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REVIEW
Coagulation and fibrinolysis in individuals with advanced liver disease

Geç dönem karaciğer hastalıklarında koagulasyon ve fibrinolizis

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An overview of normal coagulation and fibrinolysis is presented. The abnormalities of coagulation and fibrinolysis seen in individuals with advanced liver disease is reviewed. The necessary steps in the management of bleeding in patients with advanced liver disease is outlined. Finally those liver diseases associated with vascular thrombosis are identified.

Key words: Coagulation, thrombosis, bleeding, hemorrhage clotting

Bu derlemede normal koagulasyon ve fibrinolisiz sunulmaktadır. Karaciğer hastalarında görülen koagulasyon ve fibrinolizis anormallikleri derlenmiştir. Karaciğer hastalarında ki kanama tedavisinin ana basamakları ve vasküler trombozla birlikte olan karaciğer hastalıkları konu edilmiştir.

Anahtar kelimeler: Koagulasyon, tromboz, kanama, pıhtılaşma

INTRODUCTION

Hepatic disease, particularly advanced hepatic disease is characterized by a severe coagulopathy after confounded by a prominent fibrinolytic process and the laboratory manifestations of a disseminated intravascular coagulation (1-2). The coexistence of these combined abnormalities of blood clotting and dissolution create considerable problems for the physicians caring for, evaluating and treating patients with advanced liver disease. The phenomenon of blood clotting and dissolution in individuals with liver disease is only understandable if one is knowledgeable about the processes of coagulation and fibrinolysis as they occur in normal individuals. These two processes create clinical problems at each end of a biological spectrum as depicted in figure 1 ranging from a bleeding diathesis on the left to a thrombotic diathesis on the right with the normal situation in the middle. Thus, the status of the hemostatic system represents a delicate balance between pro- and anti-hemostatic processes. Any alteration in the system can lead to either a bleeding problem or a thrombotic process.

Liver failure is characterized by multiple alterations in the hemostatic system that can range from a clinical problem consisting of a bleeding disorder to a thrombotic disorder as a consequence of advanced liver disease, therapeutic interventions, and/or the development of new complications (varix rupture, spontaneous bacterial peritonitis, endotoxemia and others).

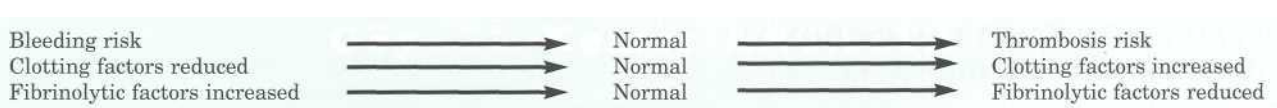

Figure 1. Clinical spectrum of coagulation and fibrinolysis

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THE NORMAL HEMOSTATIC SYSTEM

The normal hemostatic system consists of many different components that interact with each other sequentially in an ordered process to develop a clot in response to injury while simultaneously limiting clot formation to a localized area of need, thereby preventing pathological thrombosis.

The components of this system include platelets and other blood cells especially monocytes that can express tissue factor (TF), the blood vessel that is injured to include the endothelium with its various receptors and the subendothelium which is a rich source of TF and various proteoglycans, plasma with its coagulation factors, existing principally as apoenzymes that become activated to create specific clotting factors, plasma inhibitors of activated coagulation factors, fibrinolytic factor and their inhibitors, ionized calcium, phospholipids expressed on platelets and endothelial cells, prostaglandins that modulate blood vessel contractility and finally various cytokines and neurotransmitters that alter platelet, endothelial and myofibril activity and function. These cells, proteins, ligands, receptors and enzymes interact in a passive mechanism, yet in an ordered sequence and are carefully controlled by a mixture of promoters and inhibitors of both hemostasis and fibrinolysis.

The two principal methods of assessing the competence of the intrinsic and extrinsic coagulation cascade are the activated partial thromboplastin time (aPTT) and the prothrombin time (PT) respectively (3-4). These two laboratory tests are dependent upon the integrity of HK, PK, Factor XII (FXII), Factor FXI (FXI), Factor VIII (FVIII), Factor X (FX), Factor V (FV), Factor II (FII) and fibrinogen in the aPTT and Factor VII (FVII), FX , FV, FII and fibrinogen in the PT. Both systems require FX, FV, Factor II and fibrinogen as well as calcium ions and phospholipid surfaces for normal activity (Figure 2).

