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RASSEGNE — REVIEWS

HEMOSTASIS AND LIVER DISEASE

EMOSTASI ED EPATOPATIE

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We reviewed the main disturbances of hemostasis (coagulation, platelet, fibrinolysis) occurring in acute and chronic liver disease and during cholestasis. The significance of coagulation testing in the evaluation of hepatocytic synthetic function and the value of these tests in predicting bleeding episodes are also discussed in detail. Finally the role of replacement therapy with fresh-frozen plasma and prothrombin complex concentrates is evaluated for the treatment of bleeding occurring during various types of liver disease.

KEY WORDS: Acquired hemostatic disorders, chronic liver disease, coagulation tests.

The liver plays a central role in blood coagulation. This is illustrated by the fact that eleven proteins involved in clotting (fibrinogen, prothrombin, prekallikrein, high-molecular weight kininogen, factors V, VII, IX, X, XI, XII and XIII) are produced by the hepatocyte, while the synthesis of factor VIII is likely to take place in different cells of the liver as well as in other organs. Thus, liver disease due to hepatocellular damage is frequently associated with a multiple defect which combines with the hemodynamic alterations of portal hypertension in determining hemorrhagic manifestations. Since the synthesis of biologically active forms of factors II, VII, IX and X require vitamin K, coagulation defects and bleeding episodes can also accompany cholestatic jaundice, in which fat-soluble vitamin K is not absorbed from the intestine. Additional hemostatic alterations (such as thrombocytopenia, qualitative platelet defects, dysfibrinogenemia and hyperfibrinolysis) may contribute to the bleeding tendency in liver disease. Hepatic failure can also lead to intravascular clotting which is

probably related to the decrease in synthesis of naturally occurring coagulation inhibitors (i.e. antithrombin III) and to the impaired capacity of the liver to remove procoagulant substances present in the circulation.

Hemostatic Defects in Acute Hepatitis

According to our experience, hemostatic parameters are not greatly altered in the majority of cases with acute infectious or toxic hepatitis; coagulation tests are frequently normal, and in *viral hepatitis* there may be a slight thrombocytopenia (100.000-150.000 per mm^3) which seldom causes a bleeding tendency. However, it is not unusual to observe during the benign course of hepatitis marked abnormalities in coagulation tests. These do not represent an unfavourable index of short- or long-term evolution, since normalization usually occurs in parallel to the improvement of clinical symptoms and biochemical indices.

Fulminant hepatitis of infectious or toxic etiology shows early and frequent hemostatic abnormalities and hemorrhagic symptoms, and the extent of the involvement of coagulation tests is considered a prognostic index of primary importance [20]. Because of the particularly short biological half-life of factor VII (3-5 h), the specific assay of this clotting protein seems to be more useful than broad-spectrum tests such as the prothrombin time or the partial thromboplastin time [20]. Factor VII tends to show an early decrease in acute liver failure and any subsequent increase can be considered an early sign of recovery. It seems that levels lower that 10% of the normal are constantly associated with an unfavourable course, while higher values should be regarded as a good prognostic sign [20]. Factor V assay is less helpful in determining the current state of protein synthesis because the plasma levels of this protein are affected by inflammatory states and cholestasis [17].

It has been suggested that *disseminated intravascular coagulation* (DIC) plays a major role in the pathogenesis of hemostatic disturbances and hemorrhagic signs developing during fulminant hepatitis. In a number of these patients, marked hypofibrinogemia, shortening of the half-life of radiolabelled fibrinogen, thrombocytopenia and increased levels of serum fibrinogen-fibrin degradation products (FDP) have been observed [63]. These findings have led to the hypothesis that release into the circulation of necrotic hepatic tissue with procoagulant activity, the impaired removal of activated clotting factors, as well as the decrease of naturally-occurring coagulation inhibitors may condition the development of DIC with secondary fibrinolysis which

