FACTOR XI DEFICIENCY

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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The Canadian Hemophilia Society (CHS) strives to improve the health and quality of life for all people with inherited bleeding disorders, and to find a cure.

This booklet provides general information on factor XI deficiency 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 XI ("eleven" in Roman numerals) deficiency is a very rare blood coagulation disorder. It is not well known, even among health professionals. People affected by a factor XI deficiency and those close to them have very little written information about it. This booklet therefore provides a description of the disease and its treatment. We hope that people suffering from factor XI deficiency will understand their condition better, and that they will be able to reduce its impact on their lives.

Discovery

Factor XI deficiency was described for the first time in 1953 in a Jewish family in the United States by Dr. Rosenthal and his colleagues. Two sisters had abnormal bleeding after a tooth extraction and surgery to remove tonsils. Four more of the thirteen members of the family over four generations were identified as factor XI deficient. One uncle had had abnormal bleeding after a tooth extraction, but did not experience any particular problems when circumcised.

Transmission of factor XI deficiency

Factor XI deficiency is an inherited bleeding disorder. It is transmitted from parent to child at conception.

Each cell in the body contains structures called chromosomes. A chromosome is a long chain made up of thousands of units called genes. Genes determine physical characteristics, such as eye colour. The disorder is caused by an abnormal gene called a mutation. Different kinds of mutations may be responsible for the genetic defect that causes factor XI deficiency. This explains, at least in part, the great variability of symptoms in people with deficiencies that are similar in appearance to factor XI deficiency.

Each individual has a duplicate of each of the genes after receiving one copy of the pair from each parent. He could receive one or two defective genes from a single pair. Individuals who received two defective genes have a more severe form of the disorder than those who receive only a single gene. Blood factor XI levels are significantly lower than normal in persons with two defective genes, and slightly lower in persons with only one.

Unlike classical hemophilia (factor VIII deficiency), which affects mainly boys, factor XI deficiency has no distinction as to gender, and affects both girls and boys. The factor XI deficiency gene is located on chromosome 4 and is found in both males and females.

The illustrations below show the percentage possibility of passing on the disorder, dependeing on the genes carried by each parent

Figure 1 shows what can happen when one of the parents has a defective gene; each child has a 50% chance of receiving one defective gene.

D: defective gene
N: normal gene

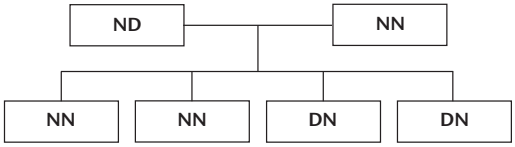


Figure 1

Figure 2 shows what can happen when one of the parents has two defective genes; all children will receive one defective gene.

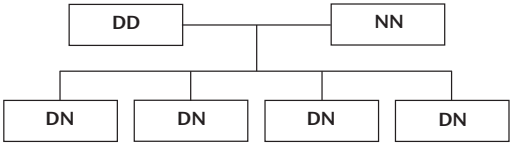


Figure 2

Figure 3 shows what can happen when both parents carry a defective gene; each child has a 25% chance of receiving two defective genes, a 50% chance of receiving one defective gene, and a 25% chance of having two normal genes.

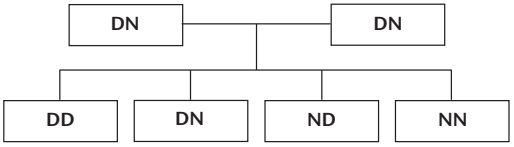


Figure 3

Figure 4 shows what can happen when one parent has two defective genes and the other a single defective gene; each child has a 50% chance of receiving two defective genes and a 50% chance of receiving one defective gene.

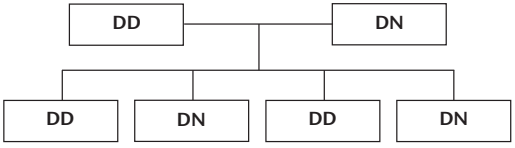


Figure 4

Figure 5 shows what can happen when both parents have two defective genes; all the children will also have two defective genes.

