

FACTOR I DEFICIENCY
FIBRINOGEN

AN INHERITED
BLEEDING DISORDER

AN INFORMATION
BOOKLET



Canadian Hemophilia Society
Help Stop the Bleeding



Canadian Association of
Nurses in Hemophilia Care
Association Canadienne des
Infirmières et Infirmiers en Hémophilie

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This brochure provides general information only. The Canadian Hemophilia Society does NOT practice medicine and does not suggest specific treatments. In all cases, we suggest that you speak with a doctor before you begin any treatment.

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Introduction

Factor I (or fibrinogen) deficiency is a very rare inherited disorder with complications that vary with the severity of the disorder. It is not well known, even among health professionals. People affected by this disorder and those close to them have very little written information about it. This booklet therefore seeks to provide information for people trying to cope with this health problem. It explains the causes of the disorder and currently available treatments.

Discovery

Factor I deficiency was described for the first time in 1920 by Fritz Rabe and Eugene Salomon. These two German physicians are credited with discovering the disorder. They studied the case of a 9-year-old boy who presented unexplained bleeding problems from birth. Blood tests finally demonstrated the absence of fibrinogen in the child's blood. His parents were first cousins, but they showed no bleeding problems. The two researchers established that it was an inherited disorder often found in subjects whose parents were blood relatives. Since then, knowledge about the condition has advanced considerably.

What is Fibrinogen?

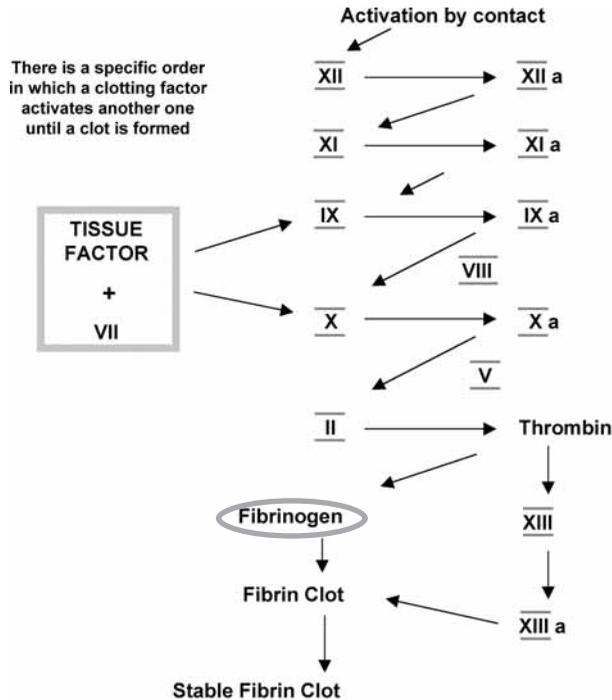
Fibrinogen, also called Factor I, is a blood plasma protein produced by the liver that plays an important role in blood coagulation. Blood coagulation is a process in which several components of the blood form a clot. When blood escapes from a rupture in a blood vessel, coagulation is triggered. Several proteins, called coagulation factors, go into action to produce thrombin. The thrombin then converts fibrinogen to fibrin. Fibrin produced from fibrinogen is the main protein in a blood clot. It surrounds the cells in the blood and plasma and helps form the clot. The resulting clot, which is stabilized by Factor XIII, remains intact from 10 to 14 days, the time required for healing to take place.

When there is a problem with fibrinogen, i.e., either it is missing or it does not function properly, the clot has difficulty forming. This can result in hemorrhaging or thrombosis.

The normal volume of fibrinogen in the blood is from 2 to 4 g/l (grams/litre).

The amount of fibrinogen in blood can be measured from a blood sample.

The following diagram was devised by a Toronto laboratory technician. It shows the stages in clot formation in a way that makes it easier to understand the theoretical notions explained above.



Patricia Blake, Senior Coagulation Technologist, St. Michael's Hospital, Toronto, Ontario, 1994.

Types of Fibrinogen Deficiency

There are three types of deficiency:

Afibrinogenemia: (absence of fibrinogen)

In this type of factor I deficiency, there is a **complete absence** of fibrinogen. The fibrinogen level is <0.2 g/L of plasma. About 5 people out of 10 million are affected by it. Of the three types, this one causes the most serious bleeding.

Hypofibrinogenemia: (lower than normal level)

In this anomaly, fibrinogen is present, but at a **lower level** than normal, between 0.2 g/L and 0.8 g/L. This anomaly is less frequent than afibrinogenemia. Bleeding problems may be mild, moderate or severe.