would aggravate the concomitant hemostatic defect due to hepatocellular damage [63]. This hypothesis is far from being proven and the evidence indicating DIC appears to be mainly indirect [69]. At autopsy, the presence of intravascular microthrombi is infrequent and of limited extent, and no relationship was found between liver histology and coagulation abnormalities [35]. Herold and Straub [34] have summarized the alternative explanations to DIC which could account for the coagulation changes in acute liver necrosis. The observed laboratory findings may be explained by the development of a generalized proteolytic state related to the liberation of endocellular proteases and to the decreased synthesis of their natural inhibitors. As a matter of fact, the methods used fail to distinguish between the degradation products of fibrinogen (aspecific indices of a generalized proteolytic state) from those of fibrin, which are a more specific parameter of fibrinolysis secondary to intravascular clotting. Other elements challenging the hypothesis of DIC in fulminant hepatitis are the possibilities that hypofibrinogemia may be caused by extravascular losses of the protein in the gastrointestinal tract and other sites (transudates, exudates, areas of inflammation and necrosis); and that increased FDP could originate from extravascular fibrin deposition or decreased removal by an altered RES [34]. It is also difficult to account for the marked increase of factor VIII [34], which is usually decreased in acute DIC. More direct evidence on the occurrence of DIC in fulminant hepatitis possibly may be provided by the radioimmunological measurement of fibrinopeptide A, which is a specific index of the action of thrombin on circulating fibrinogen; and of high molecular weight fibrinogen fibrin complexes reflecting the *in vivo* conversion of fibrinogen to fibrin.

Alterations in Chronic Liver Failure

In patients with chronic liver disease, a number of studies have attempted to identify one or more hemostatic parameters which would be of *prognostic value*. Varied results have been obtained. Factor VII, for example, does not appear to have the same prognostic value as in fulminant hepatitis [29]; recently, the assays of factor XIII, plasminogen and to a lesser extent factor V were shown to be more informative than other coagulation parameters as prognostic indices in a large series of patients with cirrhosis and other liver diseases [2]. The possibility of predicting the *bleeding risk* by means of clotting tests has also been explored. It has been claimed that a correlation exists between development of gastrointestinal bleeding and abnormal fibrin polymerization in these patients [30]. Other investigators have

stressed the role of prothrombin (factor II), whose mild reduction would have a harmful effect on hemostasis [19 46]. In practice, no specific assay is capable of assessing the extent of the bleeding risk more reliably than broad-spectrum tests, which are technically simpler and more reproducible. It also appears difficult to predict the clinical outcome of liver disease solely on the basis of coagulation tests.

Thrombocytopenia is frequently encountered in patients with chronic liver disease; its pathogenetic mechanism is recognized to be increased platelet destruction [71]. On the basis of the correlation existing between decreased platelet count and the abnormalities of some liver function tests (such as the prothrombin time, bromsulphtalein retention and serum albumin), it has been suggested that liver failure by itself is the primary cause of thrombocytopenia and that under the influence of the damaged liver platelets are either formed abnormally or altered in the periphery [23]. This may be due to the effect of substances insufficiently metabolized in the liver and/or to the intervention of other etiologic factors such as alcoholism and folate deficiency. Although the existence of a hypersplenic syndrome is generally regarded as a major cause of trombocytopenia in chronic liver disease, a detailed study has failed to show a relationship between platelet count and spleen size [23]. *Hypersplenism* is associated with increased platelet production and normal platelet survival [33], with preferential sequestration of large platelets in the spleen and a decreased mean volume of circulating platelets [38]. Since small platelets are functionally less active than large platelets, the abnormalities of platelet function tests reported in patients with chronic liver disease [1 70] may be related to the predominance of platelets with decreased size and function [38]. This interpretation, however, is challenged by our observation that an in vivo test of platelet hemostatic competence such as the bleeding time is often normal in chronic liver disease despite a significant reduction in platelet number.

Much discussed is also the pathogenetic role of a systemic activation of the fibrinolytic system in determining bleeding in chronic liver disease and particularly in cirrhosis. *Hyperfibrinolysis* is thought to be related to a diminished synthesis of naturally occurring fibrinolysis inhibitors due to the synthetic defect of the hepatocyte [55], as well as to a decreased removal by the liver of circulating plasminogen activator [21]. The demonstration of an ongoing, primary fibrinolysis is not easy in liver disease, because tests exploring the fibrinolytic system (such as the clot lysis methods and plasminogen assay) can be altered by the reduction of protein synthesis and give aspecific information. As already mentioned, the modest increase of FDP, which

is encountered quite often in liver patients [15 52], cannot be considered a specific index of primary hyperfibrinolysis because it may be attributed to various other causes. Despite these diagnostic limitations, it is held by some that chronic liver disease is one of the few cases in which primary hyperfibrinolysis occurs. It is difficult, however, to establish how important this alteration can be in the determination of the hemorrhagic syndrome.

