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Advances of knowledge on coagulation disorders in liver cirrhosis and their clinical consequences.

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Abstract

Only in the last few years the medical world has changed views on hemoragic and thrombotic risk assessment in patients with liver cirrhosis. A more accurate understanding of the mechanisms disturbance of hemostasis, coagulation and fibrinolysis, leads to a better management of these patients, that is desirable to be reflected as a decrease in bleeding episodes and the prevention of thrombotic events. In this minireview we intend to present an update of knowledge on the pathophysiology of coagulation and fibrinolysis in liver cirrhosis, the ways of exploring them, their prophylactic and therapeutic consequences. We made a review based on publication in PubMed from 1995 up to now. If in the past the main concern of clinicians on the mentioned issues was the avoidance of haemorrhage, today we know that neither the procoagulant status that cirrhotic patients have, should not be underestimated, as they are prone to thrombosis rather than to hemorrhage and the thrombosis risk is increasing if cirrhosis progresses. Primarily responsible for the prothrombotic status are: decreased anticoagulant factors (antithrombin III, protein C, and protein S), increased levels of factor VIII, elevated levels of von Willebrand factor, the possible presence of thrombophilia. To these it is also added the partial resistance to the action of thrombomodulin, observed *in vitro*. Tests that explore the intrinsic and the extrinsic pathway of coagulation do not provide information on anticoagulant factors activity. Therefore, it is recommended to study the thrombin generation, which provides a more accurate picture of the coagulation balance, taking into account procoagulant and anticoagulant factors. The dosage level of thrombin generation is easy to realize in practice, either from platelet poor plasma or from platelet-rich plasma, and the result are standardized. Reducing thrombin generation could help reduce the thrombotic events and the rate of liver fibrosis progression.

Keywords: liver cirrhosis, hypercoagulability, protein C, thrombin generation, thrombophilia, thrombosis

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Introduction

For decades it was considered that cirrhotic patients are likely to develop bleeding complications due to the hepatoprive syndrome (which also involves a lower level of coagulation factors synthesized by the liver), thrombocytopenia and local causes (portal-hypertensive gastropathy, rupture of digestive varices with various locations, and so-called hepatogen ulcer). Recently, the medical world reviewed the coagulation status of patients with liver cirrhosis and concluded that not only procoagulant factors are low, but some anticoagulants too, so that, overall, remains an equilibrium between the two categories of factors until the advanced stages of liver cirrhosis [1, 2] and in some cases there is even a hypercoagulable state [3], state reflected by the level of thrombin generation [1, 3]. In general, today it is considered that cirrhotic patients are more prone to thrombotic than bleeding events.

In this review we present the particularities of cirrhotic patients on coagulation, the utility of studying the thrombin generation level (compared to exploring the intrinsic and extrinsic coagulation path) and the particularities related to infection with hepatitis C virus in liver cirrhosis, after studying the articles published in PubMed from 1995 up to now.

Coagulation in liver cirrhosis

Particularities of coagulation mechanisms

It is accepted today that bleeding in cirrhotic patients is due to hemodynamic disorders, local causes,

