A Review on Clinical, Pathophysiological, and Diagnostic Hematological Features in Children With Liver Cirrhosis

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Abstract

Appropriate diagnostic and therapeutic measures for liver cirrhosis is critical, particularly in children. In the present review, a comprehensive approach was provided toward hematological parameters in pediatric liver cirrhosis. The literature search included MeSH terms “liver cirrhosis” and “hepatic cirrhosis” and databases such as PubMed, Web of Science, Scopus, and Google Scholar were searched up until December 2017. Hematologic changes in the liver cirrhosis mainly encompassed anemia and coagulopathies. In addition, bleeding diathesis was considered as the most clinical complication in these patients. In addition to reduced coagulation factors, hyperfibrinolysis is a common feature in childhood cirrhosis and may be an important contributor to the risk of bleeding. Based on the results, children with liver cirrhosis also demonstrated a procoagulant state at laboratory and clinical levels. This may be partly due to a reduction in coagulation inhibitors such as anti-thrombin, C1 inhibitor, and α1-antitrypsin in children with cirrhosis. The portal vein thrombosis and portal hypertension are considered as the most clinical presentations of the hypercoagulable state. Further, children with liver cirrhosis complicated with portal hypertension usually show leukopenia, anemia, and thrombocytopenia due to hypersplenism. Although the etiology of childhood and adult cirrhosis may be different, their hematological complications and clinicopathological features are somehow similar.

Keywords: Liver cirrhosis, Pediatrics, Hematology, Coagulopathy, Anemia, Portal hypertension

Introduction

The liver is the primary location for the production of blood cells from the first trimester in fetal life until birth. In mid-pregnancy and after birth, this role is transferred to bone marrow as the main location for hematopoiesis. Nevertheless, the liver still preserves a niche for the production of blood cells, which can contribute to adult hematopoiesis in some pathological conditions. In addition to this temporary role in normal hematopoiesis, the liver produces some hematopoietic growth factors for different blood lineages (e.g., leukocytes, erythrocytes, and platelets). Thrombopoietin (TPO) is the most important platelet growth factor that is mainly produced by hepatocytes.

Childhood liver cirrhosis can be secondary to either biliary atresia, congenital disorders, or viral hepatitis. The etiology of childhood and adult cirrhosis probably differ although their complications and clinicopathological features are nearly the same. Hematologic disturbances are among the most common complications in liver cirrhosis. Thrombocytopenia, leukopenia, and anemia can impose substantial clinical effects on cirrhotic patients. For example, coagulopathies limit performing procedures such as liver biopsy, paracentesis, or endoscopic surgeries. Leukopenia, on the other hand, results in the propensity to life-threatening infections and anemia negatively manipulates prognosis in patients with bleeding tendencies.
Anemia in Childhood Liver Cirrhosis

Erythrocytes are originated from hematopoietic stem cells in bone marrow by stimulating the action of erythropoietin which is mainly produced by the kidneys. Erythrocytes lack a nucleus and live for approximately 120 days after releasing into the bloodstream. In physiologic conditions, erythrocytes are destroyed at the same rate as their production rate. Anemia is a common feature in cirrhotic patients which can result from heterogeneous etiologies.

Anemia is reported in as high as 75% of patients with chronic liver diseases. In addition, anemia in cirrhotic children can follow a multivariate etiological approach encompassing gastrointestinal blood loss, hemolysis due to hypersplenism and splenomegaly, disrupted erythropoiesis due to iron or folate deficiencies, and autoimmune destruction of red cells. Further, macrocytic anemia may be observed in cirrhotic children due to either folate or cyanocobalamin deficiencies in those patients with malnutrition. Both folate and cyanocobalamin are stored in the liver and require intact enterohepatic cycle and sufficient intestinal absorption in order to take part in hematopoiesis.

Hemolytic Anemia

The hemolysis of spur cell anemia can be observed in cirrhotic children and may be partly related to vitamin E deficiency. This condition generally heralds a poor prognosis and is encountered in end-stage disease. Spur cells, also known as acanthocytes, are erythrocytes with abnormalities in lipid membrane compositions which result in irregular surface stipulations. Generally, acanthocytes show less numerous stipulations compared to spur cells and spur cells are considered as the late forms of acanthocytes. The main membrane defect is altered cholesterol to phospholipid ratio which ultimately leads to the increased destruction of erythrocytes within the spleen. Furthermore, a hypersplenism state which is commonly found along with portal hypertension and cirrhosis may exaggerate the hemolytic process in this condition. Children with cirrhosis secondary to chronic hepatitis C infection may develop hemolytic anemia following Ribavirin therapy. Hemolysis in childhood cirrhosis can also be due to the autoimmune destruction of the red cells by abnormally reacting autoantibodies. In addition, the anemia of bone marrow suppression is a potentially threatening condition in children with viral hepatitis-related cirrhosis.