An impairment of fibrin formation, shown by a significant lengthening of the thrombin time, is frequently seen in advanced liver cirrhosis [16]. A clearer understanding of this abnormality was made possible by a recent study, showing that defective fibrin polymerization is due to qualitative abnormalities of fibrinogen characterized by an increased content of sialic acid [51].

It has been claimed that a correlation exists between abnormal fibrin polymerization and gastrointestinal bleeding in patients with liver cirrhosis [30].

Intravascular coagulation is also thought to occur in chronic liver disease (see ref. 4 and 73 for review). Its development might be related by the presence in the portal system of a large vascular bed in which blood, circulating at low pressure, favours the activation of coagulation factors which are incompletely removed by the impaired liver. In addition, the free endotoxins absorbed from the intestine into the portal venous system can escape into the systemic circulation where they may be responsible for activating platelets and triggering thrombin formation [75]. The occurrence of these pathogenetic mechanisms is supported by the demonstration of the shortened biological half-life of radiolabelled fibrinogen [72], prothrombin and plasminogen [12] in liver cirrhosis, and by the reported capacity of heparin to correct these alterations [12 72]. In addition, soluble fibrin monomer complexes have been found in a large number of cases with liver cirrhosis [10]. As in fulminant hepatitis, the role of DIC has not been firmly established, and the same critical considerations can be applied to chronic liver disease. In a large post-mortem study carried out in 184 autopsy cases with liver disease (mainly chronic), the incidence of microthrombi in more than one organ seemed to be very low [57]. The observed abnormalities of clotting factors are not specific and their increased turnover might also be explained by the hemodynamic alterations of the portal circulation, which could alter the rheological properties of the coagulation proteins and determine their increased destruction [8]; and by the synthesis of an abnormal fibrinogen [67] which could be catabolized more rapidly than normal [6]. In addition, the assessment of overall fibrinogen catabolism by the survival method is likely to be an insen-

sitive and non-specific approach to the detection of enhanced fibrin formation, due to the fact that this accounts for only a small proportion of fibrinogen catabolism in man. The measurement of fibrinopeptide A and of fibrinogen-fibrin soluble complexes might offer a better insight into the problem of enhanced fibrin formation in liver disease.

Hemostasis and Cholestasis

Contrary to general belief, coagulation disturbances associated with lack of absorption of vitamin K are not frequently observed in cholestatic jaundice due to large bile duct obstruction of neoplastic or lithiasic etiology. This is probably related to the widespread use of modern diagnostic and surgical techniques which lead to a prompt recognition and management of these conditions; and to the early administration of parenteral vitamin K. Laboratory findings, rather than indicating hemostatic defects, often demonstrate a picture of *hypercoagulability* due to the increases in fibrinogen, factor V, factor VIII and to an impaired fibrinolytic activity [18 37]. These findings are probably explained by an aspecific rise of the « acute phase » glycoproteins as observed in the inflammatory and neoplastic states; and by a stimulating effect on protein synthesis exerted by cholestasis [7]. In the cholestatic man, the observations of an augmented rate of aminoacid incorporation into liver proteins provide experimental evidence of this concept [68]. It has been suggested that increased coagulability and decreased fibrinolysis render patients particularly liable to postoperative thromboembolism [37]. This view is not supported by available evidence, which shows that the incidence of deep-vein thrombosis after biliary surgery is no higher than after surgical operations of comparable severity [18]. On the other hand, it is difficult to overlook the fact that a number of patients tend to bleed abnormally during surgery. The observed prolongation of tests exploring the last phase of coagulation (such as thrombin and reptilase time) suggest the presence in these patients of some degree of *inhibition of the clotting mechanism,* independent of vitamin K deficiency and/or a defective fibrin polymerization [18]. *In vitro* studies support the hypothesis that inhibitory activity may be related to antithrombin action exerted by elevated levels of bilirubin glucuronides [41].

