Coagulation Disorders in Liver Cirrhosis with and without Hepatocellular Carcinoma

Essay

submitted for partial fulfillment of master degree

in Internal medicine

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2011

اضطرابات التخثر في التشمع الكبدي مع وبدون أورام الكبد

مقال من قبل

سماح ابراهيم قاسم ابو زامل

بكالوريوس الطب والجراحة

توطئة للحصول على درجة الماجستير فى تخصص

الأمراض الباطنة

تحت إشراف

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The liver plays a central role in the hemostatic system as it synthesizes the majority of coagulation factors and proteins involved in fibrinolysis. Furthermore, the liver produces thrombopoeitin, which is responsible for platelet production from megakaryocytes. Consequently, chronic or acute liver diseases frequently have a profound impact on the hemostatic system. An important contributor to the coagulation disturbances in liver disease is decreased plasma levels of hemostatic proteins synthesized by the liver. Additionally, thrombocytopenia as a result of decreased platelet production or increased platelet turnover and intravascular activation of hemostasis resulting in consumption of hemostatic factors contribute to alterations in the hemostatic system. Furthermore, continuous low-grade activation of endothelial cells results in continuous release of a number of hemostatic proteins whose levels are therefore frequently elevated in patients with liver disease (e.g. von Willebrand factor). Finally, portal hypertension, which is a common complication of chronic liver failure results in hemodynamic changes that may impact endothelial function and splenomegaly, which results in increased platelet sequestration in the spleen.

Routine laboratory tests of hemostasis such as the platelet count, the prothrombin time (PT) and the activated partial thromboplastin time (APTT) are frequently abnormal in patients with liver disease. The combination of thrombocytopenia with a prolonged PT and APTT is suggestive of a bleeding diathesis, and it is traditionally assumed that patients with liver failure are at risk for bleeding as a result of these hemostatic changes.

Acknowledgements

First of all, all gratitude is to God almighty for blessing this work, until it has reached its end, as a part of his generous help, throughout my life.

Really I can hardly find the words to express my gratitude to ***Prof. Dr.Mahmoud Ossman,*** *Professor of internal medicine, faculty of medicine, Ain Shams University, for his supervision, continuous help, encouragement throughout this work and tremendous effort he has done in the revision of the whole work. It is a great honor to work under his guidance and supervision.*

I am also indebted to ***Prof. Dr Mohammed Abd****ELMaeboud Professor of internal medicine, faculty of medicine, Ain Shams University for his guidance, continuous assistance and sincere supervision of this work .*

I would like also to express my sincere appreciation and gratitude to ***Dr.Maha Mohsen*** *lecturer of internal medicine, faculty of medicine, Ain Shams University, for her continuous directions and support throughout the whole work.*

Last but not least, I dedicate this work to my family, whom without their sincere emotional support, pushing me forward this work would not have ever been completed.

Samah ibrahim kassem abouzamel

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AASLD	:	The American Association for the Study of Liver Disease.
ADP	:	Adenosine diphosphate.
ADPase	:	Adenosine diphosphatase.
aPTT	:	Activated Partial Thromboplastin Time.
AT	:	Antithrombin.
COAT	:	COllagen And Thrombin stimulated.
EACA	:	ε-aminocaproic acid.
ECM	:	Extracellular matrix.
EDHF	:	Endothelium-derived hyperpolarizing factors.
EPCR	:	Endothelial protein C receptor.
FDPs	:	Fibrinogen degradation products.
FFP	:	Fresh Frozen Plasma.
FP	:	Fresh Plasma.
HCC	:	Hepatocellular carcinoma.
HG	:	high MELD group.
ISI	:	International Sensitivity Index.
LG	:	low MELD group.
LRP	:	Lipoprotein receptor-related protein.
MARS	:	Molecular adsorbent recirculating system
MDCTA	:	Multidetector Computed Tomographic Angiography.
MELD	:	Model for end-stage liver disease.
MG	:	Medium MELD group.
NO	:	Nitric oxide.
NOSs	:	Nitric oxide synthases .
PAI	:	plasminogen activator inhibitor.
PAR	:	Protease-activated receptor (The thrombin receptor).
PBC	:	Primary billiary cirrhosis.
PGI_2	:	Prostaglandin I_2 (Prostacyclin).

List of Abbreviations (Cont.)