Leucocytes

Different lineages of blood leukocytes-neutrophils, lymphocytes, monocytes, eosinophils, and basophils-share diverse functions of innate and acquired immunities. Children with liver cirrhosis complicated with portal hypertension are commonly diagnosed with leukopenia secondary to splenic sequestration. Immune cells participate in the progression of cirrhosis by the induction of vascular abnormalities in the portal vein in cirrhotic patients. Monocytes with a high expression of tissue factors (TFs) in cirrhosis are suggested as a factor that mediates liver fibrosis. Recently, high neutrophil to lymphocyte ratio has been suggested as an independent prognostic factor in cirrhosis.

Immune cells provide an opportunity for cell therapies in cirrhosis. Moreover, circulating granulocyte-macrophage colony-stimulating factor mobilized monocytes with a weak expression of progenitor markers (i.e., CD34, CD 45, and CD 44) show potential capacity for improving cirrhosis progression and survival rate in patients. Kupffer cells, as macrophages located in the liver, are essential in the primary immunologic screening of antigens. Additionally, Kupffer cells are activated in cirrhotic patients and play an important role in the pathogeneis of hepatic disorders. Recently, a modified population of regulatory macrophages has been developed in vitro that may provide an opportunity for cellular treatment in cirrhosis patients.

Hemostatic Abnormalities in Liver Cirrhosis

The hemostatic system function is essential for preserving vascular competency. This system consists of parallel coagulant and anticoagulant proteins that are responsible for preventing bleeding and thrombosis, respectively. Platelets and vascular endothelial cells are the other main components of the hemostatic system. This system is also influenced by other blood components such as monocytes, erythrocytes, and microparticles derived from these cells.

Platelets

Platelets are considered as the main components of hematopoietic and hemostatic systems. Similarly, megakaryocytes, as platelet precursors, are large cells that are located in the bone marrow. In addition, TPO constitutes the primary signal for the differentiation of megakaryocytes to platelets. The platelet life span within the blood circulation is 7-10 days. The frequency and functionality of the platelets are affected in chronic hepatic disorders. Thrombocytopenia is among the most common and very early signs in cirrhotic children, especially those with concurrent portal hypertension. The pathogenesis...
of low platelet count in cirrhosis is multifactorial. Further, thrombocytopenia may develop due to antiplatelet antibodies or increased platelet consumption in disseminated intravascular coagulation (DIC) and hepatitis C infection is a risk factor for the occurrence of autoimmune thrombocytopenia. The production of TPO in cirrhotic patients is significantly compromised and eltrombopag, as a TPO receptor agonist, can assist in the management of thrombocytopenic patients. Nevertheless, using this drug should be with caution as it can predispose to portal venous thrombosis. Some platelet indexes such as the ratio of immature platelets, as well as mean platelet volume and platelet distribution width are suggested as the predicting parameters for the diagnosis of cirrhosis. In addition to a quantitative defect, the platelets of cirrhotic patients demonstrate impaired secretory pathways which result in the low efficiency of platelet activation and adhesion functions.

Hemostatic Cascade

Primary hemostasis is initiated by the attachment of platelets surface glycoproteins (mainly GP IIb/IIIa and GP Ib/IX/V) to their specific ligands in a subendothelial surface (von-Willebrand factor [vWF] and collagen). This results in releasing high contents of platelet activators including ADP recruiting other platelets to the damaged area. This phenomenon leads to the formation of a platelet plug and temporary cease in blood loss although the platelet plug needs to be supported by the fibrin clot to permanently prevent bleeding from ruptured vascular beds.

Secondary hemostasis is initiated on the surface of activated platelets. The TF-initiator of hemostatic extrinsic pathway, which has entered into the blood circulation, forms an enzymatic complex with factor VII (extrinsic tenase complex). Subsequently, this complex leads to the activation of factor X (Xa). This factor then forms another complex with its cofactor (FV) which is known as the prothrombinase complex. This new complex excises prothrombin (FII) to its active form, namely, thrombin (FIIa) which cleaves fibrinogen (FII) molecule to fibrin. Finally, fibrin is polymerized and fibrin clot is assembled by cross-attachments between fibrin monomers. In parallel with these reactions, another enzymatic complex known as intrinsic Tenase complex (FIXa-FVIIIa) is produced in intrinsic the pathway of the hemostatic cascade. Furthermore, this complex is particularly important for the production of an appropriate amount of prothrombinase complex by the FX activation. Moreover, thrombomodulin, proteins C and S, antithrombin (AT), and the components of the fibrinolytic system (i.e., plasmin) are activated after the formation of the fibrin clot and regulate the hemostatic pathway, preventing excess thrombin production.

