Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublisher.com/sjams/

OPEN ACCESS

Paediatrics

Bleeding Disorders in Children

Dr. Ponnumony John Solomon[1], Dr. Alen Chidambaram Priya Margaret[2*]

[1]Director of Pediatrics, Sree Balaji Medical College, Chromepet, Chennai India
[2]Assistant Professor of Pediatrics, Sree Balaji Medical College, Chromepet, Chennai India

***Corresponding author:** Dr. A. C. Priya Margaret
| **Received:** 10.05.2019 | **Accepted:** 29.05.2019 | **Published:** 30.05.2019
DOI: 10.21276/sjams.2019.7.5.45

Abstract **Review Article**

Abnormal bleeding in a child creates anxiety to the parents and family. Failure to investigate and treat these children adequately may result in high morbidity and mortality. Hence a thorough knowledge about the common bleeding disorders in children is necessary for all practicing Pediatricians. Abnormal bleeding may be caused by congenital or acquired diseases. Among the congenital diseases Von Willebrand disease and Hemophilia A are common. Hemophilia B and factor XIII deficiency are less common. Among the acquired diseases the common one is Immune Thrombocytopenic Purpura. A detailed clinical history and thorough physical examination will guide the Pediatrician to decide on the tests to be done to arrive at a definitive diagnosis and to manage effectively. Hemophilia A and B are X linked recessive disorders and hence usually the males suffer from the disease. When Non Accidental Injury is suspected in a case of bruising, in addition to a detailed history, meticulous clinical examination and appropriate blood tests are essential to rule out bleeding disorder. The physiology of coagulation, the factors involved in coagulation and the various tests done to detect them are briefly presented in this article.

Key words: Bleeding, coagulation, treatment, coagulation factor, deficiency.

INTRODUCTION

Whenever there is abnormal bleeding in a child, the parents and the child will be frightened and anxious. The Pediatrician/doctor who comes across such children should have the basic knowledge to identify the cause and manage the case or refer the patient to the appropriate centre.

Abnormal bleeding may be caused by an inherited disorder or an acquired disease. The defect may be in the blood vessel wall, platelets or in the coagulation proteins.

Hemostasis is the process by which bleeding is arrested after injury to blood vessels [1]. When a blood vessel is damaged three steps occur in a rapid sequence to stop the bleeding.

1. The blood vessel contracts so that less blood flows through it.
2. Platelets get activated, they adhere to the subendothelium, aggregate and plug and seal the defect and stop the leak.
3. Clotting factors in the blood gather at the site of the damage and act together at the damaged area to form a stable blood clot.