Dysfibrinogenemia: (malfunctioning)

In dysfibrinogenemia, the fibrinogen level is normal, which means between 2 and 4 g/l, but the fibrinogen does not **function properly**. About 1 person in 1 million is affected by this condition. More than 100 different types of dysfibrinogenemia have been reported. Those affected rarely suffer from hemorrhaging problems. They may even present the opposite condition: thrombosis (blood coagulates in the blood stream).



Transmission of Fibrinogen Deficiency

Fibrinogen deficiency is a very rare inherited bleeding disorder. It is transmitted from parent to child at conception. The disorder is caused by an abnormal gene. It affects both men and women, as well as people of all races and ethnic origins.

Every cell of the body contains *chromosomes*. A chromosome is a long chain of a substance called *DNA*. DNA is organized in 30,000 units: these are called genes. The genes determine physical characteristics, such as eye colour. In the case of fibrinogen deficiency, one of the genes involved is defective.

The defective gene in fibrinogen deficiency is located on a chromosome that is not responsible for the child's sex (autosomal). As a result, both girls and boys can be affected equally.

Afibrinogenemia (absence of fibrinogen)

This is a **recessive** disorder, which means that both parents must be carriers. In order for a person to inherit fibrinogen deficiency, he must receive two defective genes, one from the mother and the other from the father. A carrier is a person who has only one of the two defective genes, but is not affected by the disorder: the second gene enables just enough

fibrinogen to be made for good coagulation. The fibrinogen level will be lower than normal, but there will be no symptoms of the disorder.

Hypofibrinogenemia and dysfibrinogenemia

These are inherited disorders that can be either dominant or recessive.

Dominant means that a single parent can transmit the disorder if he or she is a carrier.

Recessive means that both parents must be carriers of the disorder in order to transmit it.

Symptoms

Afibrinogenemia (absence of fibrinogen)

In congenital afibrinogenemia (fibrinogen level <0.2 g/L), bleeding can vary, from slight to severe. Many patients have very long intervals between bleeding episodes. A diagnosis of afibrinogenemia is generally made postnatally, usually because of bleeding from the umbilical cord and/or a hemorrhage following circumcision.

Other types of bleeding have been described:

- bruises
- bleeding from the gums
- epistaxis (nosebleeds)
- gastrointestinal hemorrhage
- genito-urinary hemorrhage
- intra-cranial hemorrhage
- rupture of the spleen and hemorrhage in the spleen

About 20% of those suffering from afibrinogenemia present hemarthroses (bleeding in the joints). Because of this particular feature, the disorder may be confused with hemophilia A or B.

Hypofibrinogenemia (lower than normal level)

Bleeding in hypofibrinogenemia is much like what is seen in afibrinogenemia. It can be more or less serious, depending on fibrinogen levels, which can vary from 0.2 to 0.8 g/L of plasma.

- The higher the fibrinogen level, the less bleeding.
- The lower the fibrinogen level, the more bleeding.

Dysfibrinogenemia (improper functioning)

In dysfibrinogenemia, the quantity of fibrinogen is normal, which means between 2 and 4 g/L. Bleeding can vary depending on how the fibrinogen is functioning. Bleeding may:

- be absent (no symptoms)
- show a tendency toward hemorrhage (as described in afibrinogenemia)
- show a tendency toward thrombosis

Congenital Fibrinogen Deficiency

Normal values: 2 - 4 g/l

COMPARISON CHART

	AFIBRINOGENEMIA	HYPOFIBRINOGENEMIA	DYSFIBRINOGENEMIA
TRANSMISSION	Autosomal recessive (both parents are carriers)	Autosomal dominant* and recessive*** only one parent is a carrier** both parents are carriers	Autosomal dominant* and recessive*** only one parent is a carrier ** both parents are carriers
IMPACT	5 in 10 million	less than afibrinogenemia	1 in 1 million
FIBRINOGEN LEVEL	<0.2 g/l plasma	between 0.2 and 0.8 g/l of plasma	between 2 and 4 g/l of plasma
SYMPTOMS	<ul style="list-style-type: none"> –umbilical cord bleeding –cutaneomucous bleeding –gastrointestinal hemorrhage –intra-cranial bleeding articular bleeding (in 20% of subjects) 	<ul style="list-style-type: none"> –umbilical cord bleeding –cutaneomucous bleeding –gastrointestinal hemorrhage –intra-cranial bleeding (infrequent) –articular bleeding (in 20% of subjects) 	<ul style="list-style-type: none"> –no symptoms –hemorrhage –Thrombosis
TREATMENT	FIBRINOGEN	FIBRINOGEN	FIBRINOGEN OR ANTICOAGULANT

How to Recognize Bleeding

It is strongly recommended that people who suffer from afibrinogenemia or severe hypofibrinogenemia learn to recognize the signs and symptoms of bleeding that could threaten their lives or the integrity of a limb, so they can react adequately and in a reasonable time.