Role of Liver in Preserving Hemostatic Balance

The liver is essential in maintaining hemostatic balance. All coagulation factors are primarily synthesized in hepatocytes except for FVII. The majority of inhibitory proteins involved in the regulation of hemostatic pathway such as plasminogen, a2-plasmin inhibitor, α1-antitrypsin, a2 macroglobulin, and AT are also produced by the liver. Liver macrophages are responsible for the removal of fibrin degraded products (FDPs) and activated coagulation factors from the circulation.

Hemostatic Abnormalities in Other Liver Diseases

Hemostatic abnormalities in liver disorders are supposed to be due to the direct damage to hepatocytes under the production of coagulation factors. However, cirrhosis is a hemostatic dilemma since an elevated risk of thrombotic events is observed despite prolonged coagulation times. This phenomenon may be related to a parallel decrease in the level of anticoagulant proteins.

Prothrombin Time

Prothrombin Time (PT) along with standard normalized ratio (INR) derived from PT is usually prolonged in cirrhotic children. This is attributed to the reduced production of coagulation factors in the liver. Although INR can be a useful marker for predicting the plasma coagulative status, it is only an indicator of coagulation factor levels with no further information on the extent of factor deficiency. Accordingly, INR can be a weak parameter for predicting the capacity of fibrin clot formation and the risk of bleeding in children with cirrhosis.

The goal of the PT test is to scrutinize the integration of the extrinsic coagulation pathway. Additionally, PT is prolonged in the isolated or combined deficiencies of either FV, FII, FV, FX, or FVII. Likewise, a prolonged PT is not specific for liver diseases but it is also considered as a marker for inherited or acquired deficiencies of coagulation factors. In the normal levels of FVIII, considering the non-hepatocyte source of this factor- a prolonged PT generally indicates coagulation factor deficiencies due to either liver or vitamin K insufficiencies. In addition, the PT test can rapidly reflect hepatic functional capacity due to the relatively short half-life of coagulation factors.

Although PT renders a valuable diagnostic test in acute liver disorders, this test cannot deliver the same validity in cirrhosis. Instead, specific coagulation factor
assessments can provide useful information for the management and screening of patients with chronic liver conditions.

**Fibrinogen**

Fibrinogen alternations encompass both quantitative and qualitative changes in cirrhotic children. Reduced fibrinogen levels can be a result of either reduced synthesis, increased destruction, or a combination of these two. The elevated levels of FDPs in cirrhotic patients demonstrate the accelerated fibrinogen consumption and/or decreased hepatic clearance rate of FDPs. The FDPs contribute to the prolongation of PT by intervening with fibrin polymerization. In addition to quantitative alternation, fibrinogen shows structural changes in cirrhosis. This acquired dysfibrinogenemia which is characterized by increased sialic acid residues on α and β chains of fibrinogen. Fibrin molecules derived from cirrhotic patients have higher contents of carbonyl that may contribute to a hypercoagulable in this condition. Furthermore, fibrin structural changes result in compromised capacity for fibrin polymerization.

**Other Coagulation Factors in Liver Cirrhosis**

The levels of vitamin K-dependent coagulation factors (i.e., FII, FVII, FIX, and FX) are markedly reduced in cirrhotic children. Further, coagulation FVIII is produced by both intra- and extra-hepatic organs such as lymphatic tissues. The vWF is also synthesized in vascular endothelial cells. Moreover, the level of FVIII usually increases in cirrhotic patients and this can be a useful marker for discriminating cirrhotic hemostatic disorders from DIC.

The half-life of coagulation factors produced in the liver is variable from six hours for FVII to four hours for fibrinogen. Similarly, the half-life of these proteins is prominently shorter than that of albumin. Therefore, measuring the levels of coagulation factors can be a highly sensitive marker for the determination of the degree of hepatic involvement in chronic liver disorders. However, many coagulation factors (i.e., fibrinogen, prothrombin, FV, FIX, and FX) have relatively sufficient stores and clinically significant reductions of these factors are observed only in end-stage and advanced liver disease.