The factors involved in coagulation are as follows

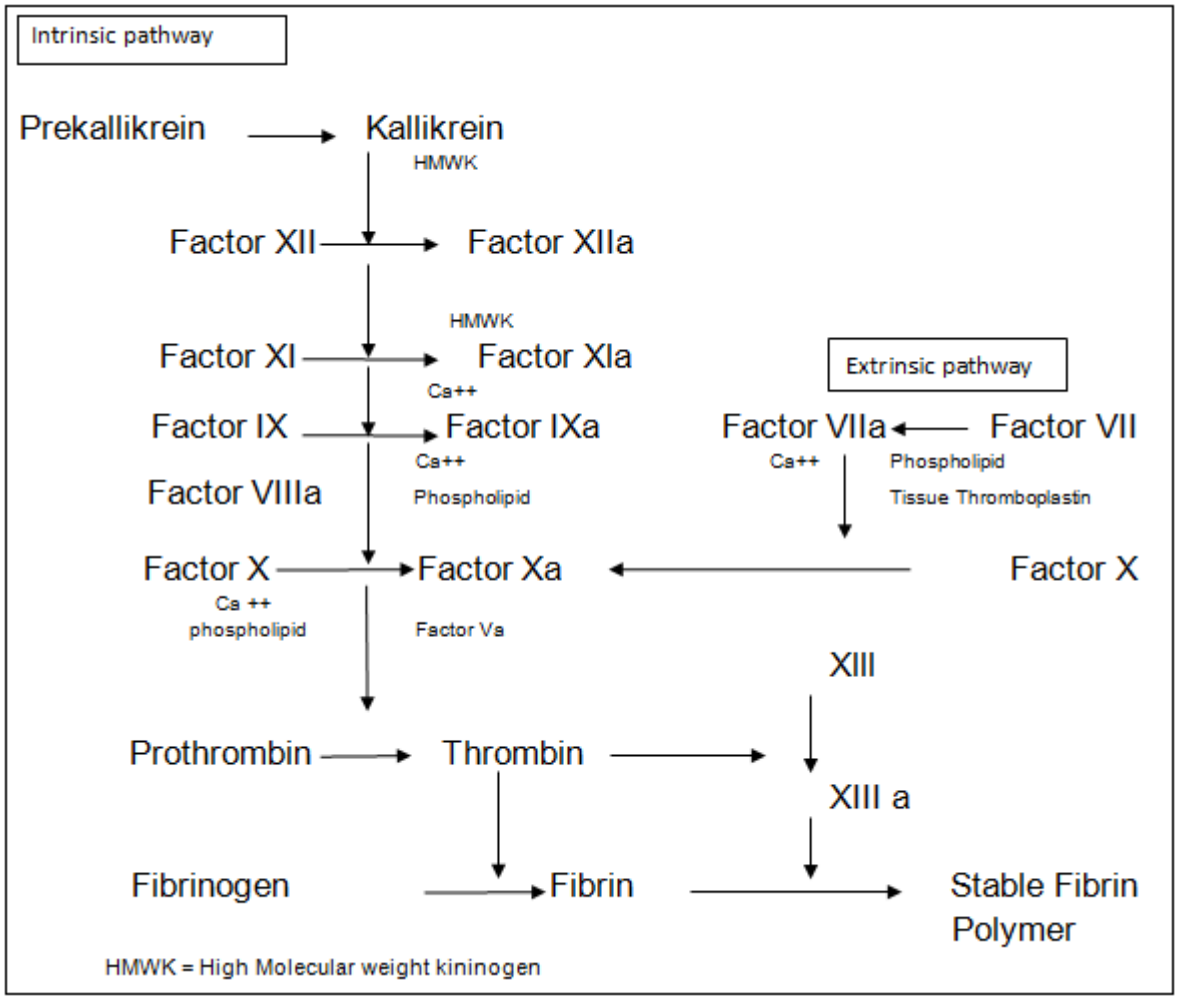
Table-1

Scientific name	Common name	Other name	pathway
Factor I	Fibrinogen	-	Both
Factor II	Prothrombin	-	Both
Factor III	Tissue thromboplastin	Tissue factor	Extrinsic
Factor IV	Calcium	-	Both
Factor V	Proaccelerin	Labile factor, Accelerator globulin	Both
Factor VI	Accelerin	-	-
Factor VII	Proconvertin	Conversion accelerator	Extrinsic
Factor VIII	Antihemophilic factor	Antihemophilic globulin	Intrinsic
Factor IX	Christmas factor	Antihemophilic factor B	Intrinsic
Factor X	Stuart factor	-	Both

Factor XI	Plasma thromboplastin Antecedent	-	Intrinsic
Factor XII	Hageman factor	Contact factor	Intrinsic
Factor XIII	Fibrin stabilizing factor	fibrinoligase	Both
-	Fletcher factor	Prekallikrein	-
-	Fitzgerald factor	High Molecular weight Kininogen	-

The blood clotting factors have all been given Roman numbers to identify them. The term 'Christmas factor' is given because this factor was identified first in the person by name Stephen Christmas.

The various steps involved in coagulation are as follows



The endothelium of the blood vessels is involved in the regulation of vasomotor tone and maintenance of blood flow [2]. Endothelial cells possess surface receptors for a variety of physiological substances which may influence vascular tone directly or indirectly through various hemostasis related events [2]. Once activated endothelial cells express a variety of intracellular adhesion molecules, some of which are released into the plasma [2]. These are vascular cell adhesion molecule (VCAM), E- selectin, P-selectin and Von Willebrand Factor (VWF) which modulate platelet adhesion, inflammation, Phagocytosis and vascular permeability [2].

VWF plays an important role in primary hemostasis by promoting platelet adhesion to the sub endothelium at sites of vascular injury. It is also a carrier of factor VIII [2]. Von Willebrand Factor is synthesized by endothelial cells, Megakaryocytes and Platelets. In endothelial cells VWF may be secreted directly into the circulation or stored in Weibel-Palade bodies. The VWF produced in megakaryocytes and platelets is not secreted, but stored in α-granules. Release of VWF from these stores occurs following activation of endothelial cells or platelets [2]. VWF contains binding sites for collagen, fibrinogen and the platelet receptor, glycoprotein (GP) 1b. When vascular injury exposes sub endothelial collagen, VWF binds and becomes unwound from its globular form. This

exposes more binding sites and allows the capture of platelets from the circulation. Thus VWF and fibrinogen act as bridges between the platelets and the injured vascular wall [2].

Platelets have a much wider role than simply supporting aggregation. Platelet dense granules and α-granules are packed with a rich diversity of small molecules and proteins that play fundamental roles in many aspects of hemostasis including vasoconstriction, leukocyte recruitment and vessel repair, as well as in other pathways including host defense [2].

The formation of the FVIIa - TF complex is regarded as the sole initiator of coagulation in both normal and pathological coagulation [2].

Plasma factor VII binds to Tissue factor, for example after vessel trauma or plaque rupture, to form a complex that initiates coagulation by directly activating factor X and to a lesser extent Factor IX [2]. Eliciting a detailed history as follows may give a clue to the diagnosis of bleeding disorders.

1. Was there any abnormal bleeding from the umbilical stump in the newborn period? This may suggest factor XIII deficiency or fibrinogen disorders.
2. Was there any prolonged bleeding following the shedding of temporary teeth?
3. Is there any unusual swelling or prolonged bleeding following Intramuscular injection? (eg. Vaccine administration)
4. Was there any prolonged bleeding following minor trauma?
5. Is the patient on any drugs like aspirin or anticonvulsants like Valproic acid which can affect the platelet function? Sometimes native drugs taken by the patient can also cause liver toxicity and affect the production of coagulation proteins and cause bleeding.
6. Has the patient undergone any surgical procedure like Circumcision, Tonsillectomy or any other Surgery without experiencing prolonged bleeding? If there was no significant bleeding following a major surgery, inherited bleeding disorders can be ruled out.
7. Is there any family history of abnormal bleeding in parents, maternal grandparents, uncles, siblings, or history of consanguineous marriage? This will suggest an inherited bleeding problem.

A discrepancy between physical findings and history is one of the cardinal signs of Child abuse [3]. When we come across a patient with bruising, non – accidental injury should also be thought of as differential diagnosis. Suspicion of non-accidental injury arises from characteristic physical signs of injury to the child, a discrepant history, and abnormal parental attitudes or behavior [3].

The routine tests done to investigate a case of suspected bleeding disorder are

1. Complete blood count (CBC) and Peripheral Blood Smear study.

If the blood sent to the lab is a clotted sample we may get a low platelet count, but peripheral blood smear will show many platelets particularly in the tail end of the slide.

A peripheral blood smear taken directly without using any anticoagulants is a simple test to assess platelet count and function. If there are good platelet clumps in the peripheral smear then the platelet count and platelet aggregation are taken as probably normal.

2. Prothrombin Time(PT)
3. Activated Partial Thromboplastin Time (APTT/PTT)
4. Thrombin time (TT)
5. Fibrinogen
6. Bleeding time or Platelet function analysis.

Blood clotting time is not done in most of the centres because it varies depending on the method used. Normal clotting time is 6-10 minutes.

The intrinsic pathway of coagulation is assessed by APTT (normal value is 25-38 seconds and it varies slightly depending upon age). Usually the patient's results are compared with a control. If the difference is less than 6 it is normal. If the difference is more than 10 it is abnormal. If the difference is between 6 and 10 it is doubtful and the test should be repeated.

The extrinsic pathway of coagulation is assessed by prothrombin time (normal value10-14 seconds). The prothrombin time gives an indication of the concentration of prothrombin in the blood. The prothrombin time is also expressed in International Normalized Ratio (INR) so that values can be compared from one laboratory to another. INR is the ratio of the person's Prothrombin time to a normal control sample raised to the power of the ISI. For each batch of tissue factor the manufacturer assigns an International Sensitivity Index (ISI) which indicates the activity of the tissue factor with a standardized sample. The normal INR is 0.9 – 1.3.

Bleeding time is the least reliable of the screening tests [1]. It can be done by Ivy Bleeding time method. The normal bleeding time is 3-9 minutes. Prothrombin time is prolonged in deficiency of fibrinogen, Prothrombin, factor V, factor VII or factor X.

Partial Thromboplastin time (APTT) is prolonged in deficiency of fibrinogen, Prothrombin,

factor V, Factor VIII, Factor IX, Factor XI or factor XII, prekallikrein and high molecular weight kininogen.

Thrombin time is prolonged when there is low or abnormal fibrinogen. It may also be prolonged by the effect of heparin. The normal thrombin time is 11-15 seconds.

When the PT or PTT are abnormal mixing studies can be done. Patient's plasma is mixed with normal plasma. If it corrects it may be due to a factor deficiency. Then the specific factor deficient plasma is mixed with patient's plasma, and thus the specific factor deficiency can be confirmed. After the screening tests we have to do specific factor assays to confirm the defects.

If all the baseline screening tests are normal then we should investigate for

1. Factor XIII deficiency. For this clot solubility test can be done. The clot is suspended in 5 mol/L urea solution for 24 hours, and if the clot dissolves within 3 hours then factor XIII is deficient. Confirmation can be done by doing factor assay.
2. Mild Haemophilia or Von Willebrand disease. APTT may be normal and hence factor assay may be required for the diagnosis. Thus a good history is most important to evaluate bleeding diathesis.
3. A defect in the blood vessel wall (eg) scurvy.

In Hemophilia carriers the blood clotting is slower than in normal women with normal gene. Hence Factor VIII and Factor IX may be slightly low. But normal level does not mean that she is not a carrier.

There are many causes for abnormal bleeding. Since the liver produces many coagulation factors severe liver dysfunction can cause abnormal bleeding. Drugs interfering with the number or function of platelets can also cause abnormal bleeding. It is not possible to give a detailed description of all the diseases in this article. Hence a brief description of only a few common disorders is given below.

Immune Thrombocytopenic purpura

This is the most common acquired cause of bleeding in the skin and mucous membranes. The classical presentation includes a previously well child with sudden onset of excessive bruising, petechiae or mucus membrane bleeding 1 to 2 weeks after a viral infection or an immunization [4]. Though the exact mechanism of ITP is not known, it usually follows a brief period of viral illness. The patient does not look ill. There is no organomegaly. A complete blood count with peripheral blood smear study will show isolated thrombocytopenia. If Bone Marrow aspiration is done in this patient it will be normal.

75% of patients go into spontaneous remission of ITP within 6 months [4]. Most of the time the patient may not require any treatment. If the bleeding is a nuisance or produces anxiety then a short course of prednisolone for 2 weeks may be given. In an emergency or before surgery methylprednisolone or IVIg can be given. Anti – D (Rh_o) immunoglobulin can be used in Rh positive patients who have not undergone splenectomy [4]. Some patients treated with Anti- D (Rh_o) immunoglobulin develop hemolysis. IVIg is more effective than Anti-D (Rh_o) immunoglobulin. A low dose of 0.8g/kg once is as effective as a higher dose of 1g/kg on 2 successive days [4].

There is an emerging experience with anti – CD20 (rituximab) in the treatment of acute and chronic ITP [4]. Some of these patients with ITP may not undergo remission within 6 months. Such chronic ITP patients have low and fluctuating platelet counts. Often when there is some infection the platelet count may go down, and the patient may start bruising. These patients should follow the advice given in this article very carefully. They should avoid constipation. Straining during defecation or severe cough can result in intracranial bleed. Hence constipation should be prevented / treated. Cough should be adequately treated. If emergency surgery is required, the patient should be given platelet concentrate, and the count should be maintained at normal levels until the wound heals.

