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REVIEW

Clinical practice

The bleeding child. Part II: Disorders of secondary hemostasis and fibrinolysis

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Abstract Bleeding complications in children may be caused by disorders of secondary hemostasis or fibrinolysis. Characteristic features in medical history and physical examination, especially of hemophilia, are palpable deep hematomas, bleeding in joints and muscles, and recurrent bleedings. A detailed medical and family history combined with a thorough physical examination is essential to distinguish abnormal from normal bleeding and to decide whether it is necessary to perform diagnostic laboratory evaluation. Initial laboratory tests include prothrombin time and activated partial thromboplastin time. Knowledge of the classical coagulation cascade with its intrinsic, extrinsic, and common pathways, is useful to identify potential defects in the coagulation in order to decide which additional coagulation tests should be performed.

Keywords Activated partial thromboplastin time · Bleeding · Fibrinolysis · Pediatrics · Prothrombin time · Secondary hemostasis

Introduction

During their clinical practice, pediatricians will be consulted by parents because of the bleeding symptoms of their children. It is the task of the pediatricians to decide whether these bleeding symptoms are "abnormal" and need further evaluation for the presence of an underlying hemostasis disorder. Knowledge of the hemostatic physiology and bleeding disorders is necessary to order proper laboratory tests and to interpret their results. This review focuses on the medical history, physical examination, and laboratory tests, which are important to diagnose disorders of secondary hemostasis and fibrinolysis. It is the second part of two contributions on the bleeding child. Diagnosing primary hemostatic disorders in children has been discussed previously in this journal [26].

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Physiology of secondary hemostasis and fibrinolysis

Hemostasis is a complex process that leads to the formation of a blood clot at the site of vessel injury. This process is divided into three components: (a) primary hemostasis, which starts immediately after endothelial damage and is characterized by vasoconstriction, platelet adhesion and aggregation, resulting in the formation of a platelet plug, (b) secondary hemostasis or coagulation and (c) fibrinolysis [10].

Secondary hemostasis is defined as the formation of fibrin through the coagulation cascade. The coagulation cascade has been classically separated in three pathways: intrinsic, extrinsic, and common pathways. The intrinsic pathway involves the contact activation factors (factor XII [FXII], FXI, high-molecular-weight kininogen [HMWK] and prekallikrein [PK]), FIX and FVIII. FVIII acts as a cofactor for the FIXa-mediated activation of FX [5]. The extrinsic pathway involves the tissue factor (TF) and FVII complex, which activates FX. Both the intrinsic and extrinsic pathways come together in the common pathway,

which involves the FXa-mediated generation of thrombin from prothrombin and subsequent generation of fibrin from fibrinogen. Over the past decades, it became clear that the main pathway for in vivo initiation of coagulation is the extrinsic, TF-dependent, pathway. Nevertheless, separation of the cascade into primary, secondary, and common pathways is very useful to understand the diagnostic coagulation tests and to identify defects in coagulation (Fig. 1).

In the current model of coagulation, coagulation is initiated by the exposure of TF after injury to the endothelium (Fig. 2). In the initiation phase, TF combines with activated FVII (FVIIa), which is present at trace levels in the circulation, to form the TF-FVIIa complex [8]. This complex activates FX and FIX. Activated FX can catalyze the conversion of prothrombin (FII) into thrombin (FIIa). The amount of thrombin generated by this initiation step is very small and insufficient to produce an adequate amount of fibrin to stabilize the platelet plug. However, in the amplification phase, thrombin also activates platelets, causing changes in phospholipid asymmetry resulting in the assembly of coagulation factors on the platelet membrane, and release of granule contents including FV. Furthermore, thrombin activates FV, FVIII, and FXI. Activation of factor VIII by thrombin results in dissociation of FVIII from its carrier protein von Willebrand factor (VWF). Cofactor FVIIIa together with the initial FIXa formed by the TF-FVIIa complex, activate factor X, which forms a protected complex with its cofactor FVa. This FIXa is supplemented by factor IXa generated on the platelet surface by factor XIa. The FXa/Va complex generates a burst of thrombin, which is required for the formation of a stable fibrin clot [17]. Finally, thrombin prevents early removal of the clot by the fibrinolytic system by activating FXIII, which is not only responsible for crosslinking of soluble fibrin monomers into an insoluble fibrin matrix, but also for incorporating α_2-antiplasmin into a forming clot to protect against premature degradation by fibrinolytic proteases [7].

