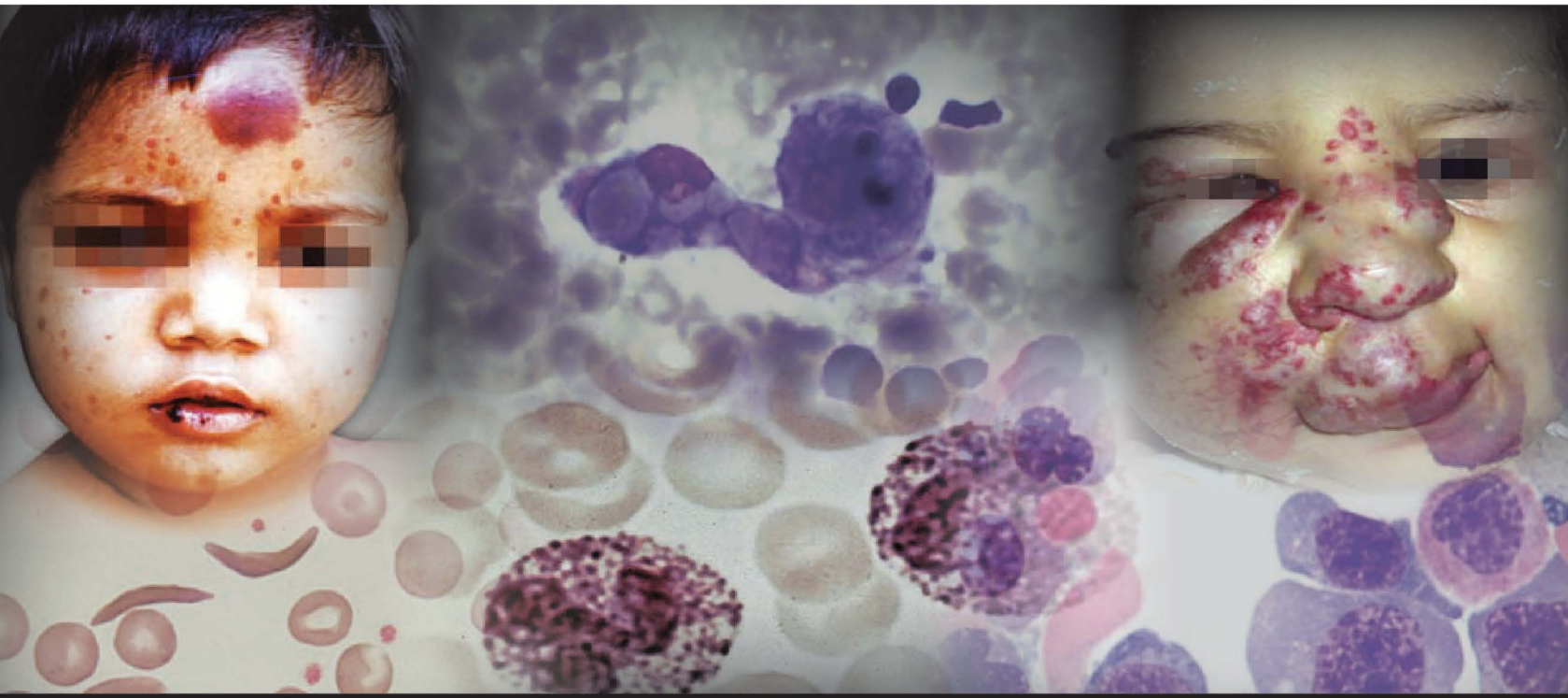
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Textbook of
PEDIATRIC HEMATOLOGY & HEMATO-ONCOLOGY



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CHAPTER 2

Physiology of Blood Coagulation

Shrimati Shetty

The three major components of blood coagulation are platelet, plasma and the endothelium. The platelets adhere to damaged endothelium with the help of von Willebrand factor (VWF) and when activated, they aggregate and make a platform for coagulation factors which then initiate a series of reactions on the damaged blood vessels. The reaction begins with the activation of contact factors which then results in the sequential activation of these clotting factors, resulting in thrombin generation, which converts fibrinogen to fibrin clot. A series of inhibitors to these coagulation factors keep them under check to maintain the thrombohaemorrhagic balance. The most important of these inhibitors are protein C, protein S, antithrombin, tissue factor pathway inhibitor (TFPI) and heparin cofactor II . The fibrinolytic system has an important role in the removal of clot formed, thus maintaining the hemostatic balance. Thrombin has both pro- and anticoagulant role in the coagulation cascade and it is thrombomodulin which converts thrombin into an anticoagulant enzyme by a negative-feedback regulation of its prothrombotic activity through its association with activated protein C (APC). It also has an important role of linking coagulation with fibrinolysis through thrombin activable fibrinolytic inhibitor (TAFI). The deficiency of factors in the Kallekrein-kinin system does not result in a bleeding phenotype; have a role in various noncoagulant functions including apoptosis, proinflammatory and prothrombotic manifestations.

PLATELET ACTIVATION

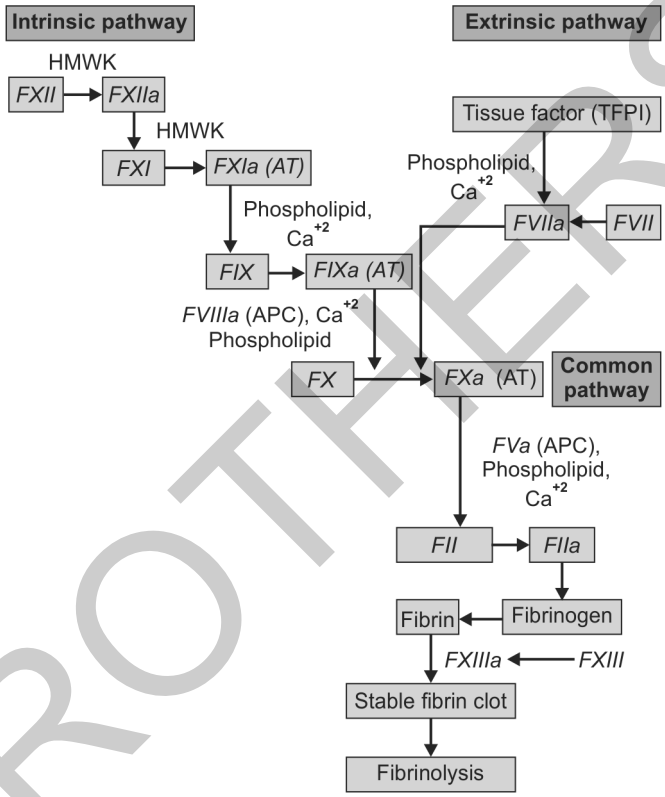
Upon breach of vasculature, platelets get exposed to collagen and VWF which facilitate their adhesion to the subendothelium through GP-1b-V-IX receptors. The adhesion of the platelets to the subendothelium results in platelet activation which results in an "inside out" signal, causing the exposure of phosphatidyl serine to the outer surface, which forms catalytic surface for its procoagulant activities. The activation also results in secretion of platelet contents along with the exposure of fibrinogen receptors resulting in platelet aggregation at the site of injury. Platelets when activated also trigger the coagulation reaction by providing a catalytic surface which results in the formation of thrombin. More than 250 active substances are released into circulation from the granules present within platelets, when platelet gets activated. Thrombin further stimulates platelet activation through G-protein-coupled protease activated receptors (PAR-1 and PAR-4), resulting in the release of adenosine diphosphate (ADP) and thromboxane A2 (TXA2).[1,2] Thus both platelet activation and coagulation are interdependent. Platelets have a wide array of receptors on their surface which help both in adhesion and aggregation and it is these receptors which have become the target for anti-platelet therapies. Platelet aggregation requires the platelet membrane glycoprotein receptor i.e. GP IIb-IIIa, which helps in platelet aggregation by binding to fibrinogen and fibronectin.[3] Once the platelets are activated, they release different types of granules into the circulation which include ADP, platelet-activating factor (PAF), VWF, serotonin, TXA2 and platelet factor 4.[4] These stimulate and activate more and more platelets resulting in the primary hemostatic platelet plug at the site of wound. It is the same nature of the platelets of showing a quick response to the vascular breach, which is responsible for myocardial infarction or stroke under pathological conditions.

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THEORIES OF BLOOD COAGULATION

Morawitz in 1905 put forward the first theory of blood coagulation which is also referred as "four clotting factor" theory.[5] According to this theory, blood clotting is possible due to the presence of four clotting factors, namely, thromboplastin, prothrombin, thrombin and calcium. The thromboplastin gets released on tissue injury which converts prothrombin to thrombin in the presence of calcium. Subsequent to the identification of the remaining coagulation factors, two groups independently put forward a revised blood coagulation model referred to as the "waterfall cascade" model.[6,7] According to this model, all the blood coagulation factors remain in an inactive state and they get activated by the upstream clotting factor. The coagulation cascade shows two distinct pathways i.e. extrinsic pathway initiated by the interaction of tissue factor (TF) with the circulating serine protease factor VIIa. This increases the catalytic activity of FVIIa several fold which then activates factor X to Xa. Similarly in the intrinsic pathway, there is a sequential activation of factors XII, XI, IX the activated form of which then activates factor X to Xa . Thus the two pathways converge into the common pathway by the activation of FX to FXa which then binds to FVa to form prothrombinase, which rapidly converts prothrombin to thrombin. Calcium and phospholipids are required for these sequential activation of coagulation factors. Both extrinsic and intrinsic pathways cannot work independent of each other as deficiencies of any of these factors in either of the two pathways (excluding contact factors and factor XII) can lead to lifelong bleeding tendency (Flow chart 1).