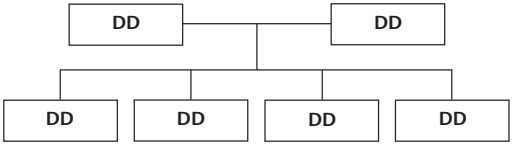


Figure 5

The clotting mechanism

Blood is carried throughout the body in a system of blood vessels. When we are injured, one or more blood vessels may be punctured, resulting in loss of blood. When they are punctured at the surface, as in the case of a cut, the blood is lost outside the body. Or the blood vessel can be damaged deep inside the body, causing a bruise or internal hemorrhage, which produces different symptoms depending on the severity and location of the bleeding.

The body uses different mechanisms to stop bleeding. First, when a blood vessel ruptures, it contracts as a reflex, which reduces the amount of blood loss.

The second mechanism is coagulation. Clotting, or coagulation, is a complex process that makes it possible to stop the bleeding from damaged blood vessels. As soon as a vessel wall breaks, the components responsible for coagulation come together to form a plug at the break. Several steps are involved in forming a plug.

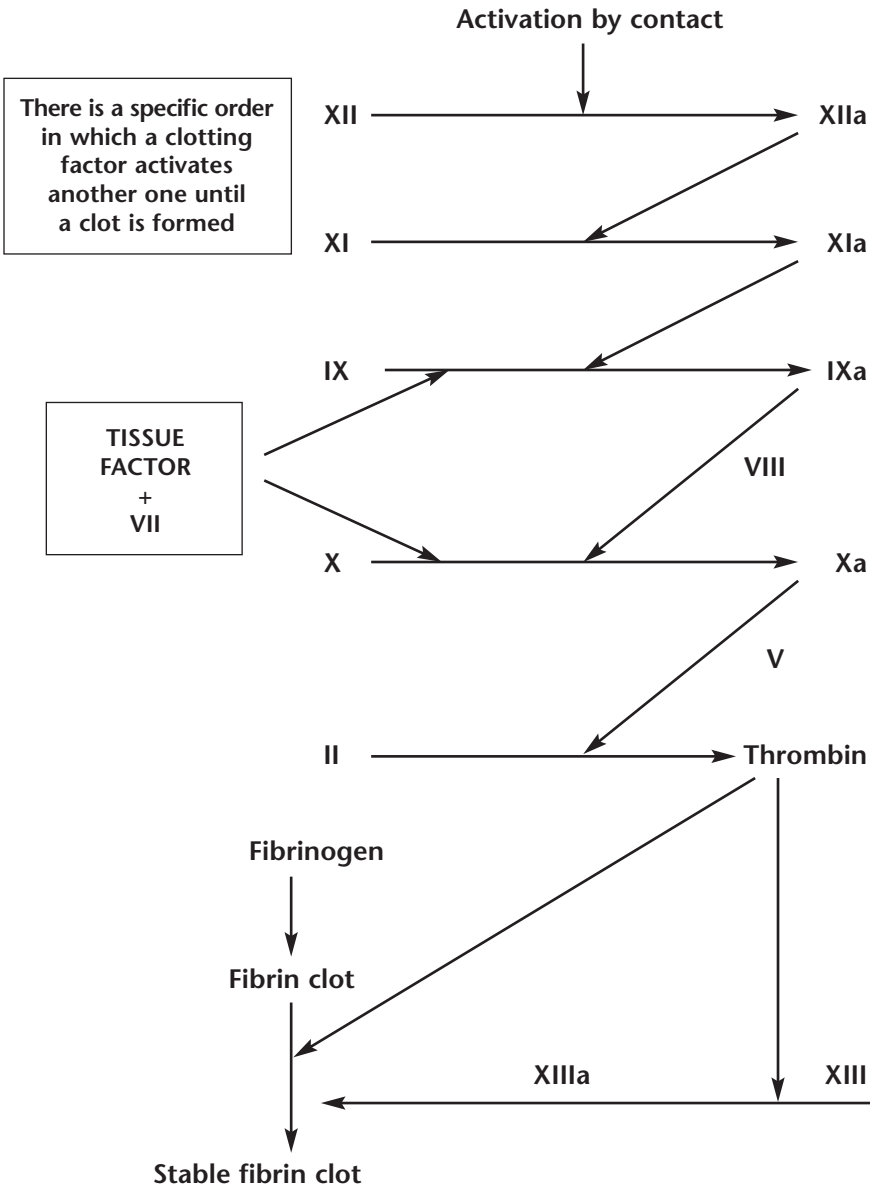
The platelets, very small cells, are the first to arrive at the site where the vessel is ruptured. They stick to one another and attach themselves to the damaged vessel wall.