thrombocytopenia and thrombocytopathy [2]. Activated partial thromboplastin time and prothrombin time are often prolonged in cirrhosis because they reflect deficiency of clotting factors, but they don't accurately reflect the risk of thrombotic or hemorrhagic disease [4] and they don't provide information on the mechanisms involved in thrombin regulation. They provide information on thrombin generation as function of procoagulant factors, but much less on the inhibition of thrombin by anti-coagulant factors [5]. Activated protein C (in the presence of its cofactor - protein S) is a vitamin K - dependent factor, that inactivates through proteolytic mechanism the activated factor V and activated factor VIII. Factor VIII, is the cofactor of factor X, which, once activated in the presence of factor V and of calcium ions with which it formes the prothrombinase complex, contributes to the thrombin generation by cleavage of prothrombin. In order to explore the role of protein C in the coagulation mechanism in liver cirrhosis, it was added in vitro protein C in the plasma taken from 50 patients in order to restore its normal levels (as it has low serum levels in these patients). Then, it was studied the thrombin generation in each sample, with or without the addition of thrombomodulin or Protac (a snake venom). Protac and thrombomodulin activates protein C, which has anticoagulant effect. The report of endogenous thrombin potential with thrombomodulin (or Protac) / endogenous thrombin potential without thrombomodulin (or Protac) decreased significantly after the addition of protein C [from 0.83 (0.44-1.00) to 0.60 (0.14-0.84)]. Protein C activity was inversely correlated with this report [6]. These findings prove the existence of protein C deficiency in cirrhotic patients, which tends to unbalance the equilibrum between pro- and anticoagulant factors in favor of the procoagulants. Without the addition of thrombomodulin, protein C levels, the most important anticoagulation factor, are therefore significantly lower in cirrhosis compared to healthy subjects, which explains the low level of thrombin generation in cirrhosis (unless thrombomodulin was added) [1 ,5], which also reflects the decrease of coagulations factors [1]. In vitro thrombin generation is, however, normal in patients with cirrhosis if thrombomodulin was added [1, 2]. In hepatic cirrhosis not only the level of protein C is low, but also the level of protein S – which acts as a cofactor of tissue factor pathway inhibitor (TFPI), while TFPI levels are normal or elevated. Using neutralizing antibodies against protein S or TFPI allowed to declare that in this disease there are damages in the function of anticoagulabt TFPI/protein S system [7].

Role of platelets

Platelets are also involved in the mechanism of thrombin generation in vivo. Severe thrombocytopenia may contribute to a decrease in thrombin generation in these patients. Increased platelet level over 100000/mm^3 contributed to the significant increase in thrombin generation. From this point of view, platelet concentrates transfusion in cirrhotic patients with spontaneous bleeding or to those who are going to be operated is recommended [2].

Thrombin generation

The level of thrombin generation in cirrhosis is not damaged unless coagulation factors decrease very much, but the ability of the coagulation system to tolerate or to recover from an injury is significantly lower in chronic liver diseases, which predisposes easier to thrombosis and also to hemorrhages [4], and that these patients have a considerable degree of instability in this regard. In order to explore coagulation in patients with cirrhosis it is preferable to use the study of thrombin generation, which explores the global coagulation, instead of prothrombin and partial thromboplastin times, because it reflects both procoagulant factor deficiency as well as the anti-coagulant factor deficiency [5]. In a study involving 73 patients with hepatic cirrhosis it was not observed any correlation between international normalized ratio (INR) and the velocity of thrombin generation or endogenous thrombin potential. In patients with hepatic cirrhosis velocity of thrombin generation was increased, especially in those with INR values of 1.21 - 2.0. Endogenous thrombin potential with Protac and the raport of endogenous thrombin potential with Protac / endogenous thrombin potential without Protac were increased in these patients, comparing to the normal control group [3]. In another study it was found that plasma taken from patients with hepatic cirrhosis without portal vein thrombosis generated more thrombin when thrombomodulin was added and they had an increased resistance to thrombomodulin, than patients with non-cirrhotic portal vein thrombosis and than the healthy subjects in the control group. Similar results (higher thrombin peak and endogenous thrombin potential) were obtained in patients with cirrhosis who had portal vein thrombosis compared with control subjects, which supports the idea that thrombomodulin resistance and hypercoagulability observed in cirrhotic patients are independent of the presence of splanchnic vein thrombosis [8]. These are arguments for hipercoagulant status of patients with cirrhosis, although INR is extended to them. It is not indicated to use prothrombin time or INR to estimate bleeding risk in these patients [3]. The dosage level of thrombin generation is easy to realize in practice, either from platelet poor plasma or from platelet-rich plasma, and the results are standardized [9]. If the platelet count is at least 100000/mm^3 patients with liver cirrhosis generate the same amount of thrombin as normal healthy subjects [10].

