WHAT ARE INHERITED PLATELET FUNCTION DISORDERS?

WORLD FEDERATION OF
HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA
Treatment for All

Published by the **World Federation of Hemophilia (WFH)**

This publication was developed by the WFH and reviewed by Dr. Amy Shapiro and the members of WFH's von Willebrand disease and rare bleeding disorders committee: Dr. Paula Bolton-Maggs (chair), Clare Cecchini, Dr. Philippe de Moerloose, Dr. Augusto Federici, Dr. Rezan Kadir, Dr. Roshni Kulkarni, Anne-Marie Nazzaro, Dr. Flora Peyvandi, and Dr. Alok Srivastava.

This publication is accessible from the WFH website at www.wfh.org. Additional print copies can be ordered from:

World Federation of Hemophilia
1425 René Lévesque Boulevard West, Suite 1010
Montréal, Québec H3G 1T7
CANADA
Tel.: (514) 875-7944
Fax: (514) 875-8916
E-mail: wfh@wfh.org

Contents

Introduction

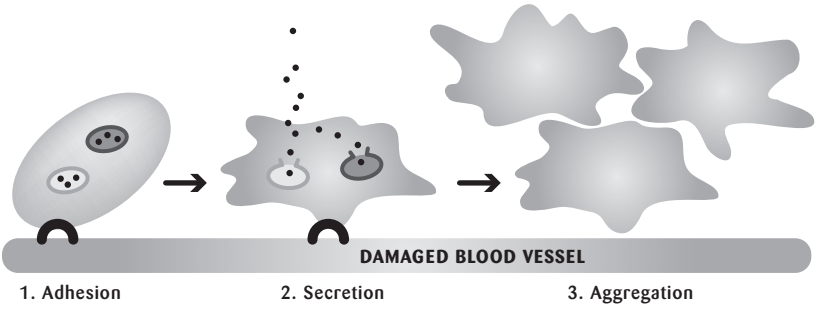
WHAT ARE PLATELETS?

Platelets are small cells that circulate in the blood. They play an important role in the formation of blood clots and the repair of damaged blood vessels.

When a blood vessel is injured, platelets begin the process to stop the bleeding by forming what is called a platelet plug. This happens in three stages:

1. **ADHESION:** platelets stick to the damaged area and spread along the surface of the blood vessel to stop the bleeding.
2. **SECRETION:** as they do this, the platelets become "activated" and chemical signals are released from small sacks inside the platelets called granules.
3. **AGGREGATION:** these chemicals attract other platelets to the site of injury and make them clump together to form the platelet plug.

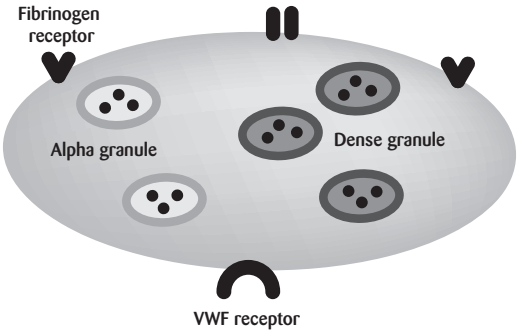
FIGURE 1. The three stages of platelet activation



Once the platelet plug is in place, other proteins called clotting factors are recruited to the site of injury. These clotting factors work together on the surface of the platelets and strengthen the platelet plug by forming a mesh called a fibrin clot.

Platelets have several important components, such as receptors and granules, which are important to the clotting process.

FIGURE 2. A platelet with surface receptors and granules



RECEPTORS

Receptors are proteins on the surface of the platelets that help the platelet interact with, and respond to, other blood cells or substances.

GRANULES

Granules are small packets inside the platelets in which proteins and other chemicals important to their function are stored. The contents of the granules are released during the secretion phase of platelet activation, acting as chemical signals to recruit more platelets and other cells to the site of injury to stop the bleeding.

There are two types of granules: alpha granules and dense granules. Each type contains different chemicals that work in different ways to stop bleeding.

WHAT ARE PLATELET FUNCTION DISORDERS?

Platelet function disorders are conditions in which the platelets do not work the way they should. Since the platelet plug does not form properly, bleeding can continue for longer than normal and people with platelet function disorders have a tendency to bruise or bleed. Platelet function disorders can be caused by a problem with the platelets themselves, with one of the receptors, or with the granules.

There are inherited (i.e. passed down from parent to child) and acquired platelet function disorders. This booklet addresses inherited platelet function disorders.

Bernard-Soulier Syndrome

Bernard-Soulier syndrome is an inherited platelet function disorder caused by an abnormality in the receptor for von Willebrand factor (VWF; see Figure 2). This receptor is also called the GpIb/V/IX receptor. Receptors are proteins on the surface of the platelets that help them interact with, and respond to, other blood cells or substances. Since the VWF receptor is absent or does not work properly, the platelets do not stick to the injured blood vessel wall the way they should and it is difficult for a normal blood clot to form.

Bernard-Soulier syndrome is an autosomal recessive disorder, meaning that both parents carry a genetic change (even though they themselves do not usually have the disorder), and pass this changed gene on to their child. Like many autosomal recessive disorders, it may be more frequent in areas of the world where marriage between relatives is more common. Bernard-Soulier syndrome affects both males and females.

SYMPTOMS

The symptoms of Bernard-Soulier syndrome vary from one individual to another. Signs of the disorder are usually first noticed during childhood.

People with Bernard-Soulier syndrome may experience:

- Easy bruising
- Nose bleeds (epistaxis)
- Bleeding from gums
- Heavy or prolonged menstrual bleeding (menorrhagia), bleeding during ovulation, or bleeding during or after childbirth
- Abnormal bleeding during or after surgery, circumcision, or dental work

- Rarely, vomiting blood or passing blood in stool due to bleeding from the intestines (gastrointestinal hemorrhage)

Bernard-Soulier syndrome may cause more problems for women than men because of the risk of bleeding associated with menstruation and childbirth.

DIAGNOSIS

No single test can diagnose all platelet function disorders. The diagnosis of Bernard-Soulier syndrome requires a careful medical history and a series of laboratory tests that should be performed by a specialist at a bleeding disorder treatment centre.

In people with Bernard-Soulier syndrome:

- The bleeding time (a standardized test that measures the time it takes for a small cut to stop bleeding) is longer than normal. This test may be difficult to perform in young children and is not commonly used where more specific tests are available.
- The closure time (the time it takes for the platelet plug to form in a sample of blood) is longer than normal. This screening test is performed using a special instrument called a platelet function analyser (PFA-100®).
- Platelets appear larger than normal under a microscope.
- There are usually fewer platelets than normal.
- Platelets do not clump together normally in a laboratory test called ristocetin-induced platelet aggregation.
- Specific blood tests reveal a reduced amount or absence of the VWF receptor (Gp1b/V/IX) on the platelet surface. This is the most conclusive diagnostic test but is not available everywhere.

Note: Some tests are not available in all centres.

In children, Bernard-Soulier syndrome is sometimes misdiagnosed as immune thrombocytopenic purpura (ITP), an acquired platelet disorder in which there are fewer platelets than normal.

TREATMENT OPTIONS

Most people with Bernard-Soulier syndrome need treatment during surgical procedures (including dental work) or after injury or accidents. Some people will need treatment for severe nose bleeds. When needed, Bernard-Soulier syndrome may be treated with:

- Antifibrinolytic drugs
- Recombinant factor VIIa
- Desmopressin
- Fibrin sealants
- Hormonal suppressive therapy (birth control medications) and/or levonorgestrel-releasing intrauterine device/system (Mirena IUS) to control excessive menstrual bleeding
- Iron replacement as needed to treat anemia caused by excessive or prolonged bleeding
- Platelet transfusions for severe bleeding

See **TREATMENT PRODUCTS** on page 14 for more details.

People with Bernard-Soulier syndrome ***should not take*** Aspirin®, nonsteroidal anti-inflammatory drugs (such as ibuprofen and naproxen), and blood thinners, as these can worsen bleeding symptoms.

For more information about medicines and herbal remedies that should not be used by people with bleeding disorders, visit the WFH website at **www.wfh.org**.

Glanzmann Thrombasthenia

Glanzmann thrombasthenia is an inherited platelet function disorder caused by an abnormality in the receptor for fibrinogen (also called the GpIIb/IIIa receptor; see Figure 2). Receptors are proteins on the surface of the platelets that help the platelet interact with, and respond to, other blood cells or substances. Since the fibrinogen receptor is absent or does not work properly, the platelets do not stick to each other at the site of injury and it is difficult for the normal blood clot to form.

Glanzmann thrombasthenia is an autosomal recessive disorder, meaning that both parents carry a genetic change (even though they themselves do not usually have the disorder), and pass this changed gene on to their child. Like many autosomal recessive disorders, it may be more frequent in areas of the world where marriage between relatives is more common. Glanzmann thrombasthenia affects both males and females.

SYMPTOMS

Symptoms of Glanzmann thrombasthenia vary from one individual to another and range from very mild to potentially life-threatening bleeding. Signs of the disorder are usually first noticed during childhood.

People with Glanzmann thrombasthenia may experience:

- Easy bruising
- Nose bleeds (epistaxis)
- Bleeding from gums
- Heavy or prolonged menstrual bleeding (menorrhagia), bleeding during ovulation, or bleeding during or after childbirth
- Abnormal bleeding during or after surgery, circumcision, or dental work

- Rarely, vomiting blood or passing blood in stool due to bleeding from the intestines (gastrointestinal hemorrhage) or genito-urinary tract (kidneys, ureters, bladder, and urethra)

Glanzmann thrombasthenia may cause more problems for women than men because of the risk of bleeding associated with menstruation and childbirth.

DIAGNOSIS

No single test can diagnose all platelet function disorders. The diagnosis of Glanzmann thrombasthenia requires a careful medical history and a series of laboratory tests that should be performed by a specialist at a bleeding disorder treatment centre.

In people with Glanzmann thrombasthenia:

- The bleeding time (a standardized test that measures the time it takes for a small cut to stop bleeding) is longer than normal. This test may be difficult to perform in young children and is not commonly used where more specific tests are available.
- The closure time (the time it takes for the platelet plug to form in a sample of blood) is longer than normal. This screening test is performed using a special instrument called a platelet function analyser (PFA-100®).
- Platelets do not clump together the way they should with several different chemicals in a series of laboratory tests called platelet aggregation studies.
- Specific blood tests reveal a reduced amount or absence of the fibrinogen receptor (GpIIb/IIIa) on the platelet surface. This is the most conclusive diagnostic test but is not available everywhere.

Note: Some tests are not available in all centres.

TREATMENT OPTIONS

Most people with Glanzmann thrombasthenia need treatment during surgical procedures (including dental work) or after injury or accidents. Some people will need treatment for severe nose bleeds. When needed, Glanzmann thrombasthenia may be treated with:

- Antifibrinolytic drugs
- Recombinant factor VIIa
- Fibrin sealants
- Hormonal suppressive therapy (birth control medications) and/or levonorgestrel-releasing intrauterine device/ system (Mirena IUS) to control excessive menstrual bleeding
- Iron replacement as needed to treat anemia caused by excessive or prolonged bleeding
- Platelet transfusions for severe bleeding

See **TREATMENT PRODUCTS** on page 14 for more details.

People with Glanzmann thrombasthenia ***should not take*** Aspirin®, nonsteroidal anti-inflammatory drugs (such as ibuprofen and naproxen), and blood thinners, as these can worsen bleeding symptoms.

For more information about medicines and herbal remedies that should not be used by people with bleeding disorders, visit the WFH website at **www.wfh.org**.