RESPONSE TO VASCULAR INJURY AT THE LEVEL OF THE BLOOD VESSEL

The immediate response to any vascular injury occurs immediately and consists of vasoconstriction, followed by platelet adhesion to the injured surface that occurs within seconds and platelet aggregation that occurs within minutes. This immediate hemostatic response is followed by secondary hemostasis which results in the sequential activation of coagulation factors and terminates in the formation of a stable fibrin plug or clot. This phenomenon also occurs in seconds to minutes and is followed by activation of the fibrinolysis pathway that occurs in minutes and initiates lysis of clots that takes hours to days to occur.

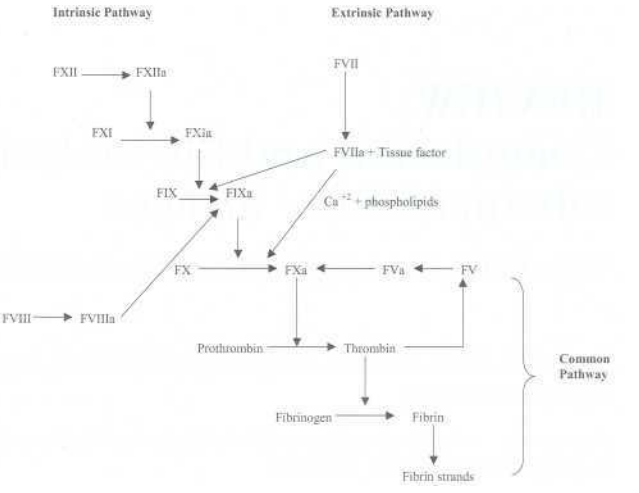

Figure 2. Coagulation cascade

The response of the vascular wall to injury and subsequent hemostasis is multifactorial and is presented in (Table 1). All of these processes occur and are activated within seconds to minutes of vessel wall injury.

Table 1. Contribution of the vessel wall to hemostasis

I. Vasoconstruction
- Immediate
- Reduces or prevents blood loss

II. Biosythesis and partial activation of the active components of hemostasis that occurs in seconds to minutes after injury
- a) Von Willebrand Factor (VWF)
- b) Factor Villa
- c) Tissue plasminogen activator (tPA)
- d) Plasminogen activator inhibitor-1 (PAI-1)
- e) Thrombomodulin (TM)
- f) Expression of cell surface receptor for various factors, proteins, cells
- g) Nitric oxide and angiotensin converting enzyme synthesis
- h) Prostacyclin (PGI2), an inhibitor of platelet aggregation and vasoconstriction

III. Binding of proteins and cells
- Synthesis and expression of adhesion proteins, adhesion molecules and integrins
- The binding of factors X and IX and their activation

IV. Inhibition of uncontrolled coagulation
- Binding of anti-thrombin to proteoglycans
- Binding of thrombin to thrombomodulin with the activation of protein C
- Degradation of ADP by vascular ADPase

THE ROLE OF PLATELETS

Platelets are discoid "cells" actually fragments of megakaryocytes that are 0.5 to 3.0mm in diameter. Their level in plasma is regulated indirectly by the level of thrombopoietin (TPO) in plasma. TPO is actually a megakaryocyte growth factor and not a platelet growth factor per se. Platelets are produced in the bone marrow and represent differentiated megakaryocyte membrane packets rich in cytokines, growth factors and various low molecular weight substances. The normal platelet number in whole blood is 150,000 to 300,000cells/µL. In the presence of normal platelets, less than 10,000 platelets are adequate for normal hemostasis. In the case of various disease conditions, particularly those affecting platelet number (hematologic disorders) or activity (renal and hepatic failure), many more are needed and a reasonable nadir value for hemostasis can be set at 50,000cells/µL. Two thirds of the body's platelets circulate in the blood while 1/3 are held in reserve in the spleen. The average life span of a platelet, once released from the bone marrow, is 10 days. Platelets are very reactive and a large number of platelet activators have been identified and are found in the endothelium, the subendothelium and walls of blood vessels and as result of their release from these sites as well as platelets themselves and other cells in the blood and tissue. The platelets are rapidly activated following any vascular injury. Other platelet activators are iatrogenic. A partial listing of the recognized platelet activating factors is shown in (Table 2).

NORMAL PRIMARY HEMOSTASIS

Platelets bind transiently to Von Willebrand factor (VWF) expressed on the vascular endothelium and subendothelial collagen. This is followed by a progressive binding of platelets to subendothelial receptors and ligands leading to platelet adhesion and the formation of a platelet plug. Platelet activation with the release of thromboxane A2 and ADP further enhances platelet aggregation and clustering of platelets that bind to fibrinogen and VWF resulting in the bridging of fibrinogen and VWF between adjacent platelet clusters further enhancing platelet aggregation and platelet plug formation. This sequence of events is shown sequentially in (Figure 3).

