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Review

The risk of bleeding and encephalopathy in surgical patients with liver cirrhosis

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Abstract

Liver cirrhosis is a disease with an increasing incidence. Surgical procedures in patients with cirrhosis are also increasing, due to a longer life expectancy in these patients and also to the improvement of therapeutic and diagnostic resources.

Digestive hemorrhage in the cirrhotic patient requires emergency medical intervention (intensive therapy, endoscopic or even surgical approaches), being at the same time a factor that precipitates episodes of encephalopathy, i.e. the conventional complication of cirrhosis. Hepatic encephalopathy represents one of the most severe clinical events of cirrhosis, being associated with high morbidity and mortality. The causes of hepatic encephalopathy are briefly presented in this paper. Therapeutic approaches currently available consist in the administration of non-absorbable disaccharides such as lactulose and non-absorbable antibiotics such as rifaximin. New therapeutic perspectives are under evaluation, e.g. ammonia scavengers and the modulation of gut microbiota.

Clotting disorders in patients with liver cirrhosis are more severe as the disease progresses and involves complex mechanisms, as presented in this review. The correction of possible disorders of hemostasis should be promptly made as a sine qua non condition prior to surgery.

Keywords

: liver cirrhosis, hemostasis, hypocoagulability, hypercoagulability, bleeding, encephalopathy.

Highlights

- ✓ It is difficult to determine the hemostatic profile of cirrhotic patients only by running the usual laboratory tests, due to the existence of a fragile balance between hypo- and hypercoagulability factors.
- ✓ Most cases of hepatic encephalopathy are precipitated by events such as digestive hemorrhage and infections, which must be carefully monitored to prevent encephalopathy in cirrhotic patients as much as possible.

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Introduction

In the last decades, there has been a spectacular increase in the life expectancy of patients with liver cirrhosis thanks to the improvement of therapeutic and diagnostic resources. On the background of these data, but also because of the increase in cirrhotic incidence, the number of surgical procedures in patients with cirrhosis is also increasing. Due to limited cases that are suited for liver transplantation, the medical and surgical therapeutic approaches focus especially on complications, which have become the main concern of the long-term management of cirrhosis (1).

One of the mandatory requirements for the cirrhotic patient who is about to undergo surgery is the evaluation of the hemostatic profile, since liver cirrhosis is accompanied by clotting disorders that increase as the disease progresses. The correction of the possible disorders of hemostasis should be promptly made as a *sine qua non* condition prior to surgery (2).

Clinically, hemostatic disorders are revealed by the presence of bruises, purpura, epistaxis or gingivorragia. Hemostatic abnormalities in cirrhosis are multifactorial. They are a consequence of the decreasing capacity of hepatocyte synthesis, reticuloendothelial dysfunction and portal hypertension (3).

Hepatic encephalopathy (HE) is a relatively frequent complication encountered especially in the advanced stages of cirrhosis. HE is expressed through several (neuropsychiatric, neuromuscular, metabolic etc.) dysfunctions. According to literature, minor HE affects up to 60-70% of patients with cirrhosis to a certain extent. Although many patients with minor HE (subtle alterations of the cognitive functions) seem to be clinically asymptomatic, the condition has a considerable impact on the patients' life quality, such as poor driving performance, an increased risk of falls, predispositions to hospitalizations and even death (4).

Severe HE usually implies more severe signs and symptoms, represented by alterations in consciousness, temporal and spatial disorientation, behavioral and emotional changes, and generalized motor dysfunction. During its evolution, this form of HE is encountered in about 30–45% of patients with cirrhosis, representing a significant cause of hospitalizations for patients with poor evolution and prognosis (5).

Possible precipitating factors of HE are gastrointestinal bleedings, bacterial infections, and accumulation of gut-derived toxins (especially ammonia). All these factors (causing inflammation and oxidative

stress) lead to cerebral edema, which underlies the core symptoms of HE (6).