Storage Pool Disorders

Storage pool disorders are a group of inherited disorders caused by abnormalities with platelet granules. Granules are small packets inside the platelets in which proteins and other chemicals important to their function are stored. The contents of the granules are released during the secretion phase of platelet activation (see Figure 1), acting as chemical signals to recruit more platelets and other cells to the site of injury to stop the bleeding. There are two types of granules: alpha granules and dense granules.

Some storage pool deficiencies are caused by a lack of granules or their contents, but the most common ones are caused by a failure of the platelets to release their contents into the bloodstream.

The way storage pool deficiencies are inherited (i.e. passed down from parent to child) is less consistent than for other types of platelet disorders and varies from one individual to the next.

1. **RELEASE DEFECTS** are a diverse group of disorders caused by an abnormality in the secretion mechanism. Even though the granules are present within the platelets, their contents are not emptied into the bloodstream properly.
2. **DELTA STORAGE POOL DEFICIENCY** is a platelet function disorder caused by a lack of dense granules and the chemicals normally stored inside them. Without these chemicals, platelets are not activated properly and the injured blood vessel does not constrict to help stop bleeding. This type of bleeding problem can be seen in other inherited conditions such as Hermansky-Pudlak and Chediak-Higashi syndromes.

3. **GREY PLATELET SYNDROME** is a very rare platelet function disorder caused by a lack of alpha granules and the chemicals normally stored inside them. Without these chemicals, platelets cannot stick to the blood vessel wall, clump together, or repair the injured blood vessel the way they should.

SYMPTOMS

Symptoms of storage pool deficiencies vary from one individual to the next and are usually mild to moderate.

People with storage pool deficiencies may experience:

- Easy bruising
- Nose bleeds (epistaxis)
- Bleeding from gums
- Heavy or prolonged menstrual bleeding (menorrhagia), bleeding during ovulation, or bleeding during or after childbirth
- Abnormal bleeding during or after surgery, circumcision, or dental work

DIAGNOSIS

No single test can diagnose all platelet function disorders. The diagnosis of storage pool disorders requires a careful medical history and a series of laboratory tests that should be performed by a specialist at a bleeding disorder treatment centre.

In people with storage pool deficiencies:

- Platelets do not clump together the way they should in a series of laboratory tests called platelet aggregation studies. Platelet aggregation tests are the most useful way to diagnose these disorders.
- Granules may not be visible when platelets are looked at with a specific microscope called an electron microscope.

- The bleeding time (a standardized test that measures the time it takes for a small cut to stop bleeding) is longer than normal. This test may be difficult to perform in young children and is not commonly used where more specific tests are available.

TREATMENT OPTIONS

Most people with storage pool deficiencies need treatment during surgical procedures (including dental work) or after injury or accidents. When needed, storage pool deficiencies may be treated with:

- Antifibrinolytic drugs
- Desmopressin (may not be useful in alpha granule deficiency)
- Platelet transfusions
- Hormonal suppressive therapy (birth control medications) and/or levonorgestrel-releasing intrauterine device/system (Mirena IUS) to control excessive menstrual bleeding
- Iron replacement as needed to treat anemia caused by excessive or prolonged bleeding
- Fibrin sealants

See **TREATMENT PRODUCTS** on page 14 for more details.

People with storage pool deficiencies ***should not take*** Aspirin®, nonsteroidal anti-inflammatory drugs (such as ibuprofen and naproxen), and blood thinners, as these can worsen bleeding symptoms, unless prescribed for a specific reason by a physician familiar with their disorder.

For more information about medicines and herbal remedies that should not be used by people with bleeding disorders, visit the WFH website at **www.wfh.org**.

Treatment Products

ANTIFIBRINOLYTIC DRUGS

The antifibrinolytic drugs tranexamic acid and aminocaproic acid are used to prevent the breakdown of a clot in certain parts of the body, such as the mouth, bladder, and uterus. These medications are very useful in many situations, such as during dental work, but are not appropriate for major internal bleeding or surgery. Antifibrinolytic drugs are also used to help control excessive menstrual bleeding. They can be applied topically in areas such as the mouth, and can also be given orally or by injection.

RECOMBINANT FACTOR VIIa

Recombinant factor VIIa may be effective to treat bleeding in some patients with Glanzmann thrombasthenia or Bernard-Soulier syndrome and to prevent bleeding prior to surgery. It is particularly useful as an alternative to platelet transfusion to prevent patients from developing antibodies to platelets, or to continue treatment in cases where antibodies have already developed (see 'Platelet Transfusions,' below). Recombinant factor VIIa is made in a laboratory and not from human plasma.

DESMOPRESSIN

Desmopressin is a synthetic hormone that may help control bleeding in an emergency or during surgery. It can be injected intravenously, administered under the skin (subcutaneously), or given as a nasal spray. Desmopressin does not work for every platelet disorder or individual.

FIBRIN SEALANTS

Fibrin sealants (also called fibrin glue) are available in some countries. They can be used to treat external wounds and during dental work such as tooth extraction. Fibrin sealants must be applied directly to the bleeding site.

HORMONAL SUPPRESSIVE THERAPY

Hormonal suppressive therapy (birth control medications) and the levonorgestrel-releasing intrauterine device/system (Mirena IUS) can be used by women to help control excessive menstrual bleeding.

IRON REPLACEMENT

Iron replacements can be taken as needed to treat anemia, or iron deficiency without anemia, caused by excessive or prolonged bleeding.

PLATELET TRANSFUSIONS

Platelet transfusions may be necessary to treat severe or uncontrolled bleeding or to prevent bleeding during or after surgery. Although platelet transfusions may be very effective, they are avoided whenever possible because some people may develop antibodies to the platelets, which makes future transfusions less effective.

All these treatments may have side effects. People affected with inherited platelet disorders should talk to their physician about possible side effects before taking any medication.

Tips for Living with an Inherited Platelet Function Disorder

COPING WITH THE DIAGNOSIS

Learning that you or a family member has an inherited platelet function disorder can be upsetting and you may experience a range of different emotions. For some people, it may cause fear and anxiety while for others, being able to put a name to symptoms they have been experiencing can be a tremendous relief. Parents may feel guilty to learn their child has inherited a genetic disorder. All these feelings are normal, and are likely to change over time as you learn more about the condition and the impact it will have on you or your family member's life.

Talking to others—friends, parents, healthcare professionals, and other people with inherited platelet function disorders—can be comforting. Learning as much as you can about the disorder will help you feel more confident and relieve your fears. Get in touch with your local patient organization or bleeding disorder treatment centre to ask questions and discuss options. Patient groups and treatment centres can be located through the WFH website at www.wfh.org.

HEALTHY LIVING

People with inherited platelet function disorders should be followed by a treatment centre that specializes in the diagnosis and treatment of bleeding disorders, as they are most likely to offer the best care and information.

A healthy diet and regular exercise keep the body healthy and strong. Exercise can also help reduce stress, anxiety and depression, and reduce the frequency and severity of bleeding events.

Some food or food additives, such as alcohol, fish oils, Chinese black tree fungus, aijoene (a component of garlic), and several herbal remedies may affect platelet function and make symptoms worse.

DENTAL CARE

Good oral hygiene is essential to prevent tooth decay and gum disease. For people with inherited platelet function disorders, maintaining good dental health is very important to reduce the need for dental surgery, which can be complicated by excessive or prolonged bleeding. People with platelet function disorders should:

- Brush teeth at least twice a day
- Floss regularly
- Use a toothpaste containing fluoride (fluoride supplements may be prescribed if appropriate)
- Get regular checkups

Invasive procedures, such as scaling, extractions, or root canals, may cause bleeding in people with platelet function disorders. The dentist should consult with the hemophilia/bleeding disorder treatment centre to determine the individual potential risk and develop an appropriate plan to prevent or treat bleeding for any procedure. Medications may be needed beforehand to prevent bleeding and ensure an uncomplicated procedure and recovery.