Endogenous anticoagulants inhibit coagulation and prevent thrombosis. The most important inhibitors are

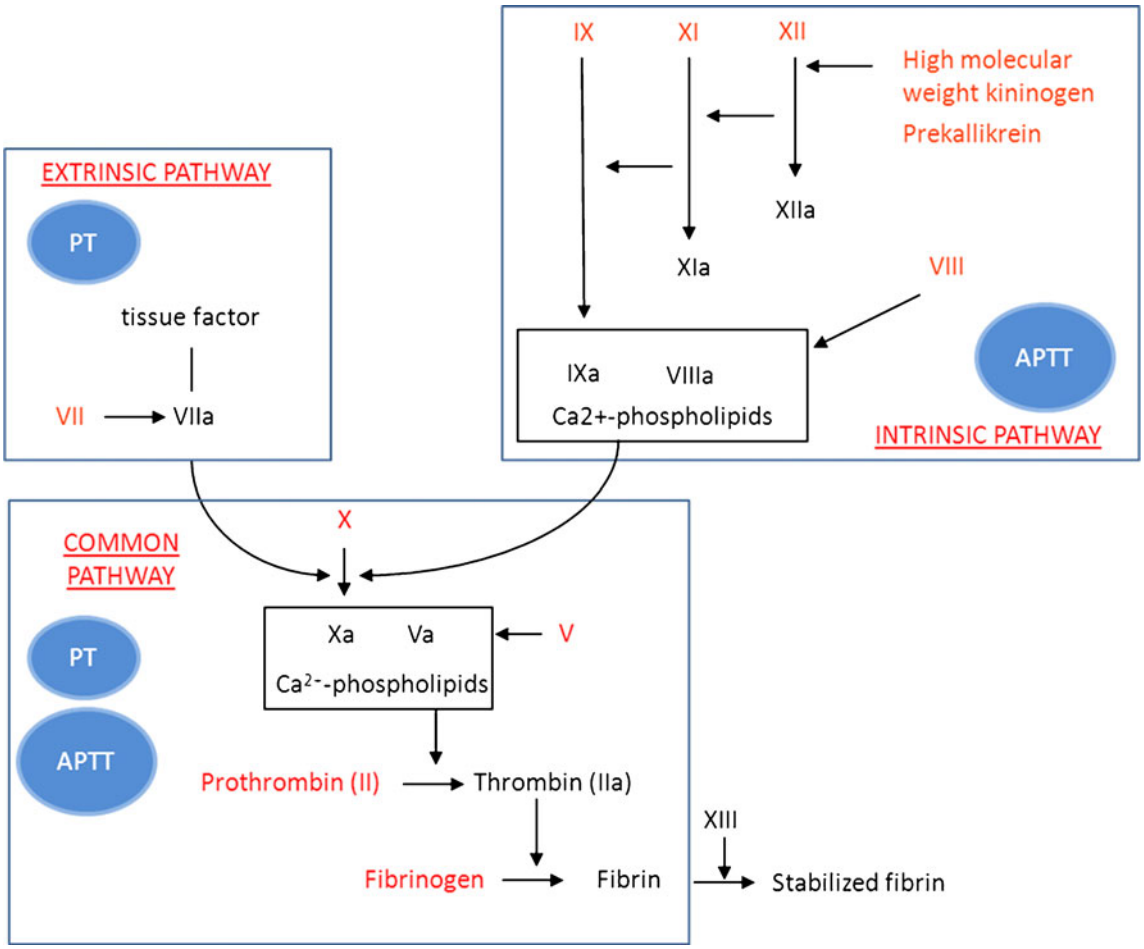

Fig. 1 The classical coagulation model: two pathways, intrinsic and extrinsic, come together in the common pathway at the level of factor X (FX). This model is useful for interpretation results of the core coagulation tests prothrombin time (*PT*) and activated partial thromboplastin time (*APTT*)

