

ANTITHROMBIN DEFICIENCY

What Is Antithrombin?

Antithrombin is a protein in our bloodstream which functions as a naturally occurring mild blood thinner. It is like a police protein that prevents us from clotting too much. It blocks our blood clotting mechanism by inactivating the clotting protein "thrombin". It is, therefore, called "antithrombin". While antithrombin III was the original name given to this protein, the correct name now is just antithrombin, with the "III" dropped. Common names and abbreviations for the same protein are antithrombin, antithrombin III, AT, ATIII and heparin cofactor I.

Why Is Antithrombin Important?

Antithrombin protects us from clotting too much. If antithrombin levels are low, a person will have a tendency to clot more easily. If antithrombin levels are too high a person could, theoretically, have a bleeding tendency. However, elevated levels of antithrombin do not appear to cause bleeding or have any clinical significance.

How Are Antithrombin Levels Measured?

The best test to determine whether a patient has AT deficiency is a blood test called "AT activity" or "functional AT". Any physician's office can order antithrombin tests and many laboratories can perform them. Two different antithrombin tests can be done; a) an antithrombin antigen level and b) an antithrombin activity level (also called "functional test"). The antithrombin antigen test determines how much of the protein is present in the blood. The antithrombin activity test determines whether the antithrombin that is present actually works. There are 2 types of AT deficiency, depending on which of these two tests results is low. This sub-classification is interesting from a scientific point of view, but is clinically not relevant.

(a) Type 1 deficiency

If an individual does not produce enough antithrombin, antigen or activity levels are both low. This is called type 1 deficiency or a quantitative deficiency. It is either due to an inherited gene defect or due to an acquired problem, where less antithrombin is made in liver disease or antithrombin is lost in the urine (as may happen 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, therefore, 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. A normal antithrombin antigen level therefore never fully rules out an AT deficiency. Thus to fully rule out AT deficiency, one always needs to obtain an antithrombin activity level. The antithrombin activity level is the best initial test to obtain if one suspects that a patient may have AT deficiency.

Antigen level and activity level are typically expressed in "percent". Normal ranges differ from lab to lab, but typically are in the order of 80-120%. Healthy newborns have only half the antithrombin levels of adults, but gradually reach the adult levels by 6 months of age. This is important to keep in mind when interpreting the tests of newborns. Being on the birth control pill, hormone replacement therapy, or being pregnancy does not change antithrombin test results significantly and results are, thus, reliable. However, being on warfarin can increase antithrombin levels; therefore a normal level while a person is on warfarin does not absolutely rule out the presence of AT deficiency. Once a patient is off warfarin the antithrombin activity test should be repeated. Heparin levels may transiently lower antithrombin levels. There are many different

mutations in the antithrombin gene that can lead to inherited AT deficiency. Genetic testing is therefore not possible in routine clinical practice. It is reserved for research studies.

Antithrombin Deficiency

Inherited AT deficiency increases the risk for blood clots, acquired AT deficiency often does not. There are 2 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 table, bullet 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 definitive 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 advisable to make a definitive diagnosis. Sometimes family testing is necessary to help clarify the diagnosis of inherited versus acquired deficiency. Practical advice for any patient who carries the diagnosis of "AT deficiency" is to question the diagnosis and make sure the diagnosis was not based in a low level obtained at the time of an acute clot. Sometimes AT levels increase when a person is on warfarin. Therefore, 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 occurs in 0.2-0.02% of the general population i.e.: 1 out of 500-5,000 people has it. Thus there may be between 60,000 and 600,000 people with this disorder in the U.S. It is inherited in dominant pattern, i.e. 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. It is independent of blood types. If a person has inherited one defective (mutated) antithrombin gene, he/she is heterozygous. If an individual has inherited 2 defective (mutated) genes i.e.: one from the mother and one from the father, he/she is homozygous. Homozygous individuals rarely survive: the foetus usually dies before birth and a miscarriage results. Scientifically a classification of "type 1" and "type 2" deficiency is used to distinguish different types of hereditary AT deficiency (see above), but a distinction is clinically not relevant.