VACCINATIONS

People with platelet function disorders should be vaccinated. Vaccines should be given subcutaneously (under the skin) rather than directly into the muscle to avoid the associated risk of bleeding.

MEDICATIONS TO AVOID

Check all herbal remedies and medications that you take or are prescribed with your doctor. Some over-the-counter medications, such as acetylsalicylic acid (ASA or Aspirin®) or nonsteroidal anti-inflammatory drugs (such as ibuprofen and naproxen), should be avoided as they interfere with platelet function. Many other drugs can also affect platelet function, including blood thinners, some antibiotics, heart drugs, antidepressants, anesthetics, and antihistamines. Medications that interfere with platelet function should not be used without specific medical advice from a physician familiar with your platelet disorder. For more information about medications that should not be taken, visit the WFH website at www.wfh.org.

HAVE MEDICAL INFORMATION ON HAND AT ALL TIMES

People with bleeding disorders should always carry information about their disorder, the treatment required, and the name and telephone number of their physician or treatment centre. In emergencies, a medical bracelet or other identification, such as the WFH International Medical Card, notifies healthcare personnel of your inherited platelet function disorder.

Before traveling, find the address and telephone number of the bleeding disorder treatment centres at your destination(s) and take this information with you in case you need care. Treatment centres can be located through *Passport: Global Treatment Centre Directory*, available on the WFH website (www.wfh.org).

SPECIAL ISSUES FOR GIRLS AND WOMEN

Women with inherited platelet function disorders may experience more symptoms than men because of the risk of bleeding associated with menstruation and childbirth. Girls may experience heavy bleeding when they begin to menstruate.

Women with inherited platelet function disorders may have heavier and/or longer menstrual flow that may lead to iron deficiency (low levels of iron, which results in weakness and fatigue) and/or anemia (low levels of red blood cells).

Women with inherited platelet function disorders should receive genetic counseling about the risks of having an affected child well in advance of a planned pregnancy and should be seen by an obstetrician as soon as they suspect they are pregnant. The obstetrician should work closely with the staff of the bleeding disorder treatment centre to provide the best care during pregnancy and childbirth, and to minimize potential complications for both the mother and newborn.

The main risk related to pregnancy and delivery is postpartum hemorrhage. Bleeding disorders are associated with an increased risk of bleeding, both immediately after and for several weeks following delivery. Women with platelet function disorders should therefore work with their doctors (both the hematologist or other bleeding disorder specialist and the obstetrician) to develop an individual delivery plan. This plan should address all stages of labour, including delivery of the placenta, to reduce the risk and severity of bleeding. Treatment is different for each woman and depends on her personal and family history of bleeding symptoms, the diagnosis and severity of the inherited platelet function disorder, and the mode of delivery (vaginal birth versus cesarean section). Women with platelet function disorders should be advised to consult a physician immediately if post-partum bleeding is excessive.

In some circumstances, infants born to women with inherited platelet function disorders may also be at risk of inheriting the disorder and experience bleeding. Difficult and prolonged labour, and deliveries that require instrumentation such as

the use of forceps or vacuum extraction, should be avoided. Some mothers with Bernard-Soulier syndrome or Glanzmann thrombasthenia can develop antibodies to platelets, particularly if they have received platelet transfusions in the past. These antibodies may affect a baby in the womb and at delivery, causing a temporary low platelet level. In women at risk, doctors will usually check for this during pregnancy so as to be prepared at birth.

For more information and a list of resources in several languages, visit the Inherited Platelet Disorders section of the WFH website at **www.wfh.org**.

World Federation of Hemophilia

1425 René Lévesque Boulevard West, Suite 1010
Montréal, Québec H3G 1T7
CANADA
Tel.: (514) 875-7944
Fax: (514) 875-8916
E-mail: wfh@wfh.org
Internet: www.wfh.org

WORLD FEDERATION OF
HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA
Treatment for All