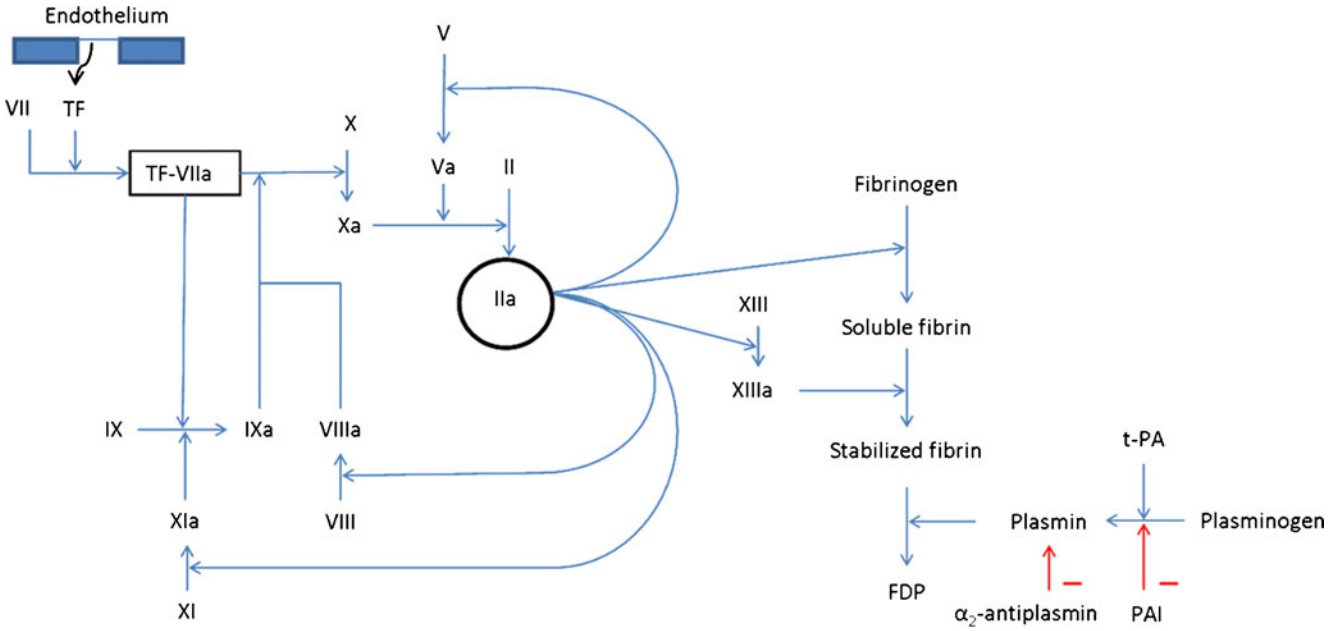

Fig. 2 The current model of coagulation and fibrinolysis. Initiation phase: after endothelium injury tissue, tissue factor (*TF*) forms a complex with activated factor VII (FVIIa) that activates FIX and FX. FXa converts prothrombin (FII) in thrombin (FIIa). In the amplification phase, thrombin activates FV, FVIII and FXI. FIXa binds to FVIIIa, activating FX. FXa binds to FVa, leading to an increased rate of prothrombin conversion to thrombin, finally converting fibrinogen into fibrin, which is stabilized by FXIIIa. Tissue-plasminogen activator (*t-PA*) converts plasminogen into plasmin that breaks down the fibrin clot into its fibrin degradation products (*FDPs*). Plasminogen activator inhibitor-1 (*PAI*-1) and α_2-antiplasmin inhibit fibrinolysis

antithrombin, protein C, and protein S. Antithrombin inactivates several activated coagulation factors, including thrombin, FXa, FIXa, and FXIa. Protein C is activated by thrombin after binding of thrombin to the protein thrombomodulin on the surface of endothelial cells. Together with its cofactor protein S, activated protein C effectively degrades FVa and FVIIIa, thus limiting further coagulation. Patients with deficiencies of antithrombin, protein C, and protein S have an increased risk for thromboembolic complications.

Fibrinolysis is the process wherein the fibrin clot is broken down into its degradation products. Plasmin is the central enzyme of the fibrinolytic system. An important activator of plasmin is tissue plasminogen activator (t-PA) that converts plasminogen into plasmin. Inhibitors of the fibrinolysis include plasminogen activator inhibitor (PAI) and α_2-antiplasmin. Deficiencies of PAI and α_2-antiplasmin result in increased fibrinolysis which may cause bleeding.

Disorders of secondary hemostasis and fibrinolysis

Hemophilia A and B

Hemophilia A and B are the most common inherited coagulation disorders, respectively resulting from a deficiency of coagulation factors VIII and IX. Both factors are crucial for normal generation of thrombin. Hemophilia is an X-linked disorder. About one third of the patients do not have a positive family history as about 30% of the mutations occur de novo. The worldwide incidence of hemophilia A is approximately 1 per 5,000 male individuals. Hemophilia B is present in 1 per 30,000 male individuals [14, 21]. The clinical severity of the disorder is related to the level of FVIII and IX. Severe hemophilia is characterized by a clotting factor level of less than 1%. In moderate hemophilia, the FVIII or IX level is between 1% and 5%. Mild hemophilia patients have a factor level between 6% and 40%.

The key manifestations of patients with severe hemophilia are muscle and joint hemorrhages, which may occur spontaneously or after mild trauma. Recurrent joint bleeds will lead to irreversible joint damage (hemophilia arthropathy). In patients with mild and moderate hemophilia, hemorrhages generally do not occur spontaneously. Treatment of bleeding episodes consists of administering recombinant or plasma-derived clotting factor VIII or IX concentrates. To prevent joint bleedings and thus arthropathy in patients with severe hemophilia, prophylactic treatment with clotting factor concentrate is mostly indicated [13].

Factor XI deficiency

FXI deficiency was discovered in 1953 by Rosenthal [23]. It is a very rare bleeding disorder with an estimated

incidence of one per million. In contrast to the incidence in the general population, congenital FXI deficiency is particularly common among the Ashkenazi Jewish population with a carrier rate up to 8% [3]. The inheritance pattern of FXI deficiency is autosomal recessive. The autosomal recessive pattern is misleading because carriers can also have bleeding symptoms. The bleeding tendency of patients with a FXI deficiency is highly variable and unpredictable. The FXI level does not correlate with the severity of the deficiency as in contrast to patients with hemophilia A and B. Bleeding episodes occur predominantly after trauma or surgery in tissue with high fibrinolytic activity (e.g., urogenital tract, oral cavity, or nasopharyngeal area). Women with FXI deficiency are prone for menorrhagia. Spontaneous joint or muscle hemorrhages are not observed in this patient group. Treatment of bleeding episodes consists of administrating plasma or FXI concentrates and anti-fibrinolytic drugs [2].

Other congenital bleeding disorders

All the other congenital bleeding disorders are extremely rare. Table 1 shows the incidence rate, inheritance pattern, clinical manifestations, and treatment modalities of these coagulation disorders [4].

Acquired coagulation disorders

Acquired coagulation disorders in sick children are more common than congenital coagulation disorders. Vitamin K deficiency is probably the most frequent bleeding disorder of childhood, which can lead to life-threatening bleeding [25]. It may be the result of inadequate intake or malabsorption in children with gastrointestinal diseases including cystic fibrosis, α_1-antitrypsin deficiency, and biliary atresia. Vitamin K deficiency causes decreased production of the vitamin K-dependent coagulation factors II, VII, IX, and X but also anticoagulant proteins protein C and protein S. Vitamin K is an essential cofactor in the carboxylation of glutamate to γ-carboxyglutamate residues, allowing calcium binding and so activating the vitamin K-dependent proteins. In the blood of vitamin K-deficient patients, undercarboxylated forms of vitamin K-dependent coagulation proteins (proteins induced by vitamin K absence) can be found [27]. Disseminated intravascular coagulation (DIC) is caused by several disorders, including sepsis, malignancy, and hypoxia. It is characterized by a systemic activation of the blood coagulation system, which results in the generation and deposition of fibrin, leading to micro-vascular thrombi and contributing to the development of multi-organ failure. Consumption of coagulation

Table 1 Incidence, inheritance, clinical manifestations, and therapeutic modalities, for both the congenital coagulation factor deficiencies and the fibrinolytic defects [4, 6, 15]

