55. Antithrombin deficiency

Last Updated: 2/15/2004

Q1: "I had a blood clot in my legs and was found to have AT-III deficiency. Can you explain what that means?"

A1: AT-III deficiency is a disorder that increases the risk for venous blood clots. It can be (a) acquired, or (b) inherited, or (c) based on a misinterpretation of lab tests (values can be temporarily low at the time of the acute clot or during heparin therapy). Rechecking the test and possibly checking other family members may be needed to come up with a solid diagnosis. In patients with true ATIII deficiency who have had one clotting episode, many physicians would recommend long-term warfarin (=coumadin®).

Q2 "If both parents test normal on blood tests for antithrombin III, how is it that a child can have antithrombin III deficiency?"

A2: It is possible, since antithrombin III deficiency can also be (a) acquired or (b) incorrectly diagnosed, if temporarily low levels at the time of an acute clot or during heparin therapy are mistaken for real antithrombin III deficiency.

"Antithrombin deficiency" (="antithrombin III deficiency" = ATIII deficiency") can be due to 3 reasons:

1. Incorrect diagnosis
2. Inherited deficiency
3. Acquired deficiency

What is Antithrombin?
Antithrombin is a protein in our blood stream. We all have it. It controls our clotting mechanism and prevents us from clotting too much. It functions as a naturally occurring mild blood thinner. It blocks the last part of our clotting mechanism and inactivates the clotting protein thrombin (= factor IIa); thus, it is called anti-thrombin.

If antithrombin levels are too low (antithrombin deficiency), a patient has a tendency to clot more easily. If antithrombin levels are too high, a patient theoretically has a bleeding tendency; however, naturally occurring elevated levels of antithrombin do not appear to be of any clinical significance. However, high doses of intravenous antithrombin concentrate function as clinically useful blood thinners; they are sometimes used to treat seriously sick patients who have DIC (disseminated intravascular coagulation).

1. **Incorrect diagnosis**
   If antithrombin levels are measured at the time of an acute clot or while the patient is on heparin, levels may be low, because antithrombin is bound by heparin and by an acute clot. However, levels typically return to normal once the patient has recovered from the acute clot (within a few days to weeks) or heparin is discontinued. Such a transient decrease does not constitute a real antithrombin deficiency. Thus, if low antithrombin levels are found at the time of the acute clot, levels need to be re-checked a few weeks later, before a patient is labeled to have "antithrombin deficiency". Also, any patient who was diagnosed with "antithrombin deficiency" in the past should probably have his/her level re-checked. I have encountered several patients who carried the diagnosis "antithrombin III deficiency" for years, who, on testing in our and in a referral laboratory, did not have antithrombin deficiency.

2. **Inherited antithrombin deficiency**
   Inherited antithrombin deficiency is a rare disorder. It occurs in approximately 0.02 % of the general population, i.e. in 1 : 5,000 people. Thus there are approximately 60,000 people in the U.S. with antithrombin deficiency. It is inherited in a dominant pattern, i.e. there is a 50 % chance that a child inherits this abnormality if one of his/her parents has the disorder (it is the same inheritance pattern as the one depicted in Q/A 12 for factor V Leiden). Men and women are equally affected. It is independent of blood types. If an individual has inherited one bad gene he/she is heterozygous. If an individual has inherited 2 bad genes, he/she is homozygous. However, homozygous individuals cannot survive and the fetus dies in utero; a miscarriage results. Antithrombin deficiency was first described in 1965.

Sometimes a classification of "type I" and "type II deficiency" is used. This is not relevant for clinical purposes and irrelevant for the patient. However, scientifically such a classification helps understand the molecular and genetic mechanism of the deficiency. In type I deficiency the patient does not have enough of the antithrombin protein; in type II deficiency the patient has enough of the protein, but the protein does not function correctly, i.e. it is dysfunctional. The result is the same: patients with both types do not have enough normally functioning antithrombin.

Antithrombin deficiency is a risk factor for venous blood clots (such as DVT and PE), but does not appear to be a risk factor for arterial clots (such as the majority of strokes or heart attacks). Individuals with antithrombin deficiency have an approximately five-fold increased risk of venous blood clots; however, this varies from family to family; in some families with antithrombin deficiency the risk for clots is much higher. A significant number of individuals develop clots before they are 30 years old; however, quite a few people also reach old age without ever developing a clot. Approximately 50% of heterozygous individuals will develop a blood clot during their life.

Many physicians would put a patient, who has true antithrombin deficiency and has had one venous blood clot, on indefinite coumadin (= warfarin) therapy. I do that, too. However, I recommend that on a regular basis (such as once per year) one reconsiders, whether the patient should still be on indefinite coumadin (= warfarin) therapy. If a person has true antithrombin deficiency but has never had a blood clot, it is difficult to decide what to do. An individual decision needs to be made whether the person should be on long-term prophylactic coumadin (= warfarin). The patient's family history and additional risk factors for venous clots will factor into the decision process.

Women with antithrombin deficiency are at particular high risk for clots during pregnancy. Treatment with heparin during pregnancy and with coumadin in the postpartum period should be considered. An important point is that heparin (and also the low molecular weight heparins) do not thin the blood very effectively, thinners, if antithrombin III deficiency is present. This is because heparin's effect depends on the presence of antithrombin. Higher heparin doses than usