Thrombosis UK

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Crystal Mark 20665
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Antithrombin deficiency

What is antithrombin?

Antithrombin is a protein in our bloodstream which works as a naturally occurring mild blood thinner. It prevents the blood from clotting too much. It blocks our blood-clotting mechanism by inactivating the clotting proteins including 'thrombin'. Because of this it is called 'antithrombin'. While antithrombin III was the original name given to this protein, the correct name now is just antithrombin, without the III. Common names and abbreviations for the same protein are antithrombin, antithrombin III, AT, ATIII and heparin cofactor I.

Why is antithrombin important?

Antithrombin protects the blood from clotting too much. If your antithrombin levels are low, your blood will have a tendency to clot more easily. Increased levels of antithrombin will not have a significant effect on your health.

How are antithrombin levels measured?

The best test to decide whether a patient has AT deficiency is a blood test called 'AT activity' or 'functional AT'. Any doctor's surgery can order antithrombin tests and many laboratories can perform them. Two different antithrombin tests can be done

a) An antithrombin antigen level
b) An antithrombin activity level (also called a functional test)

The antithrombin antigen test tells how much of the protein is present in the blood. The antithrombin activity test tells whether the antithrombin that is there actually works. There are two types of AT deficiency, depending on which of these two tests results is low. This is only really relevant to your doctor though.

(a) Type-1 deficiency

If you do not produce enough antithrombin, the antigen and activity levels will both be low. This is called type-1 deficiency or 'quantitative deficiency'. It is either due to an inherited fault with the gene or a problem which you may suffer from, for example, less antithrombin is made in liver disease or antithrombin is lost in the urine (as may happen rarely in certain kidney diseases).

(b) Type-2 deficiency

Some people produce normal amounts of the antithrombin protein yet the protein has an abnormal structure and so does not work correctly. This is called type-2 deficiency. It is due to an inherited defect (mutation). In this type of deficiency the antigen level is normal, but the activity level is low. As a result, a normal antithrombin antigen level never fully rules out an AT deficiency. So, to fully rule out AT deficiency, you need to have your antithrombin activity level checked. The antithrombin activity level test is the best to have if it is suspected you may have AT deficiency.

Antigen level and activity level are usually expressed in 'percentages'. Normal ranges differ from lab to lab, but usually are about 80% to 120%. Healthy newborns have only half the antithrombin levels of adults, but gradually reach the adult levels by six months. This is important to keep in mind when interpreting the tests of newborns. Being on the contraceptive pill or hormone replacement therapy or being pregnant does not change antithrombin test results significantly and so the results are treated as reliable. However, being on warfarin can increase antithrombin levels. Because of this, a normal level while a person is on warfarin does not absolutely rule out AT deficiency.

Once a patient is off warfarin, the antithrombin activity test should be repeated. Heparin levels may lower antithrombin levels temporarily. There are many different mutations in the antithrombin gene that can lead to inherited AT deficiency. Because of this, genetic testing is not possible in routine clinical practice. It is only carried out in research studies.

Antithrombin deficiency

Inherited AT deficiency increases the risk for blood clots. AT deficiency which develops at a later date (acquired) often does not. There are two major causes of AT deficiency:

(a) an inherited deficiency due to a genetic abnormality (mutation); and
(b) an acquired deficiency due to some other disease (see the table, bullets 1-3).

In some conditions there is only a temporary low antithrombin level and levels return to normal once the patient has recovered. This is important to know to avoid an incorrect diagnosis of AT deficiency if low values are found.

A definite diagnosis of hereditary deficiency is sometimes difficult to make because of these interfering causes. Repeat testing at a later time to confirm a low level is always a good idea to make a definite diagnosis. Sometimes family testing is needed to help clarify the diagnosis of inherited versus acquired deficiency. If you are diagnosed with AT deficiency, question the diagnosis and make sure the diagnosis was not based on a low level recorded at the time of an acute clot. Sometimes AT levels increase when a person is on warfarin. Because of this, normal levels during warfarin therapy do not reliably rule out AT deficiency. Rechecking a level once a patient is off warfarin is appropriate.

(a) Inherited antithrombin deficiency

Inherited AT deficiency is an uncommon genetic disorder. It happens in 0.2 to 0.02% of the general population, in other words, 1 out of 500-5,000 people has it. Because of this, there may be up to 120,000 people with this disorder in the UK. It is inherited in a dominant pattern, in other words, there is a 50% chance that a child will have the disorder if one of the parents has it. Men and women are equally affected. If a person has inherited one defective (mutated) antithrombin gene, they are known as heterozygous. If a baby has inherited two defective (mutated) genes, in other words, one from the mother and one from the father, they are known as homozygous. Homozygous babies rarely survive. The foetus usually dies before birth, causing a miscarriage.

