrasonography. In all cases the diagnosis was confirmed by dynamic abdominal computed tomography that also allowed a more precise distinction between partial and complete obstructive thrombosis. Portal cavernoma was defined by the presence of multiple small channels that replaced the trombosed portal trunk.

The presence and staging of oesophageal varices was evaluated by means of upper endoscopy.

2.2. Blood collection and processing

After informed consent, blood was drawn without stasis by clean venipuncture and collected in vacuum tubes containing 105 mmol/L trisodium citrate as an anticoagulant (Vacutainer; Becton–Dickinson,