	Incidence	Inheritance	Clinical manifestations	Therapeutic modalities
Congenital coagulation factor deficiencies				
Hypo-, or afibrinogenemia (FI deficiency)	1 per 1,000,000	AR	Bleeding of umbilical cord, in gastro-intestinal tract, in genito-urinary tract, in CNS, posttraumatic/post-surgery bleeding, mucocutaneous bleeding or joint bleeding (rare)	Pd-fibrinogen conc.Plasma
FII deficiency (prothrombin deficiency)	1 per 2,000,000	AR	Bleeding of muscle or joint, mucocutaneous bleeding, or CNS bleeding (rare)	Prothrombin complex conc. Plasma
FV deficiency	1 per 1,000,000	AR	Mucocutaneous bleeding, joint bleeding (rare) or umbilical cord bleeding (rare)	Plasma
FVII deficiency	1 per 500,000	AR	Bleeding of joint, CNS bleeding or mucocutaneous bleeding	Pd-FVII conc.Rec. FVIIa conc.
FVIII deficiency (hemophilia A)	1 per 5,000 males	X-linked	Bleeding of joint or muscle, in CNS, posttraumatic/ post-surgery bleeding or mucocutaneous bleeding	Rec. FVIII conc.Pd-FVIII conc.
FIX deficiency (hemophilia B)	1 per 30,000 males	X-linked	Bleeding of joint or muscle, in CNS, posttraumatic/ post-surgery bleeding or mucocutaneous bleeding	Rec. FIX conc.Pd-FIX conc.
FX deficiency	1 per 1,000,000	AR	Mucocutaneous bleeding, posttraumatic/post-surgery bleeding, umbilical cord or joint bleeding (rare)	Prothrombin complex conc. Plasma
FXI deficiency (hemophilia C)	1 per 1,000,000	AR	Posttraumatic bleeding/post-surgery bleeding, mucocutaneous bleeding	Pd-FXI conc.Plasma
FXII deficiency	25 per 1,000	AR	None	Not necessary
FXIII deficiency	1 per 1,000,000	AR	Bleeding of umbilical cord or in CNS, poor wound healing	Pd-FXIII conc. or plasma
Congenital fibrinolytic defects				
Antiplasmin deficiency	Rare	AR	Mucocutaneous bleeding, posttraumatic/post-surgery re-bleeding, bleeding of joint, umbilical cord or in CNS	Antifibrinolytic drugsPlasma
Plasminogen activator inhibitor 1 deficiency	Rare	AR	Mucocutaneous bleeding, posttraumatic/post-surgery re-bleeding, bleeding of joint or in CNS	Antifibrinolytic drugs

FV factor V, *AR* autosomal recessive, *CNS* central nervous system, *conc.* concentrate, *Pd* plasma-derived, *rec.* recombinant

factors and platelets may induce severe bleeding complications [12]. Finally, children with severe liver disease have deficiencies of almost all coagulation factors, which results in increased risk of bleeding.

Medical history and physical examination

Medical history and physical examination are important tools to decide whether it is necessary to perform laboratory testing for one of the above-discussed hemostasis disorders. In general, there is suspicion of an underlying bleeding disorder whenever the duration of the bleeding is longer and the quantity higher than one would expect. Information about the type and pattern of bleeding may help to distinguish secondary from primary bleeding disorders. Bleedings into soft tissue, muscles and joints, and recurrent bleedings are indicative for a secondary hemostasis problem in contrast to mucocutaneous bleeding symptoms and persistent bleedings, which are more suggestive for primary hemostasis disorders.

The time of onset of the bleeding symptoms can be informative about the cause of the bleedings and the severity of the bleeding disorder. Signs and symptoms of acquired disorders typically develop over a period of days to weeks. Symptoms of congenital disorders usually exist for a long time. To obtain information about previous bleeding symptoms, it is essential to ask accurately about the past, particularly about potential challenges of the hemostatic system, including birth, heel prick, shedding of the umbilical stump, immunizations, the time when the child started to become mobile, surgical and dental interventions, trauma, and menstruation. Umbilical bleeding, for example, is frequently (80%) seen in patients with FXIII deficiency. Severe congenital coagulation disorders usually present early in life, whereas mild disorders become apparent later in childhood or even in adulthood. Furthermore, family history is crucial in the quest for congenital coagulation disorder, especially in young children, who had not yet experienced challenges to their hemostatic system.

Knowledge of concomitant illnesses and medication is indispensable to find the cause of bleedings. Malabsorption may lead to impaired vitamin K absorption. Severe liver disease and/or DIC cause impaired production or concentration of almost all coagulation factors. Vitamin K antagonists, including warfarin and acenocoumarol, prevent carboxylation of the vitamin-dependent coagulation factors, making them ineffective, and over-anticoagulation may result in severe bleeding complications [1].