The platelets sticking to the wall emit chemical signals to call other platelets and coagulation factors to help them.

The coagulation factors link up to form a chain, called fibrin. The fibrin filaments intertwine to form a mesh around the platelets to solidify the clot.

When a specific coagulation factor is absent or not produced in sufficient quantities, the filaments are weakened and let the blood through, causing bleeding; since it takes longer for the vessel to be completely sealed, there is extensive blood loss.

The following diagram shows schematically the order of the cascade activation of different coagulation factors to form a clot.



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

Incidence

It is difficult to establish exactly how widespread this disease is, since many people, especially men, present few symptoms and are thus less apt to consult a doctor to obtain a diagnosis. In the American population overall, one person in 100,000 is diagnosed with factor XI deficiency, regardless of degree of severity. The Ashkenazi Jewish population and a few other isolated groups are exceptions to the rule, since they show a much higher incidence—as high as 8% of the population, including both individuals with a single abnormal gene and those with two abnormal genes. This is the most common genetic disorder found in these populations. This is due to the higher probability that parents who are carriers of one or more defective genes, in a group isolated by geographical, cultural, religious or other factors, will conceive children who are carriers of the same defective gene.

Diagnosis

The diagnosis is suspected when an individual presents symptoms of unusual bleeding or when coagulation tests are done prior to surgery. A coagulogram is then done on a blood sample from the patient to measure the rate of clot formation. If the part of the coagulogram called the APTT is abnormally long, indicating a clotting anomaly, the physician will ask for a measurement of coagulation factors. This will detect whether the level of clotting factor XI is too low.

Symptoms

For reasons that are still unknown, the tendency to bleed is not always directly proportional to the level of blood factor XI. Two people with similar factor XI levels may present completely different symptoms. As a result, it is very difficult to predict the severity and frequency of bleeding simply on the basis of the percentage of factor XI in the blood. Personal and family history of bleeding, however, can predict a tendency to bleed, even though it may be variable over time in a single individual.

A strong tendency to bleed may be due to the coexistence of two inherited disorders that affect blood coagulation in the same individual. For example, von Willebrand disease is a relatively frequent coagulation anomaly that affects up to 1% of the population, and the symptoms of this condition are similar to factor XI deficiency.

Some very small groups, such as the Ashkenazi Jewish population, have inherited more serious forms of the disorder, which manifest as more acute, more frequent episodes of hemorrhaging. The serious forms are due either to a larger mutation or to the presence of two defective genes.

Prolonged bleeding may occur in particular after a major physical trauma, after an accident, or after surgery involving the buccal, nasal, genital or urinary mucosa. Tooth extraction, tonsillectomy and ablation of the uterus or prostate are examples of surgeries that entail a high risk of bleeding. People with the disorder also have a strong tendency to develop nosebleeds and ecchymoses (bruises), and more rarely, bleeding into the urine or intestines. However, they do not have a tendency to bleed into muscles or joints; they therefore do not suffer the long-term effects associated with bleeding of this kind. Nor is there a high risk of suffering spontaneous intracranial bleeding, at least not without associated trauma.

Problems specific to women

For gynaecological and obstetrical reasons, women experience the effects of the disorder more acutely than men. Abundant menstrual flow and excessive bleeding after delivery, voluntary or spontaneous abortion, or gynaecological surgery are all situations with which women must cope regularly.