Hemophilia A or B

The clinical presentation is the same for both the diseases. Hemophilia A is 4 times more common than Hemophilia B[4]. Both are X linked recessive disorders and hence females are carriers and males are sufferers from the disease. If a carrier female marries a hemophiliac male then the female child born to them may get hemophilia but this combination is a very rare possibility. Patients with Turner syndrome can also have hemophilia.

Family history of similar illness may be present. But in 30% of the cases there is no family history and hence it may be due to a new mutation. The severity may vary from mild to moderate to severe illness.

Patients with severe deficiency (<1% clotting factor level) will get spontaneous bleeding into the joints and muscles. Sometimes infants may get ileopsoas bleeding which may present with incessant cry and may mimic acute appendicitis. The child cries and keeps the hip in a flexed and internally rotated position due to irritation of the ileopsoas. There is inability to extend the hip. Confirmation with U/S or CT may be required.

Patients with moderate deficiency (1-5% factor level) will have abnormal bleeding following trivial injury. Patients with mild deficiency (factor level = 5 - 50%) may not normally present any problem unless there is a major haemostatic challenge such as road

traffic accident with injury to liver, spleen etc, or following a Surgery eg. Circumcision, Tonsillectomy etc.

Older children with hemophilia usually complain of tingling sensation as the first sign of an early joint hemorrhage. The laboratory findings in both the hemophilias are that the PTT is prolonged and the PT, platelets, thrombin time and bleeding time are normal. Mixing of normal plasma with patients plasma results in correction of PTT value.

Specific assay for factor VIII or IX will confirm the diagnosis. When Hemophilia is suspected Factor VIII assay should be done first and if it is normal then factor IX assay can be done. The normal level of Factor VIII in the blood is between 50 – 200%.

Treatment of Hemophilia

During the past 4 decades remarkable progress has been made by doctors and scientists in the treatment of Hemophilia. With the institution of recombinant products in 1999 the outlook is even better for children with Hemophilia.

In the olden days when factor VIII concentrate was not available fresh frozen plasma was the treatment given, and it was administered during bleeding.1ml of FFP exerts 1 unit of Factor VIII activity. This may not be adequate to treat severe bleeding. To what level the factor should be raised depends upon the indication. For joint bleeds the factor level should be maintained at 30% and for muscle bleeds at 50%. For major bleeding the level should be raised to 100% activity.

Dr. Judith pool from California in 1963 observed that when FFP is thawed at 4°c, sludge (precipitate) will develop at the bottom of the pack and all the Factor VIII is concentrated in that. This is called as Cryoprecipitate. This is also used in the treatment of Hemophilia 'A'.

Mild factor VIII deficiency can be treated with desmopressin nasally. It will release the endogenously produced factor VIII. Moderate and severe deficiency can be treated with Factor concentrate.

In the 1970s scientists were able to produce concentrate of Factor VIII. Subsequently Factor IX concentrates were also prepared. This was followed by Genetic Engineering to produce recombinant Factor VIII & Factor IX.

The dose of recombinant factor VIII is as follows (in IU). % of rise required x body weight (in kg) x 0.5. It should be given 8 to12 hourly until the threat of bleeding is over. The % of rise required depends upon the situation. The dose of recombinant factor IX is as follows (in IU). % of rise required x body weight (in kg). It should be given 12 to 24 hourly until the threat of bleeding is over.

The trough levels should not fall below 0.5 IU/mL. For those children who have got inhibitors against Factor VIII or IX recombinant Factor VIIa or FEIBA (Factor Eight Inhibitor By passing Activity) which is prepared from plasma may be used.

Today prophylaxis is regarded as the standard of care for all boys with severe Hemophilia. Regular prophylaxis is begun at around the age of 1 year, before the onset of joint bleeds. This is primary prophylaxis. Ideally Factor VIII is administered every 2nd day at a dose of 25 – 40 units/ kg. Factor IX can usually be given every 3rd day. The goal is to adjust the dose and frequency to maintain a trough level of 1% and to prevent all bleeds.

Von Willebrand Disease

Von Willebrand Disease was named after the Swedish doctor Dr. Erik Von Willebrand, who first described the condition in 1926. Von Willebrand Factor circulates in the blood linked to factor VIII. This is the most common inherited bleeding disorder. It is more common than Hemophilia and it is usually milder.