Hypercoagulability in cirrhosis

Thrombomodulin is a cofactor in protein C activation induced by thrombin. It was found that cirrhotic patients are partially resistant to the action of thrombomodulin

[11, 12], because the median ratio of the thrombin generation with thrombomodulin / thrombin generation without thrombomodulin was higher in the 134 analyzed cirrhotic patients than in the group of 131 healthy subjects [11]. This partial resistance observed *in vitro* is possible, but it is not mandatory to be overlaped over the situation *in vivo* [12]. They are also resistant to the action of Protac - an activator of protein C by a thrombomodulin-like mechanism [9]. The resistance to thrombomodulin action was correlated with the levels of protein C and factor VIII in samples harvested from all 28 patients with cirrhosis and was higher in those with severe forms of disease [13]. The result of the resistance to the action of thrombomodulin and Protac is the decrease of activation of protein C, which signifies a prothrombotic status, which is more important in patients in Child-Pugh class C than those of class B or A [9, 11]. The cirrhotic patients of Child-Pugh class C have a hypercoagulability slightly higher than patients with congenital protein C deficiency thrombophilia [11] and similar to those with factor V Leiden [9]. As cirrhosis progresses from class A to C the levels of factor VIII increases gradually while the levels of protein C decrease [11], which explains the increased hypercoagulability. Thrombin generation parameters were similar in plasma samples collected from the jugular vein and portal vein in patients with transjugular intrahepatic porto-systemic shunt, but in their case endogenous thrombin potential and thrombin peaks were lower than in healthy subjects, while in their portal plasma samples activated partial thromboplastin time and protein C had lower values, and factor VIII, D-dimers and F1+2 values were higher than in plasma samples from the jugular vein. This indicates that in the portal vein of cirrhotic patients there is a procoagulant status explained by high FVIII levels and protein C and S deficiency [13]. The addition of 1pM tissue factor in the plasma samples collected from 153 patients with liver cirrhosis produced a significant increase in endogenous thrombin potential, which highlights their hypercoagulant status [14].

Fibrinolysis in liver cirrhosis

In principle, thrombomodulin has also a procoagulant effect by binding with thrombin, because in this combination activates by cleavage thrombin-activatable fibrinolysis inhibitor.

But thrombin activatable fibrinolysis inhibitor, precursor of a carboxypeptidase that has an antifibrinolytic activity, is low in patients with cirrhosis. This and impaired thrombin generation explain the *in vitro* hyperfibrinolysis detected in plasma of cirrhotic patients [15].

Transfusions in patients with liver cirrhosis

In vitro addition of pooled normal plasma to plasma of 58 cirrhotic patients in proportion of ¼ did not alter the thrombin generation, which was also in normal rates in unmixed patient plasmas, while activated partial thromboplastin and prothrombin times were shortened but not normalized after the addition of normal pooled plasma [16].

A transfusion of one standard adult platelet dose made in 26 patients with liver cirrhosis and thrombocytopenia increased the platelet count on average by 12000/mm^3, without changing the thrombin generation and without normalizing the thromboelastometry [10].

Liver transplantation

Studying the thrombin generation in serial plasma samples collected from 10 consecutive patients after liver transplantation it was found that, although the tests exploring the extrinsic and intrinsic pathway of coagulation were extended substantially, the endogenous thrombin potential was slightly lower than in healthy subjects at all time points. But when thrombomodulin was added, the endogenous thrombin potential had the same value or was even higher than in the control subjects. Decreased levels of antithrombin, protein C, S, and increased levels of factor VIII in patients after liver transplantation can explain the efficient thrombin generation *in vitro* after the addition of thrombomodulin. This thrombin generation equal or superior to that of healthy subjects in the presence of exogenous thrombomodulin, advocates for the restriction of plasma transfusions during liver transplantation and suggests the necessity of studies to examine the potential benefits of prophylactic anticoagulation for avoiding further thromboembolic complications [17].

Infections in liver diseases

Extrinsic coagulation pathway can be activated by severe sepsis with decrease of zymogen forms of factors VII, X, V, and prothrombin. This decrease of zymogen levels was independently correlated with the severity of cirrhosis and the presence of severe sepsis, which causes the consumption of the mentioned factors by activating the coagulation [18].

Acute infection with viruses that infect the liver may be involved in the occurrence of venous thromboembolism (especially the portal vein thrombosis) in some patients. There are clinical data that pleads for the intervention of Epstein-Barr virus, cytomegalovirus, and hepatitis A, B and C viruses in the development of venous thrombosis [19].

