

# Inherited Bleeding Disorders in Egyptian Pediatric Patients: Updated Types and Management

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## **Abstract**

**Background:** *The bleeding disorders are known to treating physicians since 16th century. Congenital bleeding disorders are found in all racial groups and have worldwide distribution but very limited information is available in developing countries. Deficiencies of congenital coagulation factors result in patients with bleeding disorders. Among all, hemophilia A (HA), hemophilia B (HB), and von Willebrand disease (vWD) are the commonest and are characterized by low levels of factor VIII, factor IX or von Willebrand factor (vWF), respectively. According to the World Federation of Hemophilia (WFH), 2015 around one of every 10,000 individuals are born with hemophilia A and roughly one of every 50,000 individuals are born with hemophilia B.*

**Keywords:** *Bleeding disorders, Hemophilia.*

## **1. Bleeding Disorders:**

Bleeding disorders are a heterogeneous group of diseases influencing the hemostatic system. They reflect irregularities of the blood vessels, coagulation proteins as well as platelets. People with bleeding disorders may give a long-lasting history of simple wounding and bleeding. Bleeding disorders usually introduce itself in childhood, yet mild cases may manifest sometime down the road after a hemostatic challenge (traumatic injury, medical procedure like surgery or tooth extraction). (1)

The severity of the bleeding disorder can differ from mild to extreme however stays steady for a specific individual during their lifetime and is additionally typically constant inside a family. Individuals with mild bleeding disorder might be unconscious that they are influenced until they experience medical procedure or have some traumatic injury. In spite of the fact that there is no cure at present for these conditions, effective treatment is accessible. (2)

According to etiology, bleeding disorders are classified into I) Vascular disorders, for example, Scurvy, Henoch-Schonlein purpura. ii) Platelet disorders, for example, thrombocytopenia (quantitative deformity) or qualitative defects as disorders of platelet function as Glanzman and von Willebrand disease (platelet type). iii) Coagulation disorders which might be hereditary as

hemophilia (A, B) or acquired as Vitamin-K deficiency, Liver ailment. iv) Mixed/Consumption as disseminated intravascular coagulation (DIC). (3)

Bleeding disorders are mainly inherited, despite the fact that in some conditions they can be acquired further down the road as an autoimmune disease if the body forms antibodies that battle against the blood's common coagulating factors. These acquired defects in the hemostatic system may also be seen with antiplatelet or antithrombotic drugs. (4)

### 1.1 Inherited Bleeding disorders

Inherited bleeding disorders (IBDs) are a group of hereditary coagulopathies that result when deficiencies of the proteins essential for coagulation, platelet function or fibrinolysis happen. (5)

Inherited bleeding disorders (IBDs) can be classified according to the underlying defect into; Hemophilia – deficiency of coagulating factor 8 {F VIII} (hemophilia A) or Factor 9 {F IX} (hemophilia B) and Von Willebrand disease (VWD) where there is inadequacy of VWF and along these lines defect in platelet adhesion and aggregation. Likewise, platelet function defects, as influencing the platelet receptor or platelet signaling pathways. (6)

Other uncommon inherited bleeding disorders incorporate lack of factors V, VII, IX, and XIII, fibrinogen disorders, combined factor deficiencies like F V+VIII or vit K-dependant factors with an overall public prevalence between 1/500,000 and 1/2,000,000. (7)

### 1.2 Epidemiology

Inherited bleeding disorders (IBDs) have a wide scope of frequencies from 1 of every 1000 live births for von Willebrand Disease (VWD) and 1 of every 5000 male live births in Hemophilia A, to just 8 cases worldwide of alpha-2-antiplasmin deficiency. (8; 9)

According to the World Federation of Hemophilia (WFH), 2015 around one of every 10,000 individuals are born with hemophilia A and roughly one of every 50,000 individuals are born with hemophilia B.

Among the inherited bleeding disorders, vWD is the most widely recognized IBD affecting 1.3% of the population., followed by hemophilia A and B. It is assessed that there are 400000 hemophilia sufferers worldwide. (10)

Few published studies in Jordan, Saudi Arabia, and Egypt described the prevalence of IBDs in the population (11; 12 and 13). They announced that VWD was the second most common reason for IBDs (as it is underdiagnosed in our community), generally because of the increased rate of consanguineous marriage in the community.