Signs for secondary hemostasis disorders in physical examination are palpable deep hematomas, joint or intramuscular bleeds, especially in hemophilia. Abnormal scar formation can be present in patients with FXIII deficiency. Finally, always keep child abuse in mind while evaluating a child with bleeding complications.

Laboratory evaluation

Based on medical and family history and physical examination, the pediatrician decides to perform laboratory testing for disorders of secondary hemostasis and fibrinolysis. The first-step screening tests are the prothrombin time (PT) and the activated partial thomboplastin time (APTT). There are several techniques, including clot-based assays and chromogenic or color assays, to test coagulation. The end point of clot-based assays is fibrin clot formation, whereas the generation of thrombin is that of chromogenic assays. In general, the PT and APTT are clotting assays. As a result of various assays and reagents used, each laboratory has its own normal values ranges.

Prothrombin time

The PT clotting assay was introduced by Armand Quick in 1935 [19]. PT represents the time in seconds, required for clot formation after the addition of thromboplastin (a combination of TF and phospholipids) and calcium to citrated plasma [20]. It evaluates the integrity of the extrinsic and common pathways of the coagulation cascade. The PT reagents have a variable sensitivity to different coagulation factors. For instance, PT reagents are more sensitive to deficiencies of FVII than to deficiencies of the common pathway. Deficiencies of coagulation factors within the extrinsic and common pathways may prolong the PT, including FVII, FX, FV, FII, and fibrinogen (Fig. 1). PT is normal in patients with a-, hypo- or dysfibrinogenemia using a chromogenic assay, as the end point of this test is the generation of thrombin instead of a fibrin clot.

Activated partial thromboplastin time

This screening test was introduced by Langdell and has been used since the 1850s as a screening test [11]. The APTT clotting assay evaluates the integrity of the intrinsic and common pathways. The test is performed by adding a "partial thromboplastin" reagent (phospholipids without TF) to the patient's citrated plasma. To introduce controlled activation of the contact factors, incubation with a surface contact activator (such as celite, kaolin, silica, or ellagic acid) must take place. Hereafter, calcium chloride is added and the time in seconds required for clot formation is recorded. Deficiencies of coagulation factors of the intrinsic (HMWK, PK, FXII, FXI, FIX, FVIII) and common pathways (X, V, II, and fibrinogen) result in prolongation of the

APTT (Fig. 1) [20]. As for the PT reagents, the APTT reagents have various sensitivities to different clotting factors. Furthermore, APTT is normal in patients with a-, hypo- or dysfibrinogenemia using a chromogenic APTT assay, as the end point of this test is the generation of thrombin instead of a fibrin clot.

Interpretation of laboratory results

A prolonged PT and/or APTT should be further evaluated. It is important to realize that several factors may influence the accuracy of the tests. The tubes should be correctly filled; otherwise, the ratio of blood to anticoagulant (3.2% trisodium citrate) will change. The anticoagulant in the collection tubes prevents activation of the coagulation by chelating calcium. The ratio of whole blood to anticoagulant should be 9:1 in patients with hematocrits of 35–50%. Underfilling of the tubes, as well as high hematocrit, will result in falsely high results. A clot in the tube will lead to consumption of coagulation factors and cause prolongation of the PT and APTT. Furthermore, contamination with heparin may occur when the blood is drawn from a central venous catheter, leading to prolongation of APTT. In other words, before ordering further laboratory tests to investigate the prolongation of PT and/or APTT, clinicians should consider to repeat the screening tests to exclude false results.

Prolonged PT with normal APTT

An isolated prolongation of the PT indicates an acquired or congenital FVII deficiency (Fig. 3). As the incidence of congenital FVII deficiency is very low, an acquired deficiency of FVII should be considered first. FVII is one of the vitamin K-dependent coagulation factors and has the shortest half-life. In mild vitamin K deficiency, FVII levels drop first, causing prolongation of PT. The diagnosis is confirmed if the PT normalizes after administration of vitamin K. If prolongation of PT persists in spite of extra vitamin K, a congenital factor VII deficiency must be considered [18]. Administration of vitamin K antagonists causes an isolated PT prolongation as well. The PT is used