Flow chart 1 The coagulation cascade



Cell Based Model of Blood Coagulation

Though the waterfall hypothesis of blood coagulation has expanded our understanding of blood coagulation, more recent observations demonstrate that the cascade/ waterfall hypothesis does not fully simulate the *in vivo* hemostasis. The cascade model of blood coagulation highlights the importance of coagulation factors *in the* generation of thrombin and overall hemostasis and the role of cells is only to provide phospholipids surface for the coagulation factors to generate thrombin. The cell based model of coagulation shows the significance of cells in coagulation. While the extrinsic pathway is initiated on the TF bearing cells the intrinsic pathway takes place on the platelets. The contact factors and factor XII are not included in the cell based model of coagulation as the deficiency of these factors does not result in bleeding.[8-11] According to this model coagulation takes place in 3 phases i.e. initiation phase, amplification phase and propagation phase.

Initiation Phase

This phase begins with TF bearing cells and is referred to as the 'extrinsic' pathway. TF binds to activated FVII (FVIIa) which in turn activates factor IX to Fix factor X to Xa. Subsequently FXa activates FV to FVa forming the "prothrombinase complex" on TF bearing cells. The dissociation of FXa from these TF bearing cells is prevented by inhibitors like antithrombin and tissue factor inhibitor (TFPI). The FV can either come from activated platelets at the sites of injury or from plasma, both of which can be activated by factor Xa.[12] When present on the TF bearing cells FXa is resistant to its inhibitor i.e. antithrombin. It has also been reported that some amount of FVIIa remains bound to TF even in the absence of injury thus facilitating mild activation of FX and FV all the time.[13]

Amplification Phase

The amplification phase involves the activation of platelets by the initial thrombin generated on the TF bearing cells. Besides thrombin also activates coagulation factors V, VIII and XI on the platelet surface resulting in small amounts of thrombin on the platelet surface.[14]

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Propagation Phase

This phase takes place on the surface of activated platelets. FIXa produced during the first step binds to FVIIIa to activate FX to FXa (Tenase complex). FXa then activates FV to FVa which then activates prothrombin to result in thrombin burst (prothrombinase complex). As more and more platelets are recruited to the site of injury, the thrombin generation gets amplified several fold resulting in a thrombin burst which then acts upon fibrinogen to form fibrin. The fibrin clot also consists of erythrocytes, leukocytes and platelets which are held together by fibrin chains. The thrombin activated FXIII then cross links these fibrin chains to form a firm fibrin clot.

The Kallekrein-Kinin System

The Kallekrein-kinin system consists of 3 factors: prekallekrein (PK), high molecular weight kininogen (HMWK) and factor XII (FXII). Their role in the initiation of the intrinsic pathway of coagulation is still not clear as FXII can get autoactivated even in the absence of prekallekrein.[15] The deficiency of any of these factors does not result in bleeding phenotype. Though the absence of these factors prolongs the *in vitro* investigations like activated partial thromboplastin time (APTT), their physiological significance in hemostasis is unclear. Recently there are several reports to support their role in thrombosis.[16] A polymorphism in FXII i.e. 46C/T has shown strong association with arterial thrombosis.[17] The homozygous carriers of this polymorphism were found to have reduced FXII levels which in turn will result in reduced fibrinolytic activity, thus being implicated in thrombosis.

FXIIa also activates FXI to FXIa which then activates FIX to Fix. FXIa along with PK also releases bradykinin, the proinflammatory factor from HMWK.[18]

COAGULATION PROTEASES AND COFACTORS

Biochemically, coagulation factors can be classified into two groups i.e. serine proteases–FVII, FIX, FX, FXI and cofactors-FVIII and FV. The two main cofactors required in most of the steps in blood coagulation including the formation of tenase and prothrombinase complexes are phospholipids and calcium. Calcium also has an important role of binding the coagulation factors to the platelet membrane.[19]

Vitamin K is an important cofactor for coagulation factors which require post translational modification i.e. gamma carboxylation of their glutamic residues which is important for their efficient functioning (factors II, VII, IX, X and their inhibitors i.e. protein C, protein S and protein Z). Two enzymes take part in these processes–vitamin K epoxide reductase (VKORC1) and gamma carboxylase (GGCX). The gamma carboxylase enzyme adds the gamma carboxyl group to the glutamate residues during which Vitamin K epoxide gets reduced. The VKORC1 enzyme converts it into its active form. The gamma carboxylation is required for an effective binding of these serine proteases to the phospholipid surfaces.