Portal flow velocity

There are authors who argue that reduced portal flow velocity can predict portal vein thrombosis in cirrhotic patients [20]. Venous stasis, wherever located, favors the occurrence of thrombosis, and so spleno-portal venous axis may be affected. Portal blood flow stasis is considered by some authors as the main risk factor for the occurrence of thrombosis, independent of the possible

presence of other congenital or acquired, local or systemic, predisposing factors [21].

Portal vein thrombosis is favored by splenectomy. A 24% of the 70 studied splenectomised cirrhotic patients, developed portal vein thrombosis. Only in those who had portal vein thrombosis prior to splenectomy there was a significant decreased of the portal venous flow [22].

Anticoagulant treatment in liver cirrhosis

Hemorrhagic risk

In cirrhosis thrombotic risk is greater than the hemorrhagic risk. This does not mean that cirrhotic patients can not bleed. Bleeding in these patients are usually unpredictable and are due, most often, to porto-systemic veins rupture [23]. Other factors that are favoring bleeding accidents are decreased serum levels of several coagulation factors, thrombocytopenia (by splenic sequestration and decreased thrombopoietin levels), platelet function disorders and excessive fibrinolysis (reduced clearance of tissue plasminogen activator) [15, 24, 25], and vitamin K deficiency [25]. Tests that usually explore the intrinsic and extrinsic coagulation pathway are not useful for predicting the risk of bleeding or thrombosis [3, 23, 24]. Thrombin generation and thrombelastography study could be useful in this regard and could guide the management of cirrhotic patients [23].

Thrombotic risk

Cirrhotic patients are likely to develop visceral thrombosis (especially of the portal vein and its branches) and compared to the general population they seem to have more frequent episodes of deep venous thrombosis and pulmonary embolism [12, 24]. The banner sign, that contains the rambling pulse and the fever that does not respond to antipyretics and antibiotics, but respond to anticoagulation, is the expression of repeated minor pulmonary embolism, and announced a possible future massive pulmonary embolism. The incidence of deep vein thrombosis and pulmonary embolism in cirrhotic patients is estimated to be between 0.5% and 1.9%. Only the serum albumin levels have been correlated with thrombotic accidents in a multicenter study in these patients, who have the same thrombotic risk factors as the general population [24]. A serum level of albumin lower than 1.9 g/dl increased the risk of venous thromboembolism by 5.1 times compared to patients with serum albumin $\geq$ 2.8 g/dl in a retrospective case-control study [26]. The connection between albumin and coagulation can be the reflection of hepatoprive syndrome or the hepato-renal syndrome, which implies a decrease of anti-coagulant factors (antithrombin III, protein C, and protein S) and of the coagulation factors synthesized in the liver (I, II, V, VII, IX, X, and XI) [25], with modification of their balance in favor of procoagulant ones. Other prothrombotic factors are elevated levels of von Willebrand factor, the possible presence of thrombophilia (like factor V Leiden), and increased factor VIII levels [25]. Particularly for cirrhotic patients, liver resection creates a hipercoagulant status [24].

Thromboprophylaxis

When circumstances that increase their risk of thrombosis arise, thromboprophylaxis should be indicated because they are not auto-anticoagulated patients, although they may bleed. Due to the potential risk of bleeding, the current guidelines that relate to the prevention of thrombosis does not make reference to anticoagulant therapy in liver cirrhosis [24], but the anticoagulant therapy in these patients is rational [12] and is based increasingly on the clinical and laboratory arguments. There are subgroups of patients with cirrhosis where anticoagulant therapy may be beneficial for prevention of thrombosis [12].

Anticoagulants

In cirrhotic patients therapy with low molecular weight heparins seems to be relatively safe [24]. To assess the effectiveness of enoxaparin there were studied 30 patients with liver cirrhosis located in all 3 Child-Pugh class, and was found that average levels of antithrombin were significantly lower in patients of all subgroups (as in those with inherited type 1 antithrombin defect) versus healthy subjects that were analyzed. The endogenous thrombin potential ratio at 0.35 U anti-Xa ml was lower in patients with liver cirrhosis compared to healthy subjects and was even lower as the cirrhosis was more severe, although the levels of anti-Xa activity and antithrombin both decreased. Therefore patients with cirrhosis have an increased response to enoxaparin, which correlates with the severity of the disease. Thrombin generation may be used to monitor the treatment with low-molecular-weight heparin in patients with liver cirrhosis [27].