The information below describes the main types of bleeding that may occur in someone with a coagulation disorder.

Bleeding that affects the head, neck, thorax (chest) or abdomen can be life-threatening and may require immediate medical attention. Bear in mind that this kind of bleeding can occur either following an injury or **spontaneously** (without injury).

Head

The brain, which is protected by the skull, controls all bodily functions that are essential to life. Bleeding in the brain is very serious.

Signs and symptoms:

- Headache
- Vision problems
- Nausea and vomiting
- Change of personality
- Somnolence
- Loss of balance***
- Loss of the fine motor skills (clumsiness)***
- Fainting***
- Convulsions***

*** These symptoms appear later in the event of serious injury to the head. If these symptoms appear, consult a physician immediately in order to receive treatment.

Neck

The tissue of the nose, mouth and throat are highly *vascularized*, which means that they contain many veins and arteries. The slightest lesion or infection can cause an accumulation of blood in this tissue. When the tissue swells with blood, it compresses the respiratory tract, making breathing difficult or even blocking it completely.

Signs and symptoms:

- Pain in the neck or throat
- Swelling
- Difficulty swallowing
- Difficulty breathing

Thorax (chest) Infrequent

The rib cage (thorax) contains the lungs and heart, as well as large blood vessels. If bleeding occurs in the lungs, the alveoli, which normally contain air, fill with blood, and breathing becomes difficult.

Signs and symptoms:

- Chest pain
- Difficulty breathing
- Coughing, blood in sputum

Adomen (stomach)

The abdomen contains the stomach, spleen, liver and intestines, as well as other organs. An injury in this area can result in massive hemorrhaging of an organ or major blood vessel. If the hemorrhage is not treated, it can be fatal.

Signs and symptoms:

- Pain in the abdomen or lower back
- Nausea and vomiting
- Blood in the urine
- Blood in the stool or black stool

If one of these symptoms occurs, consult a physician immediately.

There are other kinds of bleeding that are not necessarily life-threatening, but for which treatment is necessary. These are described below.

Soft Tissue Bleeding

The signs and symptoms of bleeding of the soft tissue are as follows:

- Redness in the affected area: Use a tape measure to check the size of the affected area regularly. If you don't have a tape measure, you must check the area every hour to see if the redness is increasing.
- Increase in the size of a bruise: Take a pen and draw a line around the bruise; this way you can see if it is spreading, shrinking or staying the same.
- Pain: Note whether it gets stronger, and if you can pinpoint the source.

Bleeding in the Joints

The signs and symptoms of bleeding in the joints are as follows:

- Pain during normal use of a joint or even at rest, especially if there is no bruise.
- Swelling and heat in the joint, with or without bruising.
- Reduced mobility of the joint.

- Hesitation to move the joint - For example, a child who walks normally may suddenly start limping because of a hemorrhage in the ankle; a right-handed child can only use its left hand to grab objects because of bleeding in the elbow.
- Agitation or crying when a child moves a joint. This behaviour may be caused by pain due to bleeding, especially in infants. Parents must learn to feel and assess joint movement; this is especially important for the knees, ankles and elbows.

Treatments

Many people who have hypofibrinogenemia or a dysfibrinogenemia do not need treatment

To control or prevent bleeding, all that's required is to increase the fibrinogen level in the blood with blood products or substitutes. This kind of treatment is called factor replacement treatment. The aim of the treatment is to increase the fibrinogen level to 1 g/L when there is minor bleeding, and 2 g/L for serious bleeding or for surgery.

Fibrinogen concentrate can be administered by drip:

- at the time of surgery
- to the mother during childbirth or after delivery
- after a trauma
- before dental surgery
- as prophylaxis (prevention) for subjects with afibrinogenemia to prevent bleeding

At the present time, the most frequently used treatment in Canada is **fibrinogen concentrate**. The concentrate is obtained from human plasma and contains fibrinogen only. The concentrate undergoes a viral inactivation process, which eliminates viruses such as HIV and hepatitis A, B and C.

It is impossible to completely eliminate the risk of transmitting infections that are currently unknown.

There are other options that can be considered for treatment:

- plasma
- cryoprecipitate

However, their use is not recommended much nowadays for various reasons, such as:

- slight risk of viral transmission
- possible serious allergic reactions because of the large number of different substances contained in these products in addition to fibrinogen.

Anticoagulants are sometimes used to reduce the risk of thrombosis among patients with dysfibrinogenemia.

Problems Specific to Women

Fibrinogen deficiency affects both men and women. However the impact is greater for women because of menstruation and conception. Amount of bleeding may vary depending on the type of deficiency.

Afibrinogenemia (absence of fibrinogen)

MENSTRUATION

In afibrinogenemia, menstrual bleeding can be very abundant (menorrhagia) or entirely normal. When bleeding is abundant, various treatments, such as oral contraceptives and/or Cyklokapron may be useful. Cyklokapron is an antifibrinolytic agent that helps stabilize the clot and better control bleeding. It is rare to have to use fibrinogen during menstruation.

PREGNANCY

The majority of pregnancies in women presenting afibrinogenemia end in miscarriage between the 5th and 8th week of pregnancy.

To avoid abortion, it is essential to increase the fibrinogen level to at least 1 g/L in the 4th week of pregnancy, and to maintain this level throughout the pregnancy. The fibrinogen level is increased by regular infusions of fibrinogen concentrate.

CHILDBIRTH

Detachment of the placenta is frequent at the start of labour. To prevent placental detachment it is necessary to keep the fibrinogen level between 1.5 g/L and 2 g/L, if possible.

AFTER CHILDBIRTH

Bleeding after childbirth (postpartum) is usually controlled fairly well with a lower dose of fibrinogen.

Hypofibrinogenemia (lower than normal level)

Menstrual problems and problems of pregnancy with hypofibrinogenemia are much like those observed in afibrinogenemia. They can be more or less serious, depending on the level of fibrinogen in blood.

The higher the fibrinogen level, the less abundant the menstrual bleeding and the fewer miscarriages.

The lower the fibrinogen level, the more likely menstrual bleeding will be abundant and the higher the rate of miscarriages. The treatment is the same as for afibrinogenemia.

Dysfibrinogenemia (improper functioning)

Menstrual problems and problems of pregnancy vary depending on the type of dysfibrinogenemia.

Treatment must be tailored to the situation. Many patients may give birth without bleeding, and fibrinogen concentrate is often not necessary.

Prevention

Never take aspirin. Aspirin is a drug that increases the risk of hemorrhage by inhibiting the functioning of platelets.

Prevent dental problems and gingivitis. Visit your dentist every six months. Your Hemophilia Centre can recommend a dentist who is familiar with coagulation problems.

Always contact your Hemophilia Centre if you have to have surgery or a tooth extraction in order to plan adequate preventive treatment.

Always wear a Medic-Alert type bracelet or a chain explaining your coagulation problem.

Wear protective equipment (e.g., a helmet) when you do certain physical activities. Contact sports such as boxing, soccer and hockey must be avoided due to the significant risk of bleeding they represent.

Vaccination

The Canadian Pediatrics Society has published several documents promoting the Canadian vaccination program. Children must receive their first vaccinations at a young age. However, it is important to take precautions in order to avoid bleeding at the injection site. The nurse at the hemophilia treatment centre will be able to tell you what precautions to take.

Special Precautions

Children with fibrinogen deficiency must receive their vaccines on a schedule set by their pediatrician or family physician. It is also recommended that anyone receiving human source coagulation factor concentrate be vaccinated against hepatitis A and B.

The hepatitis A virus is present in the stools of infected people. It can be transmitted from one person to another by:

- food and water that have been in contact with an infected person;
- sexual relations with an infected person;
- contact with infected blood.

In the past, hepatitis B could be transmitted by blood factor concentrates. Nowadays, however, the concentrates pose no risk. This having been said, a person suffering from a coagulation disorder is more likely to need blood transfusions and these may transmit hepatitis B, albeit very rarely. That is why vaccination is recommended.

Hepatitis B is a disorder caused by a virus that attacks the liver. The liver helps to digest food and clean the blood. Some people infected by hepatitis B present no symptoms, but they can nevertheless transmit the disease to someone else. In other cases, hepatitis B makes people very sick. It can cause serious damage to the liver and an infection that lasts a very long time. There is no completely effective treatment for hepatitis B.