The level of blood factor XI varies very little during pregnancy. However, the female homones have a stimulating effect on the production of blood coagulation factor VIII and von Willebrand factor. This improves coagulation in all women, and considerably reduces the risk of bleeding during pregnancy or while taking oral contraceptives (imitation of pregnancy condition). Nevertheless, during pregnancy women must cope with situations that risk causing bleeding as a result of various medical interventions, such as amniocentesis, epidural anesthesia, or caesarean section. Moreover, after the hormones drop again, resulting in a reduction in coagulation factor VIII and von Willebrand factor in the period after delivery, women with a factor XI deficiency are at risk of abnormal bleeding. They should always consult a hematologist, preferably in a hemophilia treatment centre. The comprehensive care team there will address all aspects of blood coagulation during pregnancy and the post-partum period, and a personalized treatment plan will be set up.

Childbirth can result in bleeding if the baby has a coagulation anomaly. In order to prevent bleeding episodes in newborns at risk of being factor XI deficient, appropriate instructions are entered in the medical file so as to avoid potentially traumatic medical intervention.

It is also recommended that parents consult a hematologist in a hemophilia treatment centre when they wish to have their baby circumcised. Blood factor XI is naturally slightly lower at birth, and reaches normal levels toward the age of 6 months. It is therefore difficult to establish a diagnosis and treatment plan prior to the age of 6 months.

Outside periods of pregnancy, women have a tendency to have abundant menstruations that can result in a variety of secondary physical and psychological problems. More or less severe anemia is frequently a consequence of abundant, prolonged monthly blood loss. Individuals who suffer from anemia are generally fatigued and low in energy. Sideropenic anemia can also cause learning difficulties in young adolescents. Abundant menstruations require frequent lengthy visits to the toilet, and are often more painful. They result in a loss of productivity at work as well as higher rates of absenteeism.

Given the higher risk of causing abundant bleeding, it is important that gynaecological surgery be planned in conjunction with a hematologist who is associated with a hemophilia treatment centre.

Treatment options

A variety of treatment and prevention options are available for bleeding, though they must be chosen with care. The advantages and disadvantages of each must be weighed, based on the kind of bleeding to be treated or prevented.

Fresh frozen plasma

The first patients who were diagnosed with this disease were treated effectively with fresh frozen plasma. Plasma is a blood derivative, a yellowish liquid that is rich in coagulation factors. There is a potential danger of transmission of viruses such as HIV and hepatitis A, B and C via plasma, since it is provided by donors and is not subjected to any virus inactivation procedure. However, the risk is now low, since donors are carefully selected to minimize risk, and all plasma units are screened to ensure they contain no trace of virus.

Factor XI concentrate

Factor XI concentrate is delivered in lyophilized (powder) form in glass containers. It is distributed to hospitals by Héma-Québec or Canadian Blood Services. These factor concentrates are fully treated to inactivate blood-borne viruses such as HIV and the viruses responsible for hepatitis A, B and C. It is readily administered with a small volume of liquid. Only very rarely will patients develop allergic reactions to the product.

On the other hand, factor XI concentrates are known to pose a risk of promoting development of intra-vascular clots, which, though rarely, can endanger a patient's life.

Each International Unit (IU) of factor XI per kilogram increases the concentration of factor XI in the blood by 2.4%; the level of blood factor drops by half every two days, until it returns to the base level.

Factor XI concentrates must be used with great care, especially in surgeries where there is a high risk of thrombosis. Even when heparin is added, care must be taken with older patients who have antecedents of cardiovascular disease or a pre-existing condition that promotes the activation of coagulation (a rare condition seen in pregnant women, after delivery, or in cancer patients). When factor XI proves to be the treatment of choice to prevent or treat bleeding, it is essential that it be closely supervised by a team of experts in a hemophilia treatment centre.

Hormone therapy

Hormone therapy is administered in the form of birth control pills, injections and, in the past few years, intra-uterine devices (IUDs). Hormone therapy is an excellent way for women with factor XI deficiency to protect themselves against abundant menstrual bleeding, since it acts by adjusting hormone levels to imitate pregnancy. Hormones taken orally or by injection also help prevent factor XI deficiency related excessive bleeding.