Hemostatic Problems in Surgery on Liver Patients

Portacaval shunts are considered to be a surgical situation in which primary hyperfibrinolysis occurs [31 32]. Actually, this pathogenic interpretation of observed laboratory abnormalities is debatable, and

causes other than plasmin formation might explain the increase in clot lysis time and the changes in other fibrinolysis parameters (see Alterations in Chronic Liver Failure). This problem deserves further study by means of the more specific tests now becoming available to demonstrate the generation of plasmin in circulating blood through the measurement of plasmin-antiplasmin complexes. The hemostatic findings in cases of *partial hepatectomy* performed due to traumas or tumors is controversial. Extensive liver resection is generally associated with a transient depletion of vitamin K dependent factors accompanied by an increase in fibrinogen [66].

It is likely that the stimulus to an increased production of this protein triggered by surgical trauma counterbalances the impairment of synthesis occurring before the onset of compensatory mechanisms. On the other hand, a number of studies have shown an increased fibrinolytic activity and the positivity of paracoagulation tests, which would suggest the occurrence of intravascular clotting [13 74].

An acute coagulation disorder appears to be well documented by clinical and experimental data in *orthotopic liver transplantation.* The most critical period is the brief anhepatic phase which takes place during the surgical procedure [5 66]. It is probable that the function exerted by the liver in clearing procoagulant material and fibrinolysis activators released in the circulation (particularly during such a traumatic procedure) cannot be defective even for a short period of time and so a state of primary fibrinolysis and DIC with secondary fibrinolysis develops in this phase. The severity and the duration of the acute coagulopathy is closely related to the state of preservation of the transplanted organ [22 45]. When the graft is well preserved, the defective functions are rapidly reestablished and the hemostatic abnormalities soon corrected; on the contrary, transplantation of a severely damaged liver tends to perpetuate the hemorrhagic syndrome and to cause, by itself, a further activation of the coagulation and fibrinolytic systems. *Transplant rejection* in the liver is similar to that in the kidney, in that this event is accompanied by signs of local activation of the hemostatic mechanism of which the most frequent and typical are an increase of serum FDP and thrombocytopenia [22 53 61]. In the sequence of pathological reactions leading to transplant rejection, the earlier events involve immunologically mediated lesions of the vascular endothelium, which may then be followed by platelet adhesion and aggregation, fibrin deposition and fibrinolysis in the liver vessels. These alterations, in turn, are likely to induce ischemic damage in the hepatocyte, which then aggravates the coagulation defect through a decreased synthesis of clotting factors.

The same problems of the anhepatic phase of liver transplantation can also develop in patients with acute liver failure being treated by *extracorporeal perfusion* through the liver of other animal species [60 66]. The most recent efforts of extracorporeal perfusion based on the use of activated *charcoal columns* coated with biocompatible polymers are still limited by the formation of platelet aggregates leading to the mechanical removal of platelets and to the increase of filtration pressure. These phenomena lead to the onset of thrombocytopenia and to functional platelet defects which add to the severe coagulation disturbances of these patients; and also to hemodynamic problems, related to vasoactive amines which are released in large amounts by platelets aggregated and destroyed on the column's filter [42]. Preliminary, unpublished studies from the King's College Liver Unit in London appear to indicate that prostacyclin infused into patients might considerably reduce these side effects.

The *reinfusion of ascitic fluid* in cirrhotics with diuretic-resistant ascites appears to be associated with a prolongation of the prothrombin time and a decrease in platelet count and plasma levels of factor V, VII, IX and fibrinogen. Extravascular loss following adherence of coagulation factors and platelets to the filtration membrane is regarded as the most likely cause of those changes [44 76]. The procedure of ascites reinfusion was also shown to cause DIC with widespread hemorrhagic diathesis [43]; on the basis of our experience, these catastrophic accidents appear to be rare. It seems that the Leveen technique of peritoneovenous shunting of ascitic fluid can also lead to DIC in a number of cases [62].