The effects of different anticoagulants were studied *in vitro* in plasma taken from 30 patients with liver cirrhosis, through thrombin generation assays. Dabigatran has produced the largest decrease in endogenous thrombin potential versus healthy subjects (72.6% vs. 12.8% reduction) and this decrease was proportional with the severity of cirrhosis. Low molecular weight heparin and heparin had only a slightly increased anticoagulant effect in plasma from cirrhotic patients compared with the one from the healthy subjects, while rivaroxaban and fondaparinux had a reduced anticoagulant effect in cirrhotics [28]. These results are useful for clinical practice and require drug-specific dose adjustments when using these anticoagulants in patients with cirrhosis and thrombin generation study may be useful for running customized therapies. Discovery of hypercoagulability in patients with liver cirrhosis and deep venous thrombosis, including through the study of thrombin generation may be useful for indicating a longer or more intensive anticoagulant treatment in this subset of patients [8].

The relationship coagulation – liver fibrogenesis

It was observed that the inflammatory hepatic process and cirrhosis coexist with the presence of thrombi in the liver microcirculation and deposits of fibrin-fibrinogen. It was also found that chronic hepatitis C progresses quickly to cirrhosis in those with factor V Leiden, increased expression of factor VIII, or protein C deficiency. Moreover, this process can also be present in other types of chronic liver diseases [29]. Systemic hypercoagulability is involved in the appearance of parenchymal extinction and accelerated liver fibrosis [12, 23, 29]. Hepatic cholestasis can also develop fibrosis. Tissue factor-dependent thrombin generation and protease activated receptor-1 activation induces expression of the αVβ6 integrin, a key regulator of transforming growth factor-β1 activation, and thus contribute to hepatic fibrogenesis induced by chronic cholestasis [30]. It is logical that reducing thrombin generation or its downstream activity can help to reduce liver fibrosis [29]. Anticoagulant therapy applied to some subgroups of patients with liver cirrhosis could help not only to prevent thrombotic complications, but also to slow the progression of liver fibrosis [12].

Characteristics of hepatitis C virus related cirrhosis

Infection with hepatitis C virus is common in Europe and America, that I considered as a chapter about it is useful.

The frequency of thrombosis depending on etiology of liver cirrhosis

It has long been observed that venous thrombosis doesn't have the same frequency in all types of liver cirrhosis, but the findings differ depending on the geographical area. A case-control study made in Europe, which included 18 consecutive cirrhotic patients found that venous thrombosis is more common in hepatitis C virus cirrhotic patients [31]. A study in Asia, where the prevalence of hepatitis B virus infection is high, noted that 85% of patients with deep venous thrombosis had cirrhosis resulted from hepatitis B virus infection in advanced stages - most were in Child-Pugh classes B and C [32]. Such studies involving small numbers of patients do not allow us to draw conclusions on the thrombotic risk according to the etiology of liver cirrhosis. Large multicenter studies are needed to investigate this issue, that worth investigating. A recent published study made on a large group of patients infected with hepatitis C virus (22,733), who was compared with 68,198 witnesses matched by age and gender to comparator group, showed that thrombotic events were more frequent in hepatitis C virus infected patients (233.4/10,000 subjects-years, versus 138.5/10,000 subjects-years). The same study also compared 15,158 cirrhotic patients of various etiologies with 45,473 witnesses matched by age and gender and established that thromboembolic event appeared more frequently in the first group (561.1/10,000 subjects-years, versus 249.7/10,000 subjects-years). Arterial thromboses were the most frequent events observed in both cirrhotic and hepatitis C virus infected patients (especially transient ischemic attack and unstable angina). Portal vein thrombosis was found more frequent in patients with hepatic disease [33]. It is obvious that both liver cirrhosis, as well as infection with the hepatitis C virus are risk factors for thrombotic accidents. It would be useful a study to investigate thromboses in hepatitis C virus related cirrhosis.