In Egypt, hemophilias are the most common IBDs. On the other hand, von Willebrand disease (VWD) and platelet functions defects (PFDs) are second common reasons for bleeding. However, various studies have reported that VWD is the most widely distributed congenital bleeding disorder in the population. This difference may be due to underdiagnosis of vWD in Egypt or mild bleeding presentation of the disease which can be easily missed or underestimated. In addition, Egypt, consanguineous marriage are common, along these lines autosomal recessive coagulation disorders contribute a higher prevalence than in other countries. (14)

**Tonbary et al. (14)** assessed the epidemiological distribution of hemophilia in Mansoura, Egypt. They reported that hemophilia A is the most common IBD in our locality followed by hemophilia B. The usual presenting manifestation was bleeding after male circumcision.

**El-Bostany et al. (13)** evaluated the distribution of some IBDs. The study included 43 children with different bleeding symptoms. A sum of 12 (27.9%) children had VWD, 11 (25.5%) had hemophilia A, three (7%) had hemophilia B, seven (16.3%) had platelet function defects and 10 (23.3%) had bleeding with undiagnosed reason. Most of platelet function defects were analyzed as Glanzmann's thrombasthenia. VWD and Glanzmann's thrombasthenia should be considered not uncommon reasons for IBDs in children in Egypt and Kingdom of Saudi Arabia.

### **Hemophilia:**

The body's clotting process is a stepwise process that requires various key proteins to guarantee the end of any type of bleeding. Hemophilia is characterized by hereditary changes resulting in the deficiency of factors responsible for the normal procedure of coagulation. **(15).**

### **Inheritance pattern:**

As reported in hemophilia federation of America the accompanying diagrams show how the hemophilia gene can be inherited. In approximately 33% of individuals with hemophilia, there is no family history of the disease, and spontaneous mutation of the gene usually present.

### **1.3 Subtypes and causes:**

- **Hemophilia A** is a recessive X-linked hereditary disorder including an absence of functional clotting Factor VIII and represents about 80% of hemophilia cases.
- **Hemophilia B** is a recessive X-linked hereditary disorder including an absence of functional Factor IX. It represents roughly 20% of hemophilia cases.
- **Hemophilia C:** is an autosomal hereditary disorder (i.e., not X-linked) including an absence of functional coagulating Factor XI. Hemophilia C isn't totally recessive, as heterozygous people additionally show increased bleeding.

**Vascular hemophilia:** a form of hemophilia discovered by Erik von Willebrand; a genetic disorder that is inherited as an autosomal recessive trait; characterized by a deficiency of von willebrand coagulation factor**(16).**

### **Severity:**

Hemophilia can be also classified according to severity as follows:

- **Severe hemophilia:** factor level activity below 1%
- **Moderate hemophilia:** factor level activity 1-5%
- **Mild hemophilia:** factor level activity between 5-40%

**(17)**

**Table (1):** Classification of Hemophilia(17)

Classification	Factor level, %	Bleeding phenotype
Severe	<1	Bleed spontaneously without injury
Moderate	1 - 5	Bleed on minor haemostatic challenge/injury
Mild	6 - 40	Bleed on major haemostatic challenge/injury

**1.4 Diagnosis:**

According to **World Federation of Hemophilia (WFH)** 2012, Principles of diagnosis:

A- Understanding the clinical presentation of hemophilia and the proper clinical diagnosis.

B- Using screening tests to assess the potential reason for bleeding, for example, platelet count, bleeding time (BT; in selected situations), or the platelet function screening tests, prothrombin time (PT), and activated partial thromboplastin time (APTT).

C- Confirmation of diagnosis by factor assay and other suitable specific examinations.

**Screening tests:**

1. Platelet count, BT, PT, and APTT might be utilized to screen a patient suspected to have a bleeding disorder.
2. Bleeding time lacks specificity and sensitivity and may be also liable to performance-related errors.

**Table (2):** Interpretation of screening test (18)

INTERPRETATION OF SCREENING TESTS				
POSSIBLE DIAGNOSIS	PT	APTT*	BT	PLATELET COUNT
Normal	Normal	Normal	Normal	Normal
Hemophilia A or B**	Normal	Prolonged*	Normal	Normal
VWD	Normal	Normal or prolonged*	Normal or prolonged	Normal or reduced
Platelet defect	Normal	Normal	Normal or prolonged	Normal or reduced

**Factor Assay:**

1. Factor assay is required in the following circumstances:

To confirm diagnosis

To monitor treatment

- the laboratory monitoring of factor levels can be established by estimating clotting factor levels pre and post infusion.
- Lower than anticipated recovery as well as diminished half-infused clotting factor might be an early pointer of the presence of inhibitors.

To test the quality of cryoprecipitate

•It is helpful to check the FVIII concentration present in cryoprecipitate (cp) as a feature of the quality control of this product.