Coagulation Tests in the Diagnosis of Liver Diseases

In liver disease, it is not possible to rely only on coagulation analysis for diagnostic and prognostic purposes. However, clotting tests are useful in:

1) the evaluation of parenchymal damage, assuming that the plasma levels of clotting factors are proportional to the synthetic function of the hepatocyte in absence of consumption, vitamin K deficiency or pathologic inhibitors;

2) the assessment of the hemorrhagic tendency of these patients. Since the biological half-life of coagulation factors is much shorter than that of any protein synthesized by the hepatocyte, clotting tests are thought to demonstrate better than other parameters the actual situation of protein synthesis. Such test should be simple enough to be used by non-specialized laboratories; and sensitive enough to allow

for the identification of minor defects which are very important in the early diagnosis of liver disease. According to our experience, the specific assays of the individual clotting factors produced by the liver seem to be less useful as a diagnostic tool than broad-spectrum tests (i.e., prothrombin time, activated partial thromboplastin time, prothrombin and proconvertin time, and Normotest) which are sensitive to more than one coagulation factor. In a group of patients with documented chronic liver disease the highest incidence of abnormalities was shown by the Normotest which is the commercial and standardized version of prothrombin and proconvertin time (P & P)[47 58]. The test is thought to be sensitive to deficiencies of factors II, VII and X and contains rabbit brain thromboplastin, optimal amounts of factors V and XIII, fibrinogen and calcium ions. The higher sensitivity of the Normotest compared with the P & P test may be explained by the improved standardization and reproducibility of the commercial reagent. Its superiority as a diagnostic tool on such widely-used tests as the prothrombin time and activated partial thromboplastin time is presumably related to the steepness of the dose-response curve [58] which makes the test particularly sensitive within the range of clotting factors frequently found in patients with chronic liver disease (30-60%). Since the Normotest is not sensitive to endogenous and exogenous inhibitors of blood coagulation [58], it provides an actual picture of protein synthesis. However, in the evaluation of the bleeding risk of patients submitted to surgical procedures (such as biopsy, portacaval shunts, biliary tract surgery), it may become necessary to combine the Normotest with tests susceptible to the action of pathological inhibitors which may be important in determining hemorrhages in a number of liver diseases (such cholestasis, chronic active hepatitis and liver amiloidosis for example)[48 58 59]. Therefore, global coagulation tests such as prothrombin time and activated partial thromboplastin time should be included in the battery of tests used to screen patients before these procedures. Since the bleeding tendency in liver disease is not exclusively caused by the reduced synthesis of coagulation factors and presence of inhibitors, coagulation tests should be carried out together with platelet count and bleeding time, which not only furnishes information on the number of platelets but also on their function in hemostasis.

Management of Hemostatic Failure in Liver Disease

The hemostatic defect in liver disease is determined by numerous pathogenetic factors and it is difficult to ascertain which of such factors prevails in the occurrence of a given bleeding episode. There-

fore, no single therapeutic agent should be used but rather many with different purposes. Treatment must be differentiated in relation to the different types of hemorrhages which are encountered; from the more frequently occurring bleeding from the gastrointestinal tract to hemorrhages following procedures of minor (biopsy) and major (portacaval shunt) surgery, and to the generalized bleeding diathesis in fulminant hepatitis. Besides vitamin K, which is specifically indicated when the defect occurring in cholestatic jaundice is related to defective absorption of this compound, the hemostatic agents to be considered in other forms of liver disease are fresh-frozen plasma, concentrates of the prothrombin complex clotting factors, synthetic fibrinolysis inhibitors and heparin.

Fresh-frozen plasma contains all coagulation factors and inhibitors and is therefore theoretically the most suitable agent in the correction of the multiple defects found in liver disease. In practice, this goal is not easily achieved [28 49] and its use limited by the large amounts needed to bring about a satisfactory correction of clotting tests (1-1.5 liters), since the development of hypervolemia and hypernatremia is likely to endanger patients with ascites and esophageal varices.

Prothrombin complex concentrates are available commercially and contain in small volumes high concentrations of factors II, VII, IX and X. Since other clotting factors which are decreased in liver disease (such as factors V and XI) are not present in significant amounts in such concentrates, their administration usually fails to correct abnormal coagulation tests unless accompanied by the infusion of fresh frozen plasma [48]. They have been successfully employed alone or in combination in the management of liver biopsies in patients presenting with a marked coagulation defect [27 28 50].