People with AT deficiency are at increased risk of blood clots in the veins, such as clots in the veins of the leg (called deep-vein thrombosis or DVT) and clots in the lung (called pulmonary embolism or PE). Other venous clots may also form in the arm (upper extremity DVT), intestinal tract (portal vein thrombosis, Budd-Chiari syndrome, and so on), or veins draining the brain (sinus vein thrombosis).

The risk of developing clots in the veins can be quite high. However, this can vary from family to family. Some of this variation depends on where in the antithrombin protein the inherited abnormality is. Some is due to the presence or absence of other clotting disorders and some of this variation is not well understood. In general, about 50% of people develop clots before they are 30 years old. However, quite a few people also reach old age without ever developing a clot. AT deficiency does not appear to be a major risk factor for clots in arteries (strokes or heart attacks).

Many doctors will recommend that if you have true AT deficiency and have had a blood clot, you should be on warfarin indefinitely. If you have AT deficiency but have never had a blood clot, it is difficult to decide whether to start long-term warfarin or not. In this case, other factors need to be considered. Do you have other risk factors for blood clots? Are you obese? Do you smoke? Is your lifestyle inactive? And, is there another clotting disorder or a family history of blood clots?

Also, the doctor will need to take account of the degree of AT deficiency.

(b) Acquired antithrombin deficiency

Acquired AT deficiency is not uncommon. Low levels of antithrombin can be found in patients with the conditions listed in the table below. Usually, acquired AT deficiency does not lead to an increased risk of blood clots. This is because in these conditions, clotting factors other than antithrombin are often also lowered. However, nephrotic syndrome can be associated with blood clots.

Causes of acquired antithrombin deficiency

- Liver failure (such as liver cirrhosis)
- Nephrotic syndrome (a kidney disorder)
- Widespread (metastatic) tumours
- Acute blood clots
- Treatment with heparin
- DIC (disseminated intravascular coagulation)*
- Severe trauma
- Severe burns

*DIC is a generalised clotting and bleeding disorder often due to infection in the bloodstream (sepsis).

Antithrombin concentrates

If you have AT deficiency, you may be given intravenous AT concentrates at times of increased risk for blood clots (if you are having surgery or giving birth). You may also be given AT concentrates when blood thinners cannot be used because of an increased risk for bleeding (neurosurgery). It is not well established which people with AT deficiency need to be treated and which do not. Antithrombin can be replaced using a highly purified, human blood-derived antithrombin protein given into a vein. There are also several other products used around the world. Concentrates are prepared from the blood of tens of thousands of donors, similar to the preparation of clotting Factor VIII for haemophilia patients. The blood of each individual donor is screened for hepatitis and HIV, and other viruses. The part of the blood called plasma is then highly purified resulting in an antithrombin concentrate. Any viruses are killed using one or more different methods, such as heat inactivation or special filtration techniques.

Antithrombin is also being produced using recombinant genetic technology. In this technique the human antithrombin gene is inserted into the living cells of goats so that they produce high concentrations of human antithrombin in their milk. The milk is then purified and the antithrombin concentrated.

Typically replacement treatment is given only when there is an increased risk for clotting or when the blood thinner heparin cannot be safely given because it would lead to an increased risk of bleeding. These situations are during major surgery, suffering a major injury, and giving birth.

Heparin-resistance

In some patients with AT deficiency who need heparin therapy, antithrombin concentrate may have to be given so that heparin can work as well as possible. Heparin (including the low-molecular-weight heparins, such as enoxaparin, dalteparin and so on) may not thin the blood very effectively if you have low antithrombin levels. This is because heparin's effect depends on the presence of antithrombin. In these cases, you may need higher than normal heparin doses to be fully protected against developing blood clots.

You may be 'heparin resistant' and will not respond effectively to heparin at all, even at higher doses. In these situations treatment with intravenous antithrombin concentrates can be considered.

Antithrombin deficiency in children

If you have a child with AT deficiency, you need to be aware of the symptoms of blood clots. However, blood clots are not common in children with AT deficiency, probably because levels of another naturally occurring blood thinner (α2-macroglobulin) are higher until the person reaches age 20 so this protects most children from blood clots. There have been a few reports of clots in newborns with AT deficiency. If one parent has AT deficiency, you should discuss this with a haematologist (blood doctor) and a perinatologist (a doctor who deals with unborn babies and newborns at higher than normal risk of complications) before the delivery. As a parent, you need to be aware of the symptoms of blood clots in case your baby suffers one.