DDAVP

DDAVP, or the synthetic hormone desmopressin, is certainly a very good treatment alternative. Its administration encourages coagulation in anyone by temporarily increasing factor VIII and von Willebrand coagulation factor levels. This medication can be administered either by injection into the veins or under the skin, or by nasal vaporization. DDAVP taken intravenously is used especially for rapid control of occasional bleeding or to prevent excessive bleeding during surgery. DDAVP acts for 8 to 12 hours, with maximum effectiveness about thirty minutes to one hour after injection. It should therefore ideally be administered within an hour before surgery. DDAVP taken intranasally or subcutaneously is recommended more for those who frequently suffer bleeding episodes that are controlled well by medication. These people can easily learn to self-administer the treatment in order to avoid frequent hospital visits. It is recommended that people who bleed mainly from the nose learn the subcutaneous

injection technique. For women who have abundant menstruations, intranasal DDAVP is another treatment option that can be effective.

Cyklokapron

Cyklokapron (the commercial name of tranexamic acid) acts by helping hold the clot in place after it has formed. It has proven very useful in controlling mucosal bleeding (bleeding of the soft tissues, such as the mouth, nose, vagina, etc.). These are the parts of the body where clots dissolve quickly. Cyklokapron is available on prescription at pharmacies. It is taken orally every 8 hours for a 5- to 10-day period, depending on the kind of bleeding to be controlled or prevented. It is available in pills that can be crushed and mixed in a purée for people who have difficulty swallowing pills, such as young children. It is a drug that can also be administered intravenously in people who must be fasting in preparation for surgery. It can be used alone or in conjunction with another drug, such as DDAVP, which helps increase its effectiveness.

Recognizing, preventing, and treating bleeding

People with factor XI deficiency are considered hemophiliacs. Like other hemophiliacs, they have abnormal bleeding due to a lack of coagulation factors. However, the type and frequency of bleeding in factor XI deficiency differ significantly from other types of hemophilia, as does treatment.

Symptoms of bleeding

A tendency to bleed from the mucosa is typical for factor XI deficiency. Patients must be especially alert to the signs and symptoms associated with this kind of bleeding, and quickly consult a physician or their hemophilia treatment centre when it occurs. Here is a list of symptoms of bleeding that could quickly lead to severe anemia, which could result in the need for a transfusion:

- Black stools
- Presence of blood in vomit
- Frequent changes of sanitary napkins or tampons over an extended period
- Prolonged and/or frequent nosebleeds
- Blood in the urine
- Bleeding from the site of a tooth extraction that continues for more than a few hours after surgery

Preventive measures

Here is a list of measures you can take to avoid excessive bleeding during surgery of the buccal mucosa, such as a tooth extraction, tonsillectomy, adenoidectomy, etc.:

- Medication prescribed by the hematologist before surgery: DDAVP in the majority of cases. The physician will determine whether additional doses are needed during the post-operative period.
- Cyklokapron 2 hours before surgery if taken by mouth, and every 8 hours for a period of 7 to 10 days. Cyklokapron can be administered intravenously within an hour prior to surgery when the patient must be fasting.
- Sleep sitting up for the first 24-48 hours after surgery.
- A diet of soft, cold foods for a period depending on the severity of the operation.

Treatment measures

First aid to be administered in typical factor XI deficiency bleeding episodes:

Nosebleeds:

- Have the person sit upright.
- Pinch the widest part of the nostrils for a period of 10 to 15 minutes.
- Start administering Cyklokapron for a period of 5 to 7 days.
- Avoid hot drinks and strenuous exercise for a period of 24 hours after bleeding.
- Sleep in a seated position the night following the bleeding episode.

Bleeding from the mouth:

- Have the person sit upright.
- If possible, have the person bite on a compress for 20 minutes.
- Have a diet of cool, soft foods for 24 to 48 hours (Jello, ice cream, popsickles, etc.).
- Sleep in a seated or half seated position the night following the bleeding episode.

Healthy living

The recommendations for healthy living are the same as for anyone with or without a coagulation factor deficiency.

Follow a regular program of physical activity suited to lifestyle and capability.