Hepatitis B is transmitted by contact with bodily fluids, including:

- blood;
- mother's milk;
- semen;
- vaginal secretions.

The Comprehensive Care Team

As the name suggests, a comprehensive care team provides most of the medical services required by a child or adult with an inherited bleeding disorder, such as fibrinogen deficiency. It is important that medical monitoring be provided for affected individuals by a centre specializing in the treatment of coagulation disorder, such as a hemophilia treatment centre. This team is composed of several professionals, including:

- a medical director, usually a hematologist;
- a nurse coordinator;
- a physiotherapist, and
- a social worker.

The team works closely with other specialists—a surgeon, an orthopedist, a rheumatologist, a dentist, a geneticist and a psychiatrist, among others. The purpose of this multidisciplinary team is to ensure the well-being of the patient and, in the case of a child, the parents as well.

Conclusion

Fibrinogen deficiency is a very rare inherited bleeding disorder. There are three kinds of fibrinogen deficiency: afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia.

This disorder affects men and women in equal numbers. In some cases it can also cause serious bleeding or thrombosis.

For More Information

You can obtain a list of Hemophilia Treatment Centres by contacting the National Office of the Canadian Hemophilia Society at the following address:

Canadian Hemophilia Society
625 President-Kennedy Avenue, Suite 505
Montreal, Quebec H3A 1K2
Tel. (514) 848-0503
Toll-free: 1-800-668-2686
E-mail: chs@hemophilia.ca
Web site: www.hemophilia.ca

References

- 1 Amesse C, Lacroix S, Lupien G. Canadian Hemophilia Society. Factor VII Deficiency: An Inherited Bleeding Disorder, 2001, 31 pages.
- 2 Amesse C, Lacroix S, Lupien G. Canadian Hemophilia Society. Factor XIII Deficiency: An Inherited Bleeding Disorder, 2001.
- 3 Armin J. Reiningger, Cornelia B. Reineger, Michael Spannagl, Achim Mellinghoff, Astrid Porr, Ulrich Heinzmann, Laurenz J. Wurzinger; Thrombosis and Haemostasis, Effect of Fibrinogen Substitution in Afibrinogenemia on Hemorheology and Platelet Function, 1995, 74 (3) 853-8
- 4 Centeon. Haemocompletan P. Active ingredient Fibrinogen, human, pasteurized, German, Centeon Pharma GmbH.
- 5 Grech H, Majumdar G, Lawrie A.S., Savidge G.F., Case reports. Pregnancy in congenital afibrinogenemia: report of a successful case and review of literature. British Journal of haematology, 1991, 78 571-582
- 6 Hamid Al-Mondhiry, W. Christopher Ehmann: American Journal of Hematology, Congenital Afibrinogenemia. 1994, 46: 343-347
- 7 Harrington A, Lacroix S, Schwetz N. Canadian Association of Nurses in Hemophilia Care. Acquired Hemophilia, 2001.
- 8 Jobin F. l'Hémostase, Les Presses de l'Université Laval, 1995 496 p.
- 9 Lupien G, Amesse C, Bissonnette D, Lacroix S. Canadian Hemophilia Society. Glanzmann Thrombasthenia: An Inherited Bleeding Disorder, 2001, 14 pages.
- 10 Maura K. Whiteman, Yadong Cui, Jodi A. Flaws, Mark Espeland, Trudy L. Bush; American Journal of Hematology, 1999, 61: 271-273
- 11 R. Parameswaran, J.P. Dickinson, S. De Lord, D.M. Keeling, B.T. Colvin. Haemophilia, Spontaneous intracranial bleeding in two patients with congenital afibrinogenemia and the role of replacement therapy, 2000, 6, 705-708
- 12 Shima M, Tanaka I, Sawamoto Y et al. Successful treatment of two brothers with congenital afibrinogenemia for splenic rupture using heat and vapor solvent detergent-treated fibrinogen concentrates. Journal Pediatric Hematology-Oncology 1997; 19 (5) : 462-5
- 13 Takao Kobayashi, Naohiro Kanayama, Naoki Tokunaga, Toshihiko Asahina, Toshihiko Terao ; British Journal of Haematology, Prenatal and peripartum management of congenital afibrinogenemia, 2000, 109 : 364-366

Notes

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