Secondary hemostasis consists of the process of thrombin generation which further activates platelets and enhances their aggregation leading to the conversion of fibrinogen to fibrin. Fibrin once formed spontaneously polymerizes and forms an insoluble mesh which stabilizes the platelet plug as a fibrin clot. Secondary hemostasis is coagulation factor dependent. The plasma levels of the coagulation factors vary widely. The normal level of fibrinogen in plasma ranges from 2-4g/L while that of FVIII is normally <lmg/L. As mentioned earlier in this presentation, the coagulation factors function as substrates, cofactors and enzymes. With the exception of Factor Vila, they circulate exclusively as apoenzymes which can be activated rapidly, when needed, for thrombus formation. Factor VII is the exception and circulates in plasma in two forms: a relatively small fraction exists as FVIIa and a very much larger fraction exists as the apoenzyme FVII.

Tissue factor binds to FVIIa and activates both factors IX and X. Factors IXa + FVIIIa forms a 2 component X-ase complex that enhances FXa formation. Factors Xa, Va and Vila form a 3 component complex that act as a prothrombinase complex that converts prothrombin to thrombin further activating FV to FVa, FVIII to FVIIIa and FXI to FXIa which in turn enhances the conversion of FIX to FIXa. This conversion of FIX to FIXa serves as a potential link between the extrinsic and intrinsic clotting cascade (Figure 3).

Table 2. Recognized platelet activating factors and their sources

FACTOR	SOURCE
Collagen I	Vessel wall and subendothelium
Thrombin	Coagulation cascade
Adenosine dehydrate (ADP)	Activated platelets and other cells
Serotonin	Activated platelets and other cells
Epinephrine	Activated platelets and other cells
Thromboxane A2	Activated platelets and other cells
Arachidonic acid	Activated platelets and other cells
Platelet activating factor (PAF)	Activated platelets and other cells
Antibiotics and other drugs	Iatrogenic factors
DDAVP	Iatrogenic factors

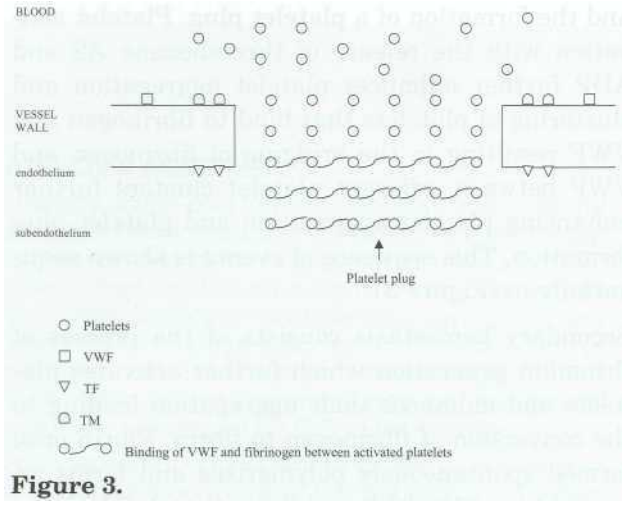

Figure 3.

Thrombin once formed as a result of activation of the common pathway of coagulation enhances fibrin formation and stabilization by activating factor XIII which stabilizes the fibrin clot by forming cross links between adjacent fibrin molecules, Thrombin also binds thrombomodulin (TM) and activates the protein C pathway and thrombin activatable fibrinolysis inhibitor (TAFI). Thus TM subserves an anticoagulant and fibrinolytic function (protein C activation) respectively that is controlled in part by the activation of TAFI which removes terminal lysine residues and to a lesser extent arginine residues from fibrin preventing tissue plasminogen activator (tPA)-plasminogen binding and subsequent fibrinolysis.

The process of thrombin generation is limited or controlled by the addition of tissue factor proteinase inhibitor (TFPI) to a 3 component complex consisting of Xa, VIIa and TF creating an inactive 4 component complex and in addition, circulating antithrombin inhibits thrombin and both IXa and Xa. Thrombin is further inhibited by heparin cofactor II.

Progressive clot formation is halted by the actions of α-2 macroglobulin which inhibits Xa, activation of the protein C pathway resulting in an inactivation of FVa and FVIII and the process of fibrinolysis wherein plasmin is formed from plasminogen via an action of tPA.