**Coagulation Inhibitors**

The hemostatic pathway is regulated through the removal of activated coagulation factors by the liver and the inactivation of these factors by coagulation inhibitors. Similar to coagulation factors, many of coagulation inhibitors are produced by the liver. Some of these inhibitors such as α2-macroglobulin and plasminogen activator are acute reactants and elevated in liver disorders. However, the level of these proteins decreases less than the normal range in advanced liver disease. Other coagulation inhibitors such as AT, C1-inhibitor, and α1-antitrypsin are typically reduced in children with liver dysfunction.

AT, as one of the most important coagulation inhibitors, binds to and inactivates thrombin and other coagulation factors in the presence of heparin. Additionally, low levels of AT in liver disorders generally herald a poor prognosis. As regards the other coagulation factors, a reduction in AT level in the context of chronic liver disease may be due to either compromised hepatic synthesis or increased consumption. A low level of AT in this condition is suggested as a contributor to DIC. In the low activity of AT, thrombin can be deactivated, at least to some extent, by α2-macroglobulin. The anti-coagulative activity of protein C pathway and tissue factor pathway inhibitor (TFPI) are also decreased in cirrhotic patients.

**Disseminated Intravascular Coagulation**

DIC is a frequently encountered phenomenon in children with liver insufficiency compared to adults. This may be partly the result of inappropriate levels of defensive proteins such as complement and opsonins which are primarily produced in hepatic tissues. The discrimination of DIC from coagulopathies resulted from hepatic failure may be somehow difficult. For example, as mentioned earlier, the reduced levels of coagulation proteins can be either due to a reduction in liver productive capacity or the elevation of protein consumption.

The primary defect in DIC disseminates thrombosis due to the inappropriate activation of the coagulation pathway that is typically secondary to endothelium damage or endotoxin releasing. Triggering factors leading to DIC in cirrhosis are not well-known although the secretion of a procoagulant mediator is proposed by necrotizing hepatic cells. In the DIC, fibrinolysis is active secondary to the activation of the coagulation pathway. Both DIC and cirrhosis can be associated with low levels of coagulation and anticoagulation factors. The mechanisms of these changes reduce the synthesis of factors in cirrhosis while increasing the consumption of DIC.

The increased levels of FDPs suggest DIC. Nevertheless, the levels of FDPs can also increase in liver disease due to the slow removal from the circulation. More information can be obtained by measuring D-dimer, which is the segment resulted from the degradation of cross-linked fibrinogen. In addition, the triad of elevated D-dimer, elevated FDPs, and decreased FVIII levels can be a diagnostic marker for DIC. Compared to the formation retrieved on multiple occasions and in several days, the levels of fibrinogen, FDPs, and D-dimer related to the one-time point are not reliable. Thus, it is best to identify a decreasing level of fibrinogen in the context of stable liver enzymes as an indicator of DIC.

Some new biochemical diagnostic markers are developed for DIC in cirrhosis. The components of the
activated coagulation factor can be useful among these markers. For example, the fragment$^{11,12}$ of prothrombin increases in DIC while it decreases in hepatic failure.$^{79}$ Heparin cofactor II (HCII) and TFPI are two newly identified coagulation regulators. HCII is a liver-derived protein which decreases in both DIC and liver disease.$^{93}$ TFPI is synthesized in vascular endothelial cells and shows normal and decreased levels in liver failure and DIC, respectively.$^{94}$ The reduced levels of both HCII and extrinsic pathway inhibitor provide a strong sign of ongoing DIC. Although these tests are currently not available in the routine practice, they have the potential for becoming useful markers for DIC diagnosis in the context of cirrhosis in the future.

**Compensatory Mechanisms for Preserving Hemostatic Balance**

Two compensatory hemostatic mechanisms in the liver cirrhosis include the reduced production of protein C and the augmented production of FVIII by liver endothelium.$^{64}$ Furthermore, the level of vWF increases in cirrhotic patients strengthening platelet adhesive capacity to subendothelium and intensifying the coagulation process.$^{95}$ However, these mechanisms are highly fragile and can be subverted by foreign factors such as the infection, leading to either bleedings or thrombosis.