Antiphospholipid syndrome and chronic infection with hepatitis C

Patients with Hepatitis C virus – related cirrhosis and thrombosis have higher levels of F1+2 fragment, a marker of thrombin generation, compared to patients with hepatitis B virus infection and / or alcoholism. Antiphospholipid antibodies are more prevalent in patients with thrombosis, but fragment F1+2 values were similar in patients with and without antiphospholipid antibodies. At least the presence of higher levels of fragment F1+2 supports the idea that hepatitis C may contribute to the activation of coagulation and may predispose to the occurrence of thrombotic complications in cirrhotic patients [31]. The presence of antiphospholipid syndrome predisposes patients to arterial or venous thrombosis. The relatively frequent discovery of anticardiolipin antibodies in patients with chronic hepatitis C virus infection apparently has no clinical consequences. However, an increased incidence of thrombosis in patients with chronic hepatitis C virus who had antiphospholipid positivity was reported by some studies [34]. A patient with hepatitis C virus-related cirrhosis and antiphospholipid syndrome (that presented IgG anti-cardiolipin-beta2-glycoprotein I complex antibody and IgG anti-cardiolipin antibody) developed portal vein thrombosis [35]. Extensive studies are needed to investigate the possible correlation between the presence of antiphospholipid syndrome and chronic infection with hepatitis C.

Thrombin generation in hepatitis C virus cirrhotic patients

How can we explain the increase of thrombin generation in hepatitis C virus cirrhotic patients? The envelope of many viruses contains proteins of the host cell and the virus. When the virus interacts with the host cell, envelope proteins become triggers for the immune processes, for the infection and for various pathological processes. For example, herpes simplex virus type 1 envelope hosts tissue factor and procoagulant phospholipid, which are physiological initiator of coagulation [36]. The expression of these factors is constitutive on the purified virus, so that it allows the activation of the extrinsic coagulation pathway (from the activation of factor VII) and the thrombin generation. Viral glycoprotein C increases the production of activated factor X and herpes simplex virus type 1 raises also the generation of plasmin. Once activated, coagulation factors

VII, X and plasmin contributes to the increase of infection in cell culture through the protease activated receptor (PAR-2) and thrombin has an additive effect by protease activated receptor 1 (PAR-1). It is believed that tissue factor and procoagulant phospholipid may be present on the surface envelope of other viruses and may be involved in the activation of PAR-1 and PAR-2 [36]. The hepatitis C virus is composed of a single stranded RNA, nucleocapsid (protein) that contains the glycoprotein C, and an envelope rich in lipid in which there are the E1 and E2 glycoproteins, involved in the process of attachment of the virus to the cell surface. The envelope of the hepatitis C virus can also host initiators factors of coagulation.

The relationship between the thrombotic risk and hepatic fibrogenesis

If hepatitis C virus cirrhotic patients are prone to thrombosis are they prone to rapid fibrogenesis too? It was found that thrombin receptor protease-activated receptor 1 (PAR-1) polymorphisms may influence the rate of progression of hepatic fibrosis. There was a trend toward a higher rate of liver fibrosis in cirrhotic patients that have the TT genotype (P = 0.06). A cross-sectional study made in Isfahan (Iran), between 2009 and 2010 on chronic infected with hepatitis C virus adult patients showed that the rate of progression of liver fibrosis was greater in those with non-O blood group. This association is probably due to the increased risk of these patients to develop venous thrombosis [37]. Another study found that non-O blood group is an independent risk factor involved in the progression of liver fibrosis in patients infected with hepatitis C virus [38]. It is questionable to what extent genetic and acquired thrombotic risk factors may contribute to hepatic fibrogenesis in patients with chronic hepatitis C virus infection. A study involving 210 female Irish patients infected with the genotype 1b of hepatitis C virus found that neither the factor V Leiden nor prothrombin G20210A polymorphisms did not affect fibrotic scores or rate of progression of liver fibosis, calculated by studying subsequent biopsies [38]. This study did not find arguments for the involving of thrombotic risk factors in hepatic fibrogenesis.