THE DISSEMINATED INTRAVASCULAR COAGULATION (DIC) PROCESS

Disseminated intravascular coagulation (DIC) is a process of continued formation of blood clot (coagulation) with a equally active process of clot lysis resulting in a clinically significant reduction in coagulation factors and platelets with a resultant enhanced risk for more active or severe bleeding than would be expected otherwise considering the degree of tissue injury. As such, the DIC syndrome is characterized by an abnormal PT and aPTT, thrombocytopenia, the presence of enhanced levels of fibrin split products and fibrin monomers as well as d-dimers or fragments of previously cross-linked fibrin monomers.

DISORDERS OF HEMOSTASIS PRESENT IN INDIVIDUALS WITH ADVANCED LIVER DISEASE

Table 3 identifies the most common abnormalities in the hemostasis-fibrinolysis continuum seen in individuals with advanced liver disease. The thrombocytopenia occurring in advanced liver disease has a multifactorial origin (5-7). This consists of a combination of reduced synthesis of TPO, the megakaryocyte growth factor produced exclusively by the liver, increased splenic sequestration as a consequence of portal hypertension and the resultant splenomegaly; a reduced half life of platelets as a result of splenic sequestration and in certain liver diseases having an autoimmune pathogenic mechanism; reduced platelet production as a result of folic acid deficiency which is common in liver disease especially alcoholic liver disease and those requiring continuous diuretic therapy; reduced platelet production as a direct consequence of exposure to a toxin or drug such as ethanol, various H2 antagonists, proton pump inhibitors and antibiotics used to treat hepatic encephalopathy and prevent spontaneous bacterial peritonitis and other infections common to debilitated individuals with advanced liver disease and finally a low grade DIC process that is a remarkably common occurrence in individuals with cirrhosis. In addition to being present in reduced numbers, the platelets of individuals with liver disease demonstrate reduced aggregation and reduced adhesion characteristics. Reduced platelet aggregation in cirrhotics can be assessed in the laboratory with the use of a wide array of platelet aggregation in-

Table 3. Abnormalities of hemostasis and fibrinolysis in individuals with abnormal liver disease

1. Thrombocytopenia
2. Platelet dysfunction
3. Reduced levels of hemostatic proteins
4. Reduced release of activated hemostatic proteins and prtein inhibitor complexes

ducers that includes ADP, ristocetin, arachidonic acid, collagen and thrombin. Moreover, the synthesis and release of nitric oxide (NO) and prostacyclin by injured endothelial cells adversely affects platelet adhesion and aggregation. Finally, a low-grade proteolysis of platelet surface receptors by plasmin occurs in individuals with chronic liver disease.

Primary hemostasis is abnormal in patients with liver disease not only because of reduced platelet numbers and function but also as a result of increased plasma levels of VWF occurring as a result of reduced platelet adhesion and endothelial cell dysfunction. Moreover, the ratio of high molecular weight multimers/low molecular weight multimers of VWF in plasma is reduced as a result of a reduced VWF cleaving protease level as a consequence of plasma and elastase proteolysis.

An additional abnormality seen in cirrhotics is hypofibrinogenemia occurring as a result of reduced hepatic synthesis as fibrinogen is synthesized solely in the liver. Reduced fibrinogen levels are common in very advanced chronic liver disease and in cases of acute hepatic failure. A third situation in which fibrinogen levels may become critical is in the presence of decompensated DIC. In this later case, it is not reduced fibrinogen synthesis but rather increased fibrinogen consumption that is responsible for the reduced fibrinogen level.

Dysfibrinogenemia occurs also in individuals with cirrhosis and is a consequence of excessive sialic acid residues on the fibrinogen molecule as a result of an abnormal processing of the fibrinogen molecule prior to hepatic secretion possibly as a result of intrahepatocyte enhanced glucosyltransferase activity.

In the unique situation of acute hepatic failure, FV levels have been shown to identify those, who will not survive without liver transplantation from those who will. Levels of FV below 10% in a child and < 20% in an adult identify those who will not survive without liver transplantation.

THE FIBRINOLYTIC SYSTEM IN LIVER DISEASE

Chronic liver disease is characterized by hyperfibrinolysis. This enhanced fibrinolysis is a result of increase plasma level of tPA, increased levels of thrombin-antithrombin complexes, plasma antiplasmin complexes and the presence of increased levels of d-dimers. In acute liver failure, a state of reduced fibrinolysis occurs as a consequence of markedly increased levels of plasminogen activating inhibitor-1 (PAI-1) which is not cleared by the dysfunctional liver.