People with AT deficiency are at increased risk for blood clots in 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 occur: in the arm (upper extremity DVT), intestinal tract (portal vein thrombosis, Budd-Chiari syndrome, etc), or veins draining the brain (sinus vein thrombosis). The risk of developing clots in the veins can be quite high, but 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 approximately 50% of individuals 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 physicians will recommend that an individual with true AT deficiency who has had a blood clot should be on indefinite warfarin therapy. If a person has AT deficiency but has 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: does the person have additional risk factors for blood clots, such as obesity, smoking, a sedentary lifestyle, presence of an additional clotting disorder or a family history of blood clots? Also, the degree of AT deficiency should be factored in. Clearly an individual decision needs to be made whether a person should be on long-term blood thinners or not.

(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. Typically, 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 frequently also lowered. Nephrotic syndrome, however, 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
- Heparin therapy
- DIC (disseminated intravascular coagulation)*
- Severe trauma
- Severe burns

** a generalised clotting and bleeding disorder often due to infection in the blood stream (sepsis)*

Antithrombin Concentrates

A person with AT deficiency may be given intravenous AT concentrates at times of increased risk for blood clots (surgery, delivery). AT concentrates may also be given when prophylaxis against blood clots with blood thinners cannot be used because of an increased risk for bleeding (neurosurgery). It is not well established which individuals with AT deficiency need to be treated and which ones do not. Antithrombin can be replaced in deficient patients using an intravenous infusion of a highly purified, human blood-derived antithrombin protein or several other products in the rest of 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, HIV, and other viruses such as parvovirus B-19. The part of the blood called plasma is then highly purified resulting in an antithrombin concentrate. Any potentially contaminating viruses are inactivated and killed using one or more different methods, such as heat inactivation or special filtration techniques.

Antithrombin is also being produced by recombinant genetic technology (by GTC Biotherapeutics, USA). 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. The recombinant antithrombin is presently undergoing clinical trials. It has not yet received FDA approval for clinical use in patients is, therefore, at this point not available for routine clinical use.

No guidelines exist as to which patients with AT deficiency should receive antithrombin concentrate. Typically treatment is given only (a) at times of increased risk for clotting, or (b) when the blood thinner heparin cannot be safely given because it would lead an increased risk for bleeding. These situations are major surgery, major trauma, and delivery.

Heparin Resistance

In some patients with AT deficiency who need heparin therapy, antithrombin concentrate may have to be given so that heparin can work optimally. Heparin (including the low molecular weight heparins, such enoxaparin & dalteparin etc) may not thin the blood very effectively if an individual has low antithrombin levels. This is because heparin's effect depends on the presence of

antithrombin. In such cases higher than normal heparin doses may need to be given to lead to full protection from developing blood clots. In some circumstances a patient can 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

Parents of children with AT deficiency need to be aware of the symptoms of blood clots. Blood clots are uncommon in children with AT deficiency, probably because another naturally occurring blood thinner (α_2 -macroglobulin) is higher during the first 2 decades of life, protecting most children from blood clots. However, there have been several reports of clots occurring in newborns with AT deficiency. Discussion between the expectant parents in whom one person has AT deficiency and the haematologist ("blood doctor") and perinatologists (a physician who deals with unborns and newborns at higher than normal risk for complications) should be held prior to delivery. Parents need to be aware of the symptoms of blood clots should they occur in their baby.

Almost all newborn infants with AT deficiency do not need preventative treatment with heparin or AT concentrate, but may benefit from particularly careful attention to hydration and their kidney and circulatory function. Most children with AT deficiency do not develop blood clots unless there is an additional triggering event such as surgery, trauma, a catheter in a blood vessel, or severe infection. Children known to have AT deficiency may receive preventative therapy with blood thinners around trigger events.