Thrombophilia in hepatitis C virus-positive patients

In a group of 47 consecutive patients with end-stage liver disease, in which it was studied antithrombin activity, protein C, protein S, and factor V Leiden mutation, it was found that 89.4% of them had at least one deficiency and in 70.2% of them all the anticoagulants factors that were studied were deficient. Deficiencies were more important in hepatitis C virus-positive patients and in those with advanced liver disease (MELD score>15). Although hypercoagulability was common, especially in hepatitis C virus-positive patients, portal vein thrombosis was present in only 12.8% of patients (all with low protein S activity), regardless of the etiology of chronic liver disease [39].

Analogs of thrombopoietin receptors in hepatitis C virus related liver cirrhosis

The treatment with thrombopoietin receptor analogs in patients with chronic liver diseases, including those caused by hepatitis C virus, can produce side effects such as thrombosis, if the number of platelets increases too much. Such adverse reaction occurred in a 50 years old woman with hepatitis C virus related liver cirrhosis and immune thrombocytopenic purpura, which under romiplostim (she took it for 9 months) developed partial portal vein thrombosis at a platelet count above 330.000/mm^3 [40]. If eltrombopag and romiplostim are administered in a correct dose and if the patients are closely monitored, they can increase platelet count and the patients can initiate the treatment with pegylated interferon and ribavirin or can be prepared for an eventual surgery. The patient described above had also primary immune thrombocytopenia, disease in which platelets have an increased average volume and are hyper-functional. They are involved in coagulation, so the risk of thrombosis by excessive thrombin generation is higher for this patient compared to those with virus C chronic liver disease without primary immune thrombocytopenia.

Hepatocellular carcinoma and thrombotic risk

The development of hepatocellular carcinoma in liver cirrhosis increases the thrombotic risk. In a multicenter study conducted on 215 consecutive hospitalized cirrhotic patients with hepatocellular carcinoma, over a third of them presented thrombosis in the past or present [41]. A case of end-stage hepatocellular carcinoma but with asymptomatic hepatitis C developed malignant thrombosis of the inferior vena cava, left pulmonary artery thrombosis and multiple bilateral pulmonary metastases [42]. In a study made on 129 patients with non-resectable hepatocellular carcinoma was found that most had hepatitis C virus etiology (51.2%). Portal vein thrombosis was one of the prognostic factors in this study [43].

Liver transplantation and thrombotic risk

A comprehensive retrospective analysis of liver transplants performed in Hungary in the period 1995-2006 in patients with hepatitis C virus related cirrhosis found that among the factors that have an impact on patient survival are hepatic artery thrombosis and amount of intraoperative colloid use and transfusions [44].

Conclusions

Hemorrhages in cirrhotic patients are related more to the presence of porto-systemic anastomoses, thrombocyto-penia, impaired platelet function and hyperfibrinolysis, but they also have a hypercoagulant status that should not be underestimated, due to increasing serum levels of factor VIII, decreased serum levels of protein C and S, normal or elevated levels of TFPI and partial resistance to the action of thrombomodulin. Along with the progress-

ion of liver cirrhosis there is an increase of hypercoagulability status in these patients.

It is not indicated to use the prothrombin time or INR to estimate the risk of hemorrhage in these patients because they do not take into account the serum levels of anticoagulant factors. The study of thrombin generation is easy to realize in practice and gives useful information on coagulation status in cirrhotic patients. A personalized therapy of these patients implies a monitoring of thrombin generation levels.

Patients with liver cirrhosis are labile in the sense that after an injury they are more likely to develop hemorrhages and thrombosis.

Extensive studies are needed to investigate the prevalence of thrombosis according to the etiology of liver cirrhosis, the correlation between antiphospholipid syndrome and chronic infection with hepatitis C, the relationship between thrombotic risk and hepatic fibrogenesis and the role of thrombophilia in hepatitis C virus-positive patients.

Thromboprophylaxis and treatment of thrombosis in patients with cirrhosis may appeal to the study of thrombin generation and this should be studied in large trials that are going to be credible sources for guidelines for prevention and treatment of thrombosis, guidelines that should not avoid this issue for cirrhotic patients in the future.

The level of thrombin generation may be a measure to estimate the risk of thrombosis and to indicate its prophylaxis in cirrhotic patients who do not have contraindications. Thrombin generation may contribute to a personalized therapy for them.

Conflict of interest

The authors have no conflicts of interest to declare.

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