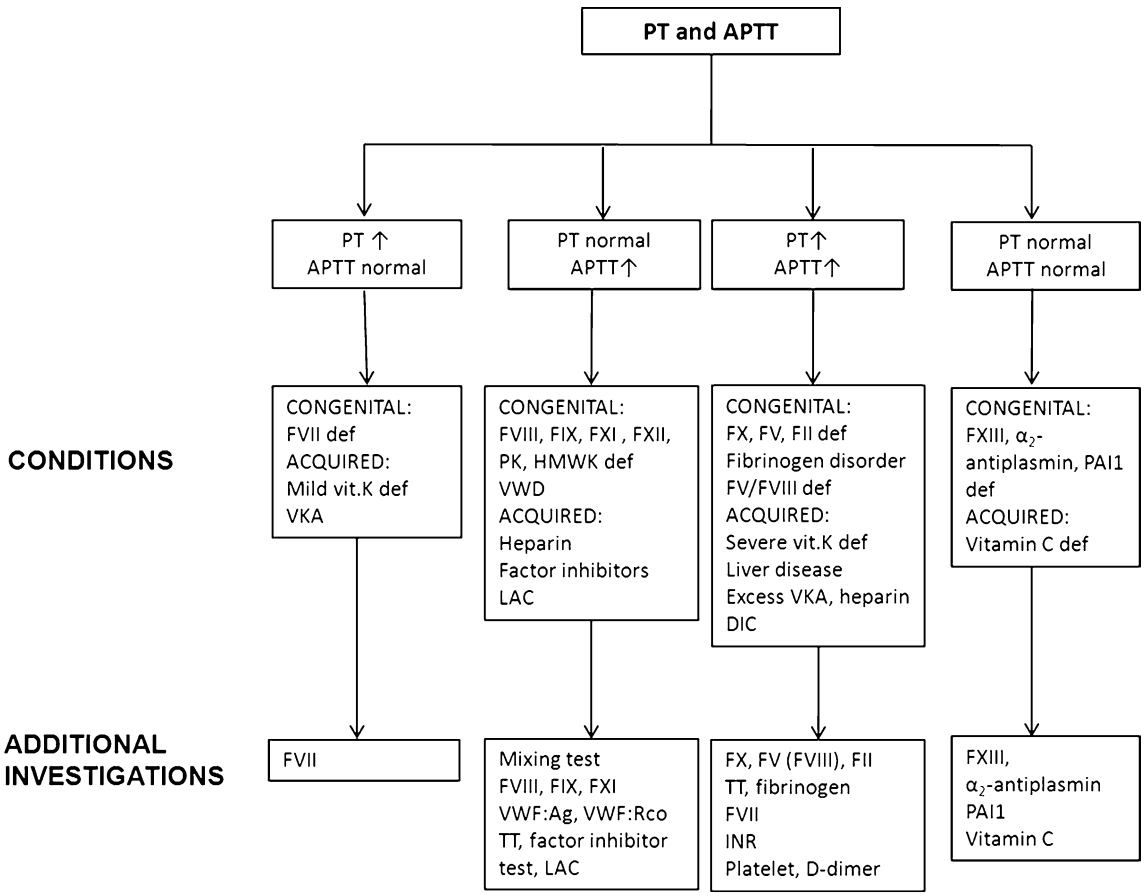

Fig. 3 Approach to children with bleeding symptoms and normal or prolonged prothrombin time (*PT*) or activated partial thromboplastin time (*APTT*). *def* deficiency, *vit*. vitamin, *VWD* von Willebrand disease, *DIC* disseminated intravascular coagulation, *PAI1* plasminogen activator inhibitor I, *VWF* Ag von Willebrand factor antigen, *RCo* ristocetin cofactor, *LAC* lupus anticoagulans, *TT* thrombin time, *PK* prekallikrein, *HMWK* high-molecular-weight kininogen, *INR* international normalized ratio, *VKA* vitamin K antagonist, *F* factor

to monitor the effect of this anticoagulant therapy. As a result of the various sensitivities of PT reagents, a standardized method of expressing the prolongation of PT as an international normalized ratio has been developed [1].