Discussions

For a long time, it has been assumed that the decrease in circulating platelets is due to hypersplenism. In 1967, Aster and Jandl correlated splenomegaly in portal hypertension with extensive platelets pooling which would cause thrombocytopenia (1, 3).

However, this assumption does not explain all the platelet changes and it is contradicted by a few observations. Splenomegaly in cirrhosis is not in a linear relation with the degree of portal hypertension, but it is rather the effect of parenchymal hypertrophy. On the other hand, surgical procedures to reduce portal hypertension, such as portacaval shunt, do not directly lead the increase of circulating platelet count (4, 5).

Radio labeled platelet studies showed that there is a shortening of the life span of platelets in liver cirrhosis. Thrombocytolysis occurs through an immunological mechanism proven by the presence of increased concentrations of autoantibodies in the serum against a major platelet antigen, GP IIb / IIIa. These antibodies are produced by B lymphocytes, the proportion of which increases (7).

Maintenance of platelet counts within normal limits depends on the ability of bone marrow to increase production, which is reflected in the proportion of young elements in the circulation. Although thrombocytopoiesis is under the direct effect of thrombopoietin, a growth factor synthesized mainly by the liver and the kidney, and whose serum levels decrease in advanced cirrhosis and portal hypertension, its titers do not correlate directly with medullary platelets synthesis (8).

This apparent discordance results from the fact that the removal of thrombopoietin from the circulation is made through its internalization in megakaryocytes and platelets, including those which are pooled in the spleen (9). In liver cirrhosis, platelets also show quantitative changes besides decreasing in number (10).

The observed hypo-aggregability has complex mechanisms, which include both platelet factors and plasma factors. On the one hand, there is a transmembrane signaling the defect after stimulation with thrombin or collagen and thus a decrease in intracellular messengers, and, on the other hand, a number of plasma factors that have a negative effect on aggregability. The latter includes: bile salts, fibrinogen degradation products, HDL or apolipoprotein E (6-8).

Preoperative thrombocytopenia requires correction by platelet transfusion to achieve a platelet level which can be considered safe depending on the type of surgical intervention. Minor surgical procedures with a low bleeding risk can be safely performed with platelet count $>50\,000/\text{mm}^3$, while major surgery requires a minimum platelet count of $100,000/\text{mm}^3$ (11).

Coagulation disorders in the cirrhotic patient may occur not only in the context of quantitative and qualitative changes in platelets, but also in the reduction of coagulation factors. Most of them are synthesized in the hepatocyte, except factor VIII (12).

The usual laboratory tests, prothrombin time (PT) and activated partial thromboplastin time (APTT), indicate a degree of hypercoagulability in patients with advanced diseases, but they do not objectively reflect their hemostatic profile. Recent studies suggest that there is a balance, albeit precarious in cirrhosis, between hypo- and hypercoagulability resulting from deficiencies in the synthesis of both pro-coagulant and anti-coagulant factors (13, 14).

In cirrhosis, there is a deficiency in the synthesis of vitamin K-dependent coagulation factors, II, VII, IX and X, which result from the decrease in hepatocyte production capacity and from the decrease in vitamin absorption in the intestinal lumen due to the antibiotic treatment which reduces the bacterial flora that produces it, the decrease in vitamin K synthesis or cholestasis (15).

Besides, there are also abnormalities of fibrinolysis due to the alteration of the synthesis of fibrinolytic factors, but also their clearance, for which the reticuloendothelial system of the liver is mainly responsible. Thus, one can see an imbalance between the plasminogen tissue activator and its inhibitor PAI1, resulting in a fibrinolysis deficiency which is amplified by a decreased clearance of circulating activated coagulation factors (16).

The protein synthesis deficiency also influences the production of anticoagulant factors, especially protein C and its cofactor, protein S, whose role *in vivo* is to reduce thrombin production by inhibiting Factors Va and VIIa (17).

Given the apparent hypocoagulability present in cirrhosis, which can be revealed by the usual laboratory tests, PT and APTT, it is considered that this category of patients is somewhat "protected" against the risk of thrombosis (16, 18).