A negative aspect in the use of these concentrates is represented by their risk of transmitting hepatitis, which carries a particularly severe prognosis in patients with preexisting liver function impairment [77]. Since the risk of hepatitis is apparently not decreased by HB_sAg screening of donors, concentrates prepared from a small number of plasma units processed in countries with a low incidence of post-transfusion hepatitis could possibly offer an alternative approach [36]. Another potential risk in the use of these products is that of thromboembolic episodes (deep-vein thrombosis, pulmonary embolism, DIC) which are probably related to the presence in the concentrates of activated forms of clotting factors which cannot be cleared by the liver, and are poorly neutralized by inhibitors due to the impairment of their synthesis [3 26 39]. The risk may be diminished by some

recent modifications in the preparational procedures; and perhaps by the concomitant administration of fresh-frozen plasma (6-8 ml/kg) or concentrates replacing naturally occurring inhibitors such as antithrombin III [49]. Taking into account all these problems, the use of concentrates must be limited to the performance of biopsies (or procedures of minor surgery) which become absolutely necessary for diagnosis in liver patients with marked coagulation defects. Their use should be avoided in major surgical procedures (such as portacaval shunt), because the combined presence of several risk factors (low levels of naturally occurring inhibitors, postoperative hypercoagulability and decreased removal by the liver of the activated factors contained in concentrates) might precipitate thromboembolism [50]. In any case, concentrate administration should be monitored by laboratory tests in order to reveal as early as possible any signs of activation of the hemostatic mechanism.

Platelet concentrates are unlikely to be effective even in the presence of severe thrombocytopenia. Infused platelets are rapidly removed from circulation by the spleen and liver, augmenting the sequestred pool unavailable for hemostasis. It should be emphasized that thrombocytopenia does not appear to have a relevant role in the pathogenesis of bleeding in liver patients, as demonstrated by the fact that the skin bleeding time is often normal in presence of a significant thrombocytopenia or less prolonged than expected by platelet number (see also Coagulation Tests in the Diagnosis of Liver Disease).

The use of *heparin* in liver disease has been proposed on the basis of limited clinical experience demonstrating the improvement of some hemostasis parameters in patients with acute and chronic liver disease [9 12 72 78], as well as on the basis of a working hypothesis that such alterations are due to DIC. As forementioned, these data are interesting from a speculative point of view, but the elements in favour of the clinical efficacy of heparin are scarce and anecdotal. A recent controlled study conducted in patients with acute liver failure due to paracetamol intoxication failed to show any benefit from the use of heparin [25]. We therefore believe that the use of this compound at full dosage in the management of hemorrhagic manifestations of liver disease is not supported by enough clinical and experimental evidence and that the addition of a powerful coagulation inhibitor in patients with already impaired hemostasis should be considered with considerable caution. The use of low-dose subacutaneous heparin, which has been advocated in liver cirrhosis, may be more reasonable, be-

cause side-effects do not appear to have any importance [11]. However the clinical benefit from this regimen still remains to be demonstrated.

The administration of *synthetic fibrinolysis inhibitors* (such as epsilon-aminocaproic acid and tranexamic acid) was largerly advocated on the assumption that primary hyperfibrinolysis plays a primary role in the pathogenesis of bleeding episodes. These therapeutic agents are likely to have a place in the management of gastrointestinal bleeding in which local hyperfibrinolysis is probably an important pathogenetic factor [14 54 56] and in the prophylaxis of pre- and postoperative blood loss in cirrhotics undergoing portacaval shunt [32].

RIASSUNTO

In questa rassegna vengono discusse le principali alterazioni dell'emostasi (coagulazione, piastrine, fibrinolisi) riscontrate nelle epatopatie acute e croniche parenchimali, nonché nelle sindromi da colestasi intra- ed extraepatica. Il significato dei test di coagulazione nella valutazione della funzione sintetica epatocitaria e la loro capacità predittiva delle manifestazioni emorragiche viene analizzato in dettaglio. Infine gli autori affrontano il problema del ruolo della terapia sostitutiva con plasma fresco congelato e concentrati del complesso protrombinico nella prevenzione e terapia delle manifestazioni emorragiche dell'epatopaziente.

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