**Bleeding in Cirrhotic Children**

Bleeding is a common sequela in children with uncompensated cirrhosis imposing a high rate of morbidities and mortalities and a multifactual mechanism is involved in bleeding tendencies in these patients. In addition, variceal bleeding due to portal hypertension is regarded as the most important event in this condition.$^{96}$ This type of bleeding is a common phenomenon in children with cirrhosis.$^{97}$ Further, acute gastrointestinal bleeding is another noteworthy complication in cirrhotic children associated with high mortality rates.$^{98}$

Managemental measures in cirrhotic children at the risk of bleeding generally fall into correcting coagulopathy through vitamin K infusion, the administration of vasocostrictors, and blood product transfusion.$^{99,100}$ Although the beneficial role of H2-receptor antagonists is noticeable in preventing gastrointestinal bleeding in cirrhotic children, the clinical applicability of these therapeutics in the prevention of bleedings in cirrhosis is under debate.$^{101}$

Hyperfibrinolysis is a condition in which fibrin degradation exceeds its polymerization which is partly involved in bleeding diatheses.$^{71,102}$ Similarly, this condition is a common feature in childhood cirrhosis, especially in uncompensated conditions.$^{103}$ Possible mediators in this phenomenon are noted as the increased activities of tissue plasminogen activator$^{104}$ and thrombomodulin$^{105}$ while the depressed levels of α2-antiplasmin, along with the decreased activity of thrombin activated fibrinolysis inhibitor.$^{106}$

**Thrombosis is Childhood Cirrhosis**

Children with cirrhosis are prone to venous thromboembolism$^{107,108}$ and the main risk factors for this event are portal venous thrombosis (PVT) and portal hypertension.

**Portal Venous Thrombosis in Cirrhotic Children**

PVT is the main cause of portal hypertension in children. Some etiologies of PVT in children are the catherization of ventricular venous, omphalitis, and intra-abdominal infections.$^{109,110}$ Furthermore, congenital thrombophilia such as FV Leiden, G20210 mutation in the prothrombin gene, and mutations in methlytetrahydrofolate reductase are suggested to play a role in pediatric PVT. A mild reduction in proteins C and S and AT levels may also be associated with the occurrence of PVT in pediatric cirrhosis.$^{109,111}$ The low serum level of vWF cleaving enzyme (i.e., ADAMTS-13) also augments the risk of PVT in cirrhosis.$^{112-115}$ Myeloproliferative disorders and antiphospholipid syndrome are relatively rare in children although a higher risk for PVT is described in cirrhotic patients harboring JAK2 V617F mutation.$^{116}$ However, no etiology could be addressed for childhood PVT in half of the cases.

Bleeding in the upper gastrointestinal tract is the primary presentation in children with PVT and the majority of these patients experience variceal bleeding at least for one occasion.$^{117}$ The most threatening bleedings usually originate from esophageal and gastric varices.$^{33,118}$ Moreover, esophagus variceal bleeding is an independent poor prognostic feature with as high as a 30% mortality rate in children.$^{31}$ Nevertheless, the prognosis of esophageal variceal bleeding is dependent on its etiology since secondary bleedings to PVT and portal hypertension have a more favorable prognosis compared to those related to hepatobiliary defects.$^{119,120}$ Growth retardation is a complication reported in nearly half of the children with PVT.$^{121}$ Additionally, splenomegaly is the second most notifiable complication in childhood PVT. In such conditions, peripheral cytopenia can be observed due to hypersplenism.$^{110,122}$

**Portal Hypertension in Childhood Liver Cirrhosis**

The most notable hematologic effects of portal hypertension include splenomegaly, anemia, thrombocytopenia, and bleedings.$^{123,124}$ Splenic sequestrations, as well as the destruction of platelets, leukocytes, and erythrocytes in an enlarged spleen are known as hypersplenism. Platelet distribution is altered in cirrhosis in this condition so that 90% of the platelet may be located in the splenic vasculature.$^{6}$ On the other hand, the splenic retention of erythrocytes leads to
anemia. Similarly, splenic sequestration may be further exaggerated due to the hepatic vein pressure gradient-as an indicator of portal hypertension intensity.\textsuperscript{125}

Conclusion
Although the etiology of childhood and adult cirrhosis may be different, their compilations and clinicopathological features are somehow similar. Hematologic changes in childhood liver cirrhosis mainly encompass anemia and coagulopathies. Children with liver cirrhosis complicated with portal hypertension usually show leukopenia, anemia, and thrombocytopenia as well. In addition, bleeding diathesis is the most clinical complication in these patients. In addition to reduced coagulation factors, hyperfibrinolysis is a common feature in childhood cirrhosis and may be an important contributor to the risk of bleeding. Further, children with liver cirrhosis demonstrate a procoagulant state at laboratory and clinical levels. This may be partly due to a reduction in coagulation inhibitors such as AT, C1-inhibitor, and α1-antitrypsin in these children. Finally, the most clinical presentations of the hypercoagulable state are portal venous thrombosis and portal hypertension which can thus result in peripheral cytopenia.

Ethical Approval
Not applicable.

Competing Interests
None to be declared.

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