Blood Coagulation Inhibitors

Blood coagulation inhibitors as well as fibrinolytic inhibitors neutralize the coagulant or fibrinolytic proteins to prevent excessive thrombosis or hemorrhage . The major anticoagulant pathway is the protein C anticoagulant pathway in which both FVIIIa and FVa required for tenase and prothrombinase complex formation get neutralized. Protein C shows a very high homology to all the remaining vitamin K dependant clotting factors. Protein C shows a very high homology to all the remaining vitamin K dependant clotting factors. Protein S is an important cofactor for activated protein C (APC) in its anticoagulant action on FVa and FVIIIa. A mutation at Arg 506 in factor V gene factor V Leiden) makes it resistant to APC cleavage. Homozygotes for this mutation show 20-30 fold increased risk of thrombosis.[20] As the concentration of thrombin increases it binds to another protein i.e. thrombomodulin which then activates the inactive protein C to its activated form. The APC inactivation by thrombin-thrombomodulin complex takes place on the surface of endothelial cells , where the APC is bound by a receptor i.e. endothelial protein C receptor (EPCR).

Though protein S has initially been reported as a cofactor for APC in neutralizing FVIIIa and FVa, studies have shown that PS can independently neutralize these factors.[21] This is possible because PS generally remains combined to C4BP protein. Besides, PS also has inhibitory action against FXa by facilitating the interaction of FXa with TFPI.[22] It has also been reported that FV acts as a cofactor in the inactivation of FVa by APC and PS.[23]

Antithrombin is another strong inhibitor which inactivates both FXa and thrombin, besides its inhibitory action against IXa, XIa and XIIa along with some of the factors in the fibrinolytic pathway. The activity of AT is increased several fold in the presence of heparin. Though rare, AT deficiency leads to one of the most severe form of thrombophilia. Heparin cofactor II is another inhibitor of thrombin. Protein Z is another inhibitor which is an inhibitor of FXa.

The major inhibitor of tissue factor is tissue factor pathway inhibitor (TFPI) which is expressed on the endothelial cells. The extrinsic pathway involving the activation of X to Xa gets inhibited and there is a shift in the

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balance towards the intrinsic pathway of coagulation. TFPI inhibits both TF-VIIa complex and FXa. Thus the initial phase of extrinsic pathway is inhibited. However once Xa takes part in the prothrombinase complex, it becomes resistant to the action of TFPI. Various strategies have been used to use inhibitors of TFPI as a novel therapeutic protocol for haemophilia.[24]

FIBRINOLYTIC PATHWAY

Fibrinolytic pathway plays an important role in maintaining the thrombohaemorrhagic balance. A bleeding tendency is seen in patients with hyperfibrinolysis, and hypofibrinolysis is often accompanied with thrombosis. The major fibrinolytic proteases are plasmin which dissolves fibrin and the two plasminogen activators i.e. tissue plasminogen activator (tPA) and urokinase (uK). One of the important regulators of fibrinolysis is thrombomodulin as it converts thrombin not only to an anticoagulant enzyme but also to a inhibitor of fibrinolysis by activating TAFI·. Fibrinolytic activity is also controlled by inhibitors of fibrinolysis like plasminogen activator inhibitor 1, alpha 2 antiplasmin, thrombin activatable fibrinolysis inhibitor, plasminogen activator inhibitor 2, alpha 2 macroglobulin. Thrombin-activable fibrinolysis inhibitor (TAFI) is a fibrinolytic inhibitor with carboxypeptidase activity and it neutralizes the lysis of fibrin clots by removal of the carboxyl-terminal lysine residues from fibrin.[25]

Platelet Interaction with Coagulant and Anticoagulant Factors

It is now well known that platelets provide the phosphatidyl serine surface for the tenase and prothrombinase reactions to take place due the high affinity of PS membranes to these coagulant proteins. The only vitamin K protein which binds through receptors is thrombin i.e. through PAR1 and PAR4 receptors on the surface of the platelets. But besides this, platelets also have other important functions in coagulation. Platelets have the most important receptor for fibrinogen i.e a2bb3, the congenital absence of which results in a platelet aggregation defect termed as "Glanzmann thrombasthenia". Though TF has been found only in small concentrations on the platelets, its inhibitor, TFPI has been found in high concentrations.[26] Similarly, about 20% of FV in the plasma comes from platelets which when activated comes out of the platelets to take part in the prothrombinase complex.[27] Whether there exists any difference between the plasma FV and platelet FV is not clear. Similarly FVIIa is known to bind platelets via GP 1b-V-IX receptor. Besides FVIIIa and FIXa also bind the phosphatidyl serine membrane facilitating the formation of tenase complex. The binding of FXIa and FXIIa to the platelet surface however is not clear. Among the anticoagulant proteins both PC, PS and TFPI can bind to the platelet surface to neutralize the corresponding proteins. Thus platelets have a important role in blood coagulation.

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