PIVKA-II	:	Protein induced in vitamin K absence-II.
POPH	:	Portopulmonary hypertension.
PSC	:	Primary scelerosing collangitis.
PT	:	Prothrombin time.
rFVIIa	:	Recombinant activated factor VII.
TA	:	Tranexamic acid.
TAFI	:	Thrombin activatable fibrinolysis inhibitor.
TEG	:	Thromboelastography.
TF	:	Tissue factor.
TFPI	:	Tissue factor pathway inhibitor.
TIPS	:	Transjugular Intrahepatic Portosystemic Shunt.
TM	:	Thrombomodulin.
t-PA	:	Tissue plasminogen activator.
TPO	:	Thrombopoietin .
TR	:	Tricuspid regurge.
TT	:	Thrombin Time.
TXA_2	:	Thromboxane A_2.
UNOS	:	United Network for Organ Sharing.
vWF	:	von Willebrand factor.

Introduction

The interface between acute and chronic liver disease and disorders of hemostasis and bleeding is historically longstanding .since a measure of clot formation ,the INR,is major component of the MELD score (the model end-stage liver disease) used for organ allocation ,a number of issues have emerged over the past few years bringing new insights into the pathogenesis and management of liver disease related coagulation disorders [**Monroe DM and Hoffman,2009**]. New insights into normal hemostatic mechanisms: great deal has changed in understanding of the normal pathways of clot formation and its regulation over the past 10-20 years. Normal clotting can be viewed in terms of several events at site of vascular injury, It begins through the combination of factor VII binding to tissue factor [TF], this complex serve to create a priming amount of thrombin from prothrombine [Xa-Va complex] [**Hoffman M etal,2007**]. Platelet adhesion to collagen at the breach mediated by glycoprotein Ib, integrn αIIB1,glycoprotein VI and Von-willebrand factor. [**Hugentholtz G etal ,2009**] in liver cirrhosis numerous forces

alter these relationships.although commonly the system becomes re-balanced into relative homeostasis.However, the balance can be delicate and fall toward relatively less or more coagulant activity with small disturbances. Recently,[**Tripodi etal.,2005**], demonstrated that thrombin production in cirrhotic patients was normal when measured in a system using endothelium-derived thrombomodulin which remains intact in cirrhosis. Also,Hyperfibrinolysis refers to premature dissolution of the fibrin clot and should be suspected in delayed post-procedure bleeding and in some cases of mucosal bleeding. Its prevalence in cirrhosis is un certain yet, in cirrhosis which is associated with an altered form fibrinogen [dysfibrinogen or fetal fibrinogen] may alter clot lysis. The presence of hyperfibrinolysis has also been shown to predict G.I.bleeding in cirrhosis. [**Violif,et al,1992**]-on the other hand Ordinas et al,1996, demonstrated impaired platelet aggregation in cirrhosis. Also, platelet lipid composition in advanced cirrhosis may be significantly altered in parallel to changes in lipoprotein metabolism associated with conditions such as spur cell anaemia [**Deguchi H et.al,2005**].

AIM of the Research:

Is to adress the complexity of liver disease-related disturbances of the hemostatic system with emphasis on these disorders in cirrhosis with and without hepatocellular carcinoma .

Normal Hemostasis

it includes :

1-vascular endothelium

2-platelets

3-plasma mediated Hemostasis.

Background

Hemostasis comprises cellular and biochemical processes that maintain intravascular blood fluidity, and promote revascularization of thrombosed vessels after injury. Vascular endothelium, platelets, and plasma coagulation proteins play equally important roles in this process. Failure to maintain balance commonly leads to excessive bleeding or pathologic thrombus formation ***(Slaughter, 2009).***

After initial injury there is a brief period of arteriolar vasoconstriction mediated by reflex neurogenic mechanisms and augmented by the local secretion of factors such as endothelin (a potent endothelium-derived vasoconstrictor).The effect is transient, however, bleeding would resume if not for activation of the platelet and coagulation systems.

Endothelial injury exposes highly thrombogenic subendothelial extracellular matrix (ECM), facilitating platelet adherence and activation. , Platelets bind via glycoprotein Ib (GpIb) receptors to von Willebrand factor (vWF) on exposed extracellular matrix (ECM) and are activated. Activation of platelets results in a dramatic shape change (from small rounded discs to flat plates with markedly increased surface area), as well as the release of secretory granules. Released adenosine diphosphate (ADP) and thromboxane A_2 (TxA_2) induce additional platelet aggregation through platelet GpIIb-IIIa receptor binding to fibrinogen, Within minutes the secreted products recruit additional platelets (aggregation) to

form a primary hemostatic plug; this process is referred to as primary hemostasis.(Hoffman and Monroe, 2007) .