Prolonged APTT with a normal PT

Isolated prolongation of the APTT can be caused by congenital factor deficiencies of the intrinsic pathway (FVIII, FIX, FXI, FXII, HMWK, or PK). Specific clotting factor assays can be performed to identify the deficient coagulation factor. FVIII (hemophilia A), FIX (hemophilia B), and FXI deficiencies are associated with bleeding complications in contrast to deficiencies of FXII, HMWK, and PK. As HMWK and PK deficiencies are extremely rare, assays for these deficiencies are not commonly performed. Acquired causes of prolonged APTT with normal PT are heparin therapy, the presence of inhibitors directed against specific coagulation factors and the presence of nonspecific inhibitors (e.g., lupus anticoagulans [LAC]), which are antibodies directed against phospholipids. A mixing test can be performed to differentiate between coagulation factor deficiencies or the presence of heparin or an inhibitor. In a mixing test, prolonged APTT plasma is mixed with normal plasma in equal proportions. Normalization of the APTT following mixing indicates a factor deficiency. Plasma FVIII levels can be low in both hemophilia A patients and von Willebrand disease (VWD) patients, as one of the functions of VWF is binding and stabilizing FVIII in the circulation. Persistent prolongation of the APTT after a mixing test is indicative for the presence of heparin, a specific coagulation factor inhibitor or LAC. A LAC test or specific factor inhibitor tests can be performed to confirm the diagnosis of a coagulation factor inhibitor. The presence of heparin causes prolongation of the thrombin time (TT). The TT evaluates the final step of the coagulation cascade, the conversion of fibrinogen to fibrin and is performed by adding thrombin to citrated plasma. Prolongation of TT is also present in patients with DIC as result of increased fibrin degradation products (FDPs) and in patients with fibrinogen disorders.

Prolonged PT and prolonged APTT

Prolongation of both PT and APTT can be caused by isolated congenital coagulation factor deficiencies of the common pathway: fibrinogen, FII, FV or FX, or a qualitative defect of fibrinogen (dysfibrinogenemia) (Fig. 1). A-, hypo-, or dysfibrinogenemia should be considered if in addition to PT and APTT, TT is abnormal. All these defects are very rare (Table 1). Combined congenital FV and FVIII deficiency causes prolongation of PT and APTT, as well. This is a very rare, autosomal recessive, mild bleeding disorder caused by mutations in genes encoding proteins involved in the FV and FVIII intracellular transport (LMAN1 and MCFD2) [24]. More frequently, PT and APTT are prolonged as result of acquired factor deficiencies in patients with liver dysfunction, severe vitamin K deficiency, DIC, or supratherapeutic dosages of vitamin K antagonists or heparin. Vitamin K deficiency is the most frequent cause. It is characterized by deficiencies of the vitamin K-dependent factors only, whereas in DIC and liver dysfunction, plasma levels of almost all coagulation factors are decreased. In contrast to DIC, vitamin K deficiency is usually not accompanied by thrombocytopenia. Thrombocytopenia may occur in liver disease, as well, due to portal hypertension or splenomegaly. DIC is associated with increased plasma levels of fibrin D-dimer, one of the major FDPs. In neonates, mild prolongation of both PT and APTT is always present as a result of physiologically low levels of vitamin K-dependent clotting factors after birth. These reach adult values by 6 months of age [16].

Normal PT and APTT

Children with a strong positive bleeding history and normal PT and APTT results should be tested for FXIII deficiency (Fig. 1). Other defects, which are not detectable with routine coagulation screening tests, are vitamin C deficiency and extremely rare fibrinolytic disorders, e.g., α_2 -antiplasmin and PAI deficiency. (Table 1) Vitamin C deficiency results in impaired collagen synthesis. Presenting signs and symptoms are mucosal bleeding, petechiae, and ecchymoses [22]. Finally, normal PT and APTT results do not exclude mild deficiencies of coagulation factors, including FVIII and FIX. It is important to realize that the results of the screening tests depend on the sensitivity of the used assay system and reagents, which vary among hospitals. Furthermore, mild deficiencies might remain undetected as result of elevated levels of other coagulation deficiencies, including FVIII. Therefore, if suspicion of a coagulation disorder is high, mild hemophilia A and B and VWD must be excluded as well as factor XIII deficiency, fibrinolytic disorders, and vitamin C deficiency [9].

Summary

Medical and family history and physical examination are important tools to decide whether children with an increased bleeding tendency need diagnostic laboratory evaluation. Initial screening tests for disorders of secondary hemostasis include PT and APTT. Disorders of fibrinolysis are rare. Knowledge of the classical coagulation cascade with its intrinsic, extrinsic, and common pathways, is useful

to identify potential defects in the coagulation and to decide which additional coagulation tests should be performed.

Conflict of interest The authors state that they have no conflict of interest.

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