However, clinical observations show a considerable incidence of thrombosis in advanced cirrhosis, especially in portal and mesenteric veins. In addition to

hypercoagulability, whose causes have been exposed above, Virchow Triad is complemented by hemodynamic changes in these cases, consisting in slowing down the blood flow through portal hypertension and vascular wall alterations (19).

In addition, there are factors that further contribute to the progression of hepatic cirrhosis such as the formation of intraparenchymatous microthrombi caused by ischemia and the activation of stellate cells by thrombin (20).

The deficiencies of the factors involved in hemostasis affect all its sequences, which leads to the occurrence of balance, but more fragile than in normal conditions, between hypo- and hypercoagulability: the procoagulant protein deficiency is offset due to the deficiency of proteins C and S, fibrinolysis is balanced by the concomitant deficiency of antifibrinolytics and the qualitative and quantitative deficiencies of platelets are offset by the increase in plasma levels of von Willebrand factor and a protein which stimulates platelet adhesion (21, 22).

The hemostatic profile of cirrhotic patients is therefore difficult to determine only by running the usual laboratory tests, but given the experience of liver transplantation centers, one can recommend major surgery even in patients with cirrhosis who are apparently in a state of hypocoagulability, without the risk of major incidents (14). Until the validation of these data, in patients undergoing surgery, the correction of coagulation deficits is practically mandatory (23).

Enteric bacterial translocation is favored in patients with cirrhosis, being influenced by immunological impairment/ presence of intestinal bacterial overgrowth, and increased intestinal permeability. This bacterial translocation increases the levels of systemic gut-derived toxins (especially in the presence of portosystemic shunt), thus having an important role in the development of HE. Moreover, bacterial translocation increases the risk of abdominal infection (bacterial peritonitis, septicemia), which negatively influence morbidity and mortality in patients with cirrhosis (24, 25).

Although the pathophysiological mechanisms involved in hepatic encephalopathy (HE) are not yet fully elucidated, literature data show that an increased accumulation of gut-derived toxins (ammonia and other derivatives), represents the main factors which determine HE. The accumulation of toxins (from bacteria, inflammation and oxidative stress) is the consequence of decreased liver function on one hand, and due to development of portosystemic shunts (which diminish the liver capacity to remove toxins from the blood-stream) on

the other hand. All these mechanisms are responsible (at least in part) for cerebral edema, which represents the main substrate of HE (26).

Most cases of hepatic encephalopathy are precipitated by events such as digestive hemorrhage, hydroelectrolytic/ acido-basal imbalance, infections, sedation, constipation or diarrhea, etc. This means that a good monitoring/ control of the hemostatic profile of cirrhotic patients can reduce the rate of digestive bleeding in these patients, and thus reduces the number/severity of hepatic encephalopathies (27-29).

Conclusions

Hemostasis disorders in patients with liver cirrhosis have complex mechanisms and are more severe in the advanced stages of the disease. In patients with cirrhosis, there is a relative precarious balance between hypo- and hypercoagulability, which is caused by deficiencies in the synthesis of both procoagulant and anti-coagulant factors.

Hepatic encephalopathy, variceal bleeding, jaundice and ascites, are diagnostic elements of decompensated cirrhosis, which is associated with high mortality rates if the patient does not benefit from liver transplantation. Decompensated cirrhosis should be delineated by acute-on-chronic liver failure (ACLF), represented by a chronic liver disease (in patients with or without cirrhosis) that presents a rapid decline (hepatic and extra-hepatic organ failures) due to the intervention of several precipitating factors.

The risk of bleeding is correlated with the type of surgery in cirrhotic patients, but prior to the surgical procedure it is mandatory to correct the clotting disorders in order to minimize the risk of intraoperative bleeding. For this purpose, the already existing diagnostic, monitoring and treatment protocols for cirrhotic patients should be improved. For example, a very recent protocol for end-stage liver disease proved to be able to evaluate morbidity and mortality more accurately than the older prognostic models in cirrhotic patients (30).

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant

bodies and that such approvals are acknowledged within the manuscript.

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