Von Willebrand factor is involved in the early stages of blood clotting, and also carries the important clotting protein factor VIII. VWD affects boys and girls equally.

There are various forms of VWD

In Type 1 the level of VW factor is low, the level of Factor VIII may also be low. This is the most common and mildest form of the disease. These patients do not bleed spontaneously, but may bleed significantly with trauma, surgery or tooth extraction.

In Type 2 the VWF level is normal, but it does not function normally. There are several subtypes in this, of which Type 2A and Type 2B are usually seen and others are very rare. Type 2B may be associated with a low platelet number as well.

Type 3 patients have very low or absent VWF and Factor VIII. Symptoms are severe in these patients and may include bleeding into joints and muscles. Pseudo or Platelet type VWD is similar to Type 2B, but the defect is in the platelets and not in the factor.

The signs and symptoms of VWD are

1. Bruising that is unusual in frequency and location
2. Bleeding in the mucus membranes
3. Prolonged or excessive bleeding following dental procedures, tonsillectomy, circumcision or cut injuries.
4. Prolonged or excessive menstrual bleeding

There are no reliable screening tests for VWD. The PTT may be prolonged when factor VIII is low. Bleeding time may be prolonged. Therefore a panel of tests is required.

VWF antigen test (VWF: Ag) which measures the amount of VWFactor. VWF activity test (VWF: Rco). This is also called as Ristocetin cofactor. Factor VIII activity test (F VIII). This is also called as Factor VIII coagulant assay. It measures the level of factor VIII and its ability to function.

VWF activity/antigen ratio (VWF: Rco / VWF: Ag)

Tests might need to be repeated because the levels may rise and fall over time. Specific testing for type 1C (clearance defects), type 2B, and type 2N VWD are also available.

Treatment

Type 1 VWD: Desmopressin increases the circulating VW factor by releasing from storage. Following trauma or Surgery VWD patients may require an intravenous preparation containing both factor VIII and VWF which is derived from human plasma. Desmopressin is ineffective in Type 2A and 2B. Type 2 and 3 VWD: Intravenous preparation derived from human plasma that contains Factor VIII and VWF.

Antifibrinolytic agents

For mucosal bleeds in Hemophilia and VWD, in addition to specific treatment antifibrinolytic agents like tranexamic acid or aminocaproic acid can be given orally to prevent removal of the clot covering the wound. This is particularly useful in oral mucosal bleeding.

When a patient is diagnosed to have bleeding disorder, he and the family should be counseled. He must be given a card containing details such as his name, blood group, name of the disease and the important emergency treatment etc. He should be given the following advice:

1. Avoid injuries as far as possible. Contact sports should be avoided.
2. Avoid IM injections. Vaccines that are usually administered intramuscularly can be given subcutaneously in these patients.
3. Avoid drugs like aspirin and non-steroidal anti-Inflammatory drugs which will interfere with platelet function. Paracetamol can be given for fever & pain.
4. If the patient has to undergo a surgery it has to be done in a well-established centre where there is facility and expertise available to treat such patients effectively.

CONCLUSION

Medical science has advanced so much today. The older methods of diagnosis and investigations have been replaced by more reliable and sensitive tests than before and a precise diagnosis can be made. Treatment options have also advanced in the area of hemostasis. Hence the treating Pediatrician and the General physicians should be knowledgeable in the basic diagnosis and treatment of bleeding disorders to give a high quality of life to such patients.

REFERENCES

1. Bashawri LA, Ahmed MA. The approach to a patient with a bleeding disorder: for the primary care physician. Journal of family & community medicine. 2007 May;14(2):53.
2. Keith Gomez and John H. Mc Vey. Normal Haemostasis. Postgraduate Haematology 7th edition, edited by A. Victor Hoffbrand, Douglas R. Higgs chapter. 36, 682-684, 699.
3. O'hare AE, Eden OB. Bleeding disorders and non-accidental injury. Archives of disease in childhood. 1984 Sep 1;59(9):860-4.
4. Manno CS. Management of bleeding disorders in children. ASH Education Program Book. 2005 Jan 1;2005(1):416-22.