Tissue factor is also exposed at the site of injury. Also known as factor III and thromboplastin, tissue factor is a membrane-bound procoagulant glycoprotein synthesized by endothelial cells. It acts in conjunction with factor VII as the major in vivo initiator of the coagulation cascade, eventually culminating in thrombin generation. Thrombin cleaves circulating fibrinogen into insoluble fibrin, creating a fibrin meshwork, and also induces additional platelet recruitment and activation. Local activation of the coagulation cascade (involving tissue factor and platelet phospholipids) results in fibrin polymerization, "cementing" the platelets into a definitive *secondary* hemostatic plug This sequence secondary hemostasis, consolidates the initial platelet plug.(Hoffman and Monroe, 2007) .

Polymerized fibrin and platelet aggregates form a solid, permanent plug to prevent any further hemorrhage. At this stage, counter-regulatory mechanisms (e.g., tissue plasminogen activator,(t-PA) and thrombomodulin) are set into motion to limit the hemostatic plug to the site of injury. ***(Hoffman and Monroe, 2007).***

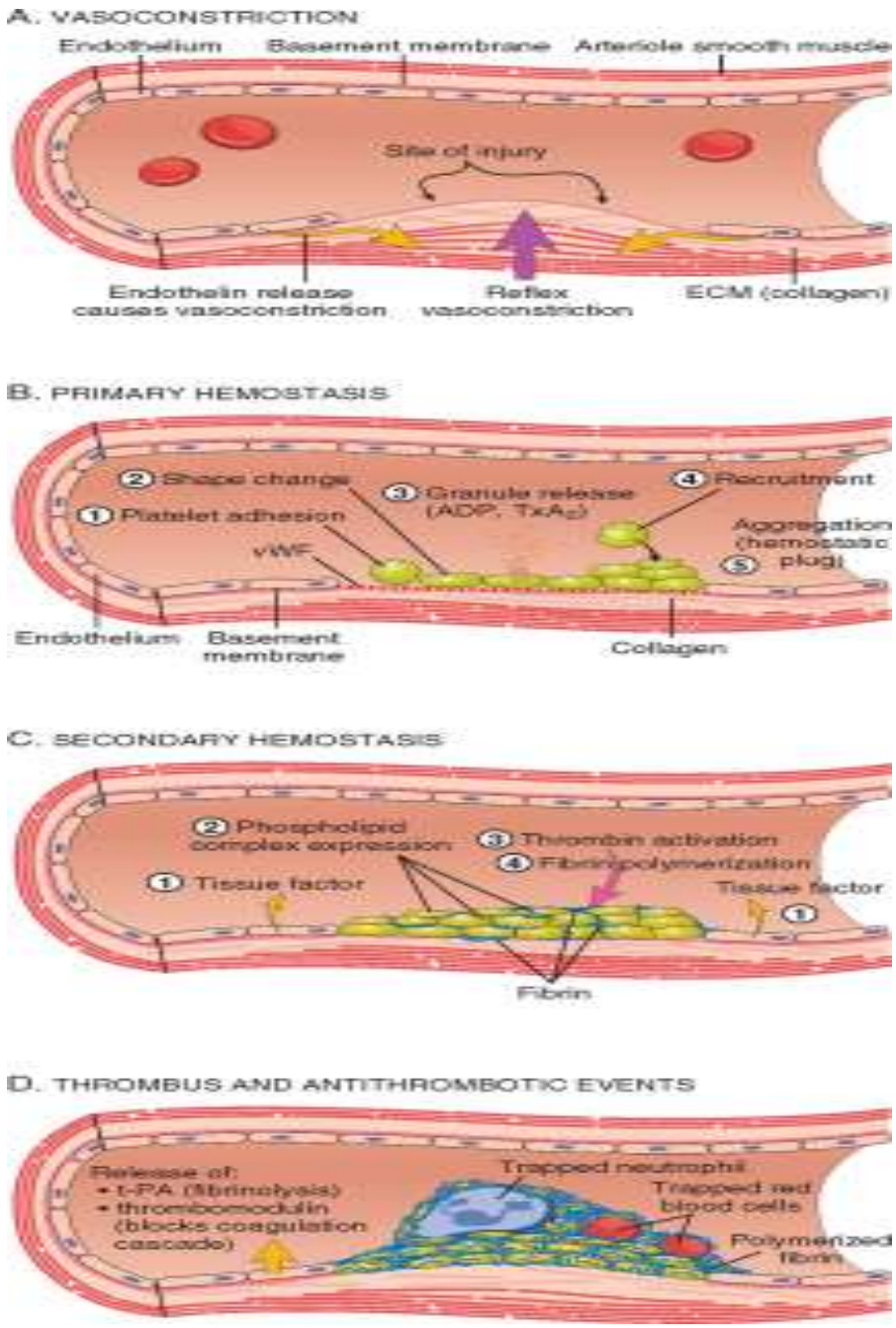

Fig.(1): Events of haemostasis at the site of vascular injury ***(Hoffman and Monroe, 2007).***