- Use high quality sports equipment appropriate for any sport (helmet, elbow pads, kneepads, proper shoes, etc.).
- Eat a well-balanced diet; maintain normal weight.
- Go to bed at regular hours and get enough sleep.
- Drink alcohol and coffee in moderation.
- Don't smoke.

Specific recommendations for people with factor XI deficiency

- Practice daily dental care and have regular visits to the dentist. In the event of a tooth extraction, contact your hemophilia centre to establish an appropriate prevention plan. Your treatment centre can recommend a dentist who is familiar with hemophilia.

- Follow the same recommendations for any other kind of surgery. If the surgery is done in a different hospital from your centre, or for emergency surgery, the attending physician can contact a member of the team at the treatment centre at any time with the information on your identification card.

- **Never take aspirin.** Aspirin is a drug that increases the tendency to bleed. Always consult the care team before taking any new medication. This includes non-prescription natural supplements or vitamins.

- Wear a MedicAlert type identification piece bearing information on your bleeding disorder. This recommendation should be discussed on an individual basis so that its relative merit can be assessed based on the seriousness of the deficiency, the age of the subject, and his or her environment. The potential social stigma of wearing a MedicAlert piece might be avoided in school aged children whose factor XI deficiency is minimal and does not pose any medical risks that would justify revealing a relatively benign medical condition.

- Always be aware of the signs and symptoms of life-threatening bleeding.

- When planning a trip, notify your treatment centre. Ask for the addresses of hemophilia centres located in your destination region.

- Always keep in contact with your Hemophilia Treatment Centre.

Vaccination

It is recommended that children receive their vaccinations on the Canadian Pediatric Society updated timetable. Bleeding only rarely occurs as a result of vaccinations in people with factor XI deficiency. However, it would be prudent to take a few precautions to ensure any loss of blood can be effectively controlled. We suggest asking the professional who administers the vaccination to use the smallest calibre needle possible, and to apply pressure to the injection site for several minutes after vaccination.

Hepatitis B and A are diseases caused by viruses that attacks the liver and may be transmitted by blood and blood derivatives. In Canada, children are vaccinated against hepatitis B at approximately age 9. The hepatitis A vaccine is available in Canada, but is not part of the vaccination schedule recommended for the Canadian public-at-large. There is a vaccine against hepatitis A only, and a combined vaccination that protects against hepatitis B and hepatitis A. No official guidelines have been set for vaccination against these diseases in people with factor XI deficiency. The decisions to vaccinate earlier against hepatitis B and to vaccinate against hepatitis A must be discussed on an individual basis with hemophilia treatment centre professionals. The risk of receiving a blood transfusion or blood derivative when planning surgery are factors to consider in making this decision.

The comprehensive care team

As the name suggests, a hemophilia comprehensive care team is a team of specialists that provides most of the medical services required by a child or adult with an inherited bleeding disorder. The team is made up of several professionals, including a medical director, a nurse coordinator, a physiotherapist and a social worker.

The team works closely with other specialists, such as a surgeon, an orthopedist, a rheumatologist, a dentist, a geneticist and a psychologist. The purpose of this multidisciplinary team is to ensure your well-being as well as your child's.

In the early 2000s, a few hemophilia treatment centres developed programs designed specifically for women with coagulation disorders. These programs pool the expertise of several care teams, including gynaecology and haematology specialists, in order to address the very special needs of women. Hemophilia associations are a good source of public information about programs for women with bleeding disorders.

Conclusion

Factor XI deficiency is an inherited bleeding disorder. It affects both sexes, although for gynaecological reasons women are more seriously affected. The tendency to bleed is difficult to predict, since it varies over time in the same individual, and between individuals with similar blood levels of factor XI. The different preventive and treatment options available to people with factor XI deficiency all have their own advantages and disadvantages. To ensure you get the right treatment, it is important that your medical condition be monitored by an expert team at a bleeding disorder care centre.

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
Montréal, Québec
H3A 1K2
Telephone: (514) 848-0503
Toll free: 1 800 668-2686
Email: chs@hemophilia.ca
Website: www.hemophilia.ca

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