(18)

. It should be noticed that all the vit K–dependant factors, including FIX, are decreased at birth, though FVIII levels are normal (even raised) at birth. thus, diagnosis of hemophilia A can be confirmed immediately after birth even from cord blood sampling. (19)

On the other hand mild hemophilia B may be hard to diagnose at birth. In such cases, estimation of the FIX level should be repeated after age of 6 months. (20)

Identification of the mutant gene is additionally significant because it might help to anticipate the risk of inhibitor formation, and can also distinguish female relatives who might be carriers of the mutant gene. (21)

## 1.5 Management:

### I-Current Therapies

#### A-Factor Replacement Therapy (On-demand therapy):

The WFH strongly encourages the utilization of viral inactivated plasma-derived or recombinant concentrates over cryoprecipitate or fresh frozen plasma for the treatment of hemophilia and other inherited bleeding disorders. (22).

#### i- Factor VIII concentrates:

- Factor VIII concentrates are the treatment of choice for hemophilia A.

#### Dose/administration:

1. In the absence of an inhibitor, every unit of FVIII per kilogram of body weight infused iv will raise the plasma FVIII level 2 IU dL<sup>-1</sup>
2. The half-life of FVIII is roughly 8–12 h.
3. The patient's factor level should be estimated 15 min after the infusion to adjust the calculated dose.
4. The dose is determined by multiplying the patient's weight in kilograms by the factor level in IU dL<sup>-1</sup> desired, multiplied by 0.5.
5. FVIII should be given by slow IV infusion at a rate not to exceed 100 units for each min in youngsters, or as determined in the product information leaflet(23).

#### bii.Factor IX concentrates

- Factor IX concentrates are the treatment of choice for hemophilia B.

#### Dose/administration:

1. In absence of an inhibitor, every unit of FIX per kilogram of body weight infused iv will raise the plasma FIX level approximately 1 IU dL<sup>-1</sup>
- 2.The half-life is around 18–24 h.
3. The patient's FIX level should be estimated around 15 min after mixture to confirm calculated doses. (24)
4. Recombinant FIX (rFIX) has a lower recovery than plasma-derived products, with the end goal that each unit of FIX per kg body weight infused will increase the FIX activity by around 0.8 IU dL<sup>-1</sup> in adults and 0.7 IU dL<sup>-1</sup> in kids under 15 years old. The purpose behind the lower recovery of rFIX isn't totally clear. (25).
5. To figure out the dose, multiply the patient's weight in kilograms by the factor level desired.

6. FIX concentrates should be given by slow IV infusion at a rate not to exceed a volume of 100 units for every min in youngsters, or as suggested in the product information leaflet. (23)

### **B-Other supportive measures**

•**Desmopressin:** Desmopressin (1-deamino-8-D-arginine vasopressin, also known as DDAVP) is a synthetic analog of vasopressin that boosts plasma levels of FVIII and VWF

•**Tranexamic acid:**an antifibrinolytic agent that competitively inhibits the activation of plasminogen to plasmin. It promotes clot stability and is useful as adjunctive therapy in hemophilia and some other bleeding disorders

•**Epsilon aminocaproic acid:**is similar to tranexamic acid, but is less widely used as it has a shorter plasma half-life, is less potent, and is more toxic(26).

### **Von willebrand disease**

Von Willebrand disease (VWD) is the most common inherited bleeding disorder affecting 1.3% of the population, its autosomal inherited disease caused by a quantitative (decreased amount) or qualitative (impaired function) deficiency in von Willebrand factor. (vWF), combination of which result in the different vWD subtypes. (10)

#### **Classification of Von Willebrand Disease**

##### **Type and Description:**

Type 1: Partial quantitative VWF deficiency

Type 2: Qualitative VWF deficiency

- ❖ Type 2A: Caused by mutations that decrease the proportion of large functional VWF multimers, leading to decreased VWF-dependent platelet adhesion
- ❖ Type 2B: Caused by mutations that pathologically increase platelet-VWF binding, leading to the depletion of large, functional VWF multimers; circulating platelets also are coated with mutant VWF, which may prevent the platelets from adhering at sites of injury
- ❖ Type 2M: Caused by mutations that decrease VWF dependent platelet adhesion, but do not reduce the large VWF multimers; distinction between 2A and 2M disease requires VWF multimer gel electrophoresis.
- ❖ Type 2N: Caused by VWF mutations that impair binding to factor VIII, lowering factor VIII levels; often masquerades as an autosomal recessive form of hemophilia A; distinction from hemophilia A may require assays of factor VIII–VWF binding.