Children with underlying medical conditions that cause acquired antithrombin deficiency such as nephrotic syndrome (a kidney disorder), protein losing enteropathy (an intestinal disorder) and L-Asparaginase chemotherapy for leukaemia may have an increased risk of thrombosis. Although it is not clear how much of the thrombotic risk is actually caused by AT deficiency, children who develop clots with such an acquired AT deficiency may benefit from antithrombin concentrate to treat the acute clot and may 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 for developing clots during pregnancy and after delivery. The exact risk of developing blood clots during pregnancy is impossible to determine accurately. One study showed that only 3% of pregnancies will be complicated by a blood clot if no concomitant prophylactic blood thinners are given. However, other studies have shown that blood clots occur in up to 50% of pregnancies. Treatment with heparin injections underneath the skin ("subcutaneously") during pregnancy should be strongly considered. However, no well designed clinical studies exist that allow strong recommendations to be made as to how exactly to treat pregnant women (dose of heparin, treatment with antithrombin concentrate). Some physicians recommend antithrombin replacement therapy during delivery when heparin may be contraindicated, since heparin might lead to an increased risk of bleeding. Warfarin is not used during pregnancy because it may cause birth defects. However, for 6-12 weeks postpartum warfarin should be considered because there is a high risk for blood clots in the post-delivery period. A summary of 45 cases in pregnancy with AT deficiency with detailed information concerning prophylactic therapy with heparin and/or antithrombin has recently been published (see reference list). However, no treatment guidelines can be derived from that publication since many different regimens were used.

Women with AT deficiency also have an increased risk for pregnancy loss, 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 flow and oxygen delivery to the foetus. Approximately 1 of 6 pregnancies in women with AT deficiency (17%) will end with an early foetal loss and 1 in 40 pregnancies (2.3%) will end in stillbirth if no blood thinners are given. Therapy with heparin with or without antithrombin throughout the pregnancy is likely to decrease that risk.

Antithrombin Deficiency And Surgery Or Trauma

Individuals with AT deficiency need very good DVT prophylaxis with blood thinners at times of surgery or major trauma; treatment with antithrombin concentrate during these times can also be considered. Major surgery and trauma are risk factors for blood clots (deep vein thrombosis or pulmonary embolism) in anybody, but they are an even greater risk for the person with AT deficiency. Extra attention to DVT prophylaxis is therefore indicated, typically with one of the heparin drugs. If trauma or excessive risk for bleeding (for example neurosurgery) does not allow blood thinners to be given, antithrombin concentrate is indicated. Also, placement of a removable filter into the inferior vena cava, the big vein in the abdomen, may be considered. Such a filter can capture blood clots that have formed in the leg and are travelling upstream on their way to the lung. They can thus prevent life-threatening pulmonary embolism. Antithrombin concentrate may be given for the first few days after surgery. Depending on the type and extent of the surgery, prolonged use of blood thinners for several weeks after surgery may be appropriate.

Family Testing

Other family members should consider testing. If a person has been diagnosed with AT deficiency and has none of the acquired factors or disorders that cause AT deficiency (see table), an inherited AT deficiency may be present. It is then appropriate to inform other family members (children, parents, uncles and aunts) of the diagnosis. These family members should seriously consider getting tested and an antithrombin activity test should be done.

Practical Issues

It is important to work with a knowledgeable health care provider. Making a correct diagnosis of inherited AT deficiency can be challenging. Treatment decisions (consideration of initiation of warfarin therapy in a person who has never had a blood clot; length of therapy with blood thinners in the person who has had a blood clot; pregnancy management) can be difficult. Haematologists ("blood doctors") preferably associated with a Thrombosis or Thrombophilia Centre often have most experience of dealing with clotting disorders such as AT deficiency.

Key Issues

- If you have been diagnosed with AT deficiency question the diagnosis. Be aware that misdiagnosis may occur if the timing of testing and interpretation of the result was incorrect.
- Be sure you 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 (typically 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 i.e.: birth control pill, patch or ring and hormone replacement therapy).
- If you have inherited AT deficiency make sure you get very good DVT prophylaxis in risk situations (surgery, major trauma, prolonged immobility, pregnancy).

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