DIC

The DIC syndrome can occur in both a compensated and decompensated state. In the former, markers of DIC such as d-dimers and fibrin split products are increased in the plasma but the majority of the plasma coagulation factors remain in the normal range or just outside and below the normal range. Moreover, the platelet count is usually normal but can be reduced in very far-advanced cirrhotic liver disease.

In contrast, in decompensated DIC, the platelet count is always reduced. Both the PT and aPTT are abnormal (prolonged) as is the thrombin time. The plasma levels of factors II, V and VII are reduced and plasma levels of fibrin split products and d-dimers are increased markedly. A smooth transition from compensated to decompensated DIC can be seen in individuals, who progress from Child class A-> B-> C. Essentially, no one in Childs class A will have laboratory evidence for DIC in contrast nearly half of those who are in Childs class B and the vast majority of individuals in Childs class C (75%) will have biochemical evidence for DIC. The DIC syndrome in advanced cirrhotics seen in the absence of overt bleeding is associated with increased levels of circulating endotoxin presumably arising as consequence of a "leaky intestine" and reduced mucosal defense mechanisms. Interestingly, the administration of oral antibiotics, particularly neomycin which binds endotoxin to the clinical regimen of decompensated cirrhotics, is associated with a reduced level of endotoxemia and reduced evidence for a decompensated DIC syndrome.

GASTROINTESTINAL BLEEDING AND ITS MANAGEMENT IN INDIVIDUALS WITH ADVANCED LIVER DISEASE

Clinical bleeding in individuals with liver disease almost never occurs as a consequence of reduced coagulation factors per se. However, the combination of low platelet numbers, reduced platelet function, increased NO levels and prostacyclin inhibitors of platelet function coupled with low levels of factors II, V, VII, IX and X can contribute to major bleeding in cirrhotics as a consequence of

minor trauma manifested as epistaxis and "spontaneous" bruising of the extremities and trunk. Qualitative and quantitative abnormalities of fibrinogen and increased levels of tPA not balanced with an equivalent increase in PAI-1 and low levels of fibrinolysis inhibitors such as a-2 macroglobulin, TAFI and histamine rich glycoprotein all contribute to defective fibrin clot formation and an enhanced dissolution of the fibrin clot. An anatomic area where fibrinolysis is a particular problem is the mouth with bleeding after dental extraction which can be extensive and in some cases lethal as a result of hypovolemia and/or complicating aspiration.

Secondary hemostasis is impaired in cirrhotics due to a reduction in all of the coagulation factors except FVIII. The presence of dysfunctional proteins containing Gla residues (vitamin K dependent proteins) is common in cholestatic liver disease but is unusual in individuals with hepatocellular disease.

With these concepts in mind, the principles of the management of bleeding in individuals with liver disease are shown in (Table 4). The use of antifibrinolytic agents is highly controversial in the management of bleeding in cirrhotics but is used frequently at some centers. No randomized controlled trials of antifibrinolytic agents have been reported in cirrhotics.

Table 4. Principles in the clinical management of bleeding in individuals with liver disease

1. Administer platelets to maintain a platelet count >50,000
2. Administration of DDAVP (0.3mcg/kg IV) to enhance platelet function
3. Administration of fresh frozen plasma to replace clotting factors and/or the administration of rhFVIIa which pre vents volume overload
4. Maintain fibrinogen levels >150mg/dL

HYPERCOAGUABILITY IN INDIVIDUALS WITH LIVER DISEASE

Several factors seen commonly in individuals with liver disease promote hemostasis. These include increased levels of FVIII and VWF, reduced levels of plasminogen and reduced levels of protein C, protein S, protein Z, anti-thrombin, a-2 macroglobulin and heparin cofactor II. In addition, the presence of anti-phospholipid autoantibodies, anticardiolipin antibodies and anti-neutrophil cytosolic antibodies are found in specific liver diseases at an increased frequency. These include autoimmune chronic hepatitis, the two cholestatic liver diseases of adults (primary biliary cirrhosis and primary sclerosing cholangitis) and less often in alcoholic liver disease.

The presence of these antibodies in individuals with these liver diseases is associated with portal vein and splenic vein thrombosis as well as peripheral deep vein thrombosis and occasionally pulmonary emboli when they experience various forms of trauma (falls, auto accidents, etc) and various surgical procedures.

CONCLUSIONS

The balance of the coagulation and fibrinolytic systems in individuals with advanced liver disease is frequently abnormal. These abnormalities vary as a function of disease severity, type of liver disease and the presence or absence of the more common complications of advanced liver disease such as bleeding, infection, encephalopathy and endotoxemia. The recognition of these abnormalities and their correction are essential for a normalization of the balance between hemostasis and bleeding.

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