### **A-Screening tests**

- **Complete blood count (CBC)** may be normal, but could also show a microcytic anemia (if the individual is iron deficient) or a low platelet count (thrombocytopenia), specifically in type 2B VWD.
- **Activated partial thromboplastin time (aPTT)** is often normal, but may be prolonged when the factor VIII (FVIII:C) level is reduced to below 30-40 IU/dL, as can be seen in severe type 1 VWD, type 2N VWD, or type 3 VWD. The normal range for FVIII:C clotting activity is approximately 50-150 IU/dL.
- **Prothrombin time** is normal in VWD.

(27)

### **B-The standard diagnostic tests include:(28)**

- Measurement of total vWF protein (vWF antigen)

- Coagulation factor VIII levels (FVIII:C level)
- Ristocetin cofactor activity assay (vWF:RCo)

#### **C-Specialized tests to identify vWF subtype:**

- ❖ vWF multimers analysis
- ❖ Ristocetin-induced platelet aggregation (RIPA): which determine the ability of vWF to bind platelets.
- ❖ Binding of FVIII by vwf (Vwf:FVIII B)
- ❖ Collagen binding assay (VWF: CB)

Various physiological and pathological events, including pregnancy, stress and bleeding, can temporarily normalize vWF levels in patients with the condition and should be taken into account when testing for vWD. The exclusion of vWD, depending on the results of laboratory tests, is therefore only made once three normal tests separated in time are obtained. Levels of vWF vary among different ethnic groups and blood types.(29).

#### **A simplified practical approach to the diagnosis of von Willebrand disease:**

1. Diagnosis of VWD should be considered within the context of an appropriate personal and/or familial bleeding history. The use of a standardized questionnaire for history collection is advisable to appreciate the severity of the bleeding tendency
2. Other common hemostatic defects should be excluded by performing a platelet count, APTT, PT and PFA-100 (or bleeding time).
3. If personal and/or familial bleeding history is significant, VWF:RCo assay should be carried out. If not possible, VWF:Ag assay or VWF:CB assay should be performed. VWF:Ag < 3 U/dL suggests type 3 VWD. VWF:Ag and VWF:RCo and FVIII:C should be measured on the same sample to assess the presence of a reduced VWF:RCo/VWF:Ag ratio (a ratio < 0.6 suggest type 2 VWD) or FVIII:C/VWF:Ag (a ratio < 0.6 suggests type 2N VWD, to be confirmed by binding study of FVIII to patient's VWF).

#### **1.6 Treatment:**

Treatment of vWD depends on normalizing vWF and factor VIII levels. Either in cases of bleeding or before an arranged surgical intervention.

#### **A-DESMOPRESSIN**

Desmopressin, an analogue of human antidiuretic hormone (ADH), releases vWF and factor VIII from endothelial cells into the circulation.

- For most patients with type 1 VWD, desmopressin (DDAVP) is the choice of treatment. Type 1 individuals generally respond well and have a sustained normalization of VWF levels after desmopressin infusion. (6)

#### **B-FACTOR REPLACEMENT THERAPY**

- ❖ vWF concentrates are used for the treatment of active bleeding or prophylaxis of bleeding with invasive procedures. There is currently no recommendation for any vWF product for routine prophylaxis to prevent recurrent, spontaneous or incidental hemorrhage. (30)
- ❖ Several plasma-derived VWF concentrates with or without FVIII are available, which may differ between various countries.
- ❖ FVIII/VWF concentrates are still most widely used and have the advantage that infusion of the concentrate leads to an immediate rise of both VWF and FVIII.

- ❖ Concentrates only containing VWF can also be used, but in emergency situations, FVIII concentrate should also be given to increase FVIII levels to a therapeutic level.
- ❖ In elective situations, VWF concentrate can be given the day before the intervention, because endogenous FVIII levels rise to 60 IU/dL after 6 hours.

(31)

- ❖ The advantage of the pure VWF concentrates is that they do not lead to strongly increased FVIII levels after several days of treatment, as this may lead to a higher risk of venous thrombosis. (26)

### C-Antifibrinolytics and general measures

- General measures include antifibrinolytic therapy, e.g., tranexamic acid, the combined oral contraceptive pill, avoidance of antiplatelet agents (such as aspirin) and treatment of resultant anaemia. (32)

### D- Novel therapy

Recombinant VWF has become available in the USA for treatment of bleeding episodes in patients with severe VWD. However, this is not yet available in many other countries. (33).