Almost all newborn infants with AT deficiency do not need preventative treatment with heparin or AT concentrate. However, they need to drink plenty of fluids and a doctor may need to keep an eye on their kidney and circulatory function. Most children with AT deficiency do not develop blood clots unless there is another triggering event such as surgery, trauma, a catheter in a blood vessel, or severe infection. Children known to have AT deficiency who develop clots may receive preventative therapy with blood thinners if they need surgery or suffer a major injury.

Children with underlying medical conditions that cause acquired antithrombin deficiency such as nephrotic syndrome (a kidney disorder), protein-losing enteropathy (an intestinal disorder) or who are undergoing L-asparaginase chemotherapy for leukaemia may have an increased risk of thrombosis. Although it is not clear how much of the risk of a thrombosis is actually caused by AT deficiency, children who develop clots who have an acquired AT deficiency may benefit from antithrombin concentrate to treat the acute clot. They may also benefit from blood-thinning therapies (including antithrombin) to prevent further blood clots.

Antithrombin deficiency and pregnancy

Women with AT deficiency are at particularly high risk of developing clots during pregnancy and after delivery. The exact risk of developing blood clots during pregnancy is impossible to accurately predict. One study showed that only 3% of pregnancies will be affected by a blood clot if no blood thinners are given. However, other studies have shown that blood clots can happen in up to 50% of pregnancies. Treatment with heparin injections underneath the skin (subcutaneously) during pregnancy is likely. Some doctors recommend antithrombin replacement therapy during the delivery if heparin will not be suitable, since heparin might lead to an increased risk of bleeding. Heparin or warfarin should be continued for six to 12 weeks after birth because there is a high risk of blood clots in the period after the delivery.

Women with AT deficiency also have a slightly increased risk of losing their baby, either early (miscarriage) or late (stillbirth) in the pregnancy. This is probably due to blood clots forming in the placenta, leading to a blockage of blood and oxygen to the foetus. Therapy with heparin with or without antithrombin throughout the pregnancy is likely to reduce that risk.

Antithrombin deficiency and surgery or injury

If you have AT deficiency, you will need very good thromboprophylaxis with blood thinners if you are going to have surgery or you suffer a major injury. You may be treated with antithrombin concentrate during these times. In anyone, major surgery and injury are risk factors for blood clots (deep-vein thrombosis or pulmonary embolism). However, they are an even greater risk if you have AT deficiency. Because of this, you may need heparin at these times. If an injury or excessive risk of bleeding (for example, neurosurgery) does not allow blood thinners to be given, you may be given antithrombin concentrate. Also, you may have a removable filter placed in your vena cava, the big vein in your abdomen. This filter can capture blood clots that have formed in the leg and are travelling upstream on their way to the lung. As a result, they can prevent a life-threatening pulmonary embolism. You may be given antithrombin concentrate for the first few days after surgery. Depending on the type and extent of the surgery, you may need to use blood thinners for several weeks after surgery.

Family testing

If you have none of the acquired factors or disorders that cause AT deficiency (see the table on page..), you may have an inherited AT deficiency. You should tell other family members (children, parents, uncles and aunts) about the diagnosis. These family members should seriously consider having an antithrombin activity test.

Practical issues

Making a correct diagnosis of inherited AT deficiency can be challenging. Decisions about treatment (whether to begin warfarin therapy if you have never had a blood clot, how long you should have therapy with blood thinners for if you have had a blood clot and how to manage a pregnancy if you have AT deficiency) can be difficult. Haematologists (blood doctors) preferably associated with a thrombosis or thrombophilia centre often have most experience in dealing with clotting disorders such as AT deficiency.

Important issues

- If you have been diagnosed with AT deficiency, question the diagnosis. Be aware that it is easy to be misdiagnosed if the timing of testing and interpretation of the result were not correct.
- Be sure to ask your doctor whether you have an acquired deficiency (not relevant to other family members) or an inherited deficiency (other family members should consider getting tested).
- If you have an inherited AT deficiency, consider being evaluated by a thrombosis specialist (usually a haematologist) at a specialised thrombosis centre.
- Know the symptoms of blood clots in the legs (deep-vein thrombosis (DVT)) or lung (pulmonary embolism (PE)) and make lifestyle changes (lose weight, stop smoking, consider stopping oestrogen therapy (such as the contraceptive pill, patch or ring, or
- If you have inherited AT deficiency, make sure you get very good DVT prophylaxis in high-risk situations (such as during surgery, if you suffer a major injury, long periods where you cannot move around much, and during pregnancy).

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For more information on how to help us, write to:

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