## 2. Inherited platelet disorders

Platelet disorders are a large group of diseases with variable bleeding diatheses ranging from mild to severe. They can be characterized quantitatively (i.e. thrombocytopenia) or qualitatively (i.e. function disorders) and can be either inherited or acquired. The majority of individuals with inherited platelet disorders (IPDs) have a platelet count within the normal range of  $150\text{--}400 \times 10^9/\text{L}$ . (34)

Inherited platelet disorders (IPDs) are considered to be rare with a frequency of 1: 10 000 but are likely to be under-recognized due to the difficulty of diagnosis, particularly in milder cases. (34).

### 2.1 Classification

Platelet disorders can be classified according to disorders of platelet function. They can be classified as hereditary macro-thrombocytopenias / micro-thrombocytopenia, and disorders of platelet signaling defects, platelet granules, platelet membrane, and defective platelet coagulant function. (35)

### Classification of inherited disorders of platelet function. Modified from (36)

A. Defects in platelet-vessel wall interaction (disorders of adhesion)

- von Willebrand disease (deficiency or defect in plasma vWF)
- b. Bernard-Soulier syndrome (deficiency or defect in GPIb)

B. Defects in platelet-platelet interaction (disorders of aggregation)

- Congenital afibrinogenemia (deficiency of plasma fibrinogen)
- Glanzmann thrombasthenia (deficiency or defect in GPIIb-IIIa)

C. Disorders of platelet secretion and abnormalities of granules

- Storage pool deficiency
- Quebec platelet disorder

D. Disorders of platelet secretion and signal transduction (primary secretion defects)

- Defects in platelet-agonist interaction (receptor defects) Receptor defects: thromboxane A<sub>2</sub>, collagen, ADP, epinephrine
  - Defects in G-protein activation G $\alpha$ q deficiency, G $\alpha$ s abnormalities or G $\alpha$ i1 deficiency
  - Defects in phosphatidylinositol metabolism PhospholipaseC-2 deficiency
  - Defects in calcium mobilization
  - Defects in protein phosphorylation (pleckstrin) PKC- $\gamma$ deficiency
  - Abnormalities in arachidonic acid pathways and thromboxaneA<sub>2</sub> synthesis, Impaired liberation of arachidonic acid, Cyclooxygenase deficiency or Thromboxane synthase deficiency
- E. Defects in cytoskeletal regulation
- Wiskott-Aldrich syndrome
- F. Disorders of platelet coagulant-protein interaction (membrane phospholipid defects).

## 2.2 Diagnosis

Careful medical, drug and family bleeding history should be taken, and a physical examination should be performed before requesting laboratory investigations for platelet disorders. (37)

**Table (3):** Screening and diagnostic tests for platelet functions (37)

<p><b>Screening tests</b></p> <ul style="list-style-type: none"> <li>Full blood count and smear review</li> <li>Bleeding time</li> <li>Platelet function analyser</li> </ul> <p><b>Diagnostic tests</b></p> <ul style="list-style-type: none"> <li>Platelet aggregation</li> <li>Flow cytometry</li> <li>Platelet secretion testing</li> <li>Electron microscopy</li> </ul>
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## 2.3 Management

According to the United Kingdom Hemophilia Centre Doctors' Organization UKHCDO guideline for patients with platelet disorders including GT and BSS and the British Society of Hematology (BSH), platelet transfusion guideline, the lines of treatment of inherited platelet disorders include the following:

### Antifibrinolytics

The cornerstone of management is supportive care. Antifibrinolytics, e.g., tranexamic acid, are an important adjuvant. Specific management depends on the particular type of disorder, as well as the severity of the bleeding. (38)

### Desmopressin (DDAVP)

Desmopressin has been shown to be effective in SPDs and mild platelet function disorders, and may be of benefit in Bernard-Soulier syndrome. However, there is no evidence that DDAVP is at all effective in GT and there are only equivocal results in BSS. (35)

**Platelet transfusion**

Platelet transfusions are considered the first line treatment for patients undergoing major surgery or with severe bleeding or other bleeding episodes when anti-fibrinolytics and local measures have failed.

(39)

**Gene therapy**

Animal studies into the possibility of gene therapy for GT are already being carried out and BSS may also be a candidate disorder for gene therapy in the future. (35)

**Recombinant human activated factor VII**

In 2004, rVIIa was approved for use in patients with GT for the treatment of bleeding episodes or prior to invasive procedures. (25)

**Stem cell transplantation**

Allogeneic bone marrow transplantation is a curative option for GT. and has been reported in one series of 19 patients with GT. The median age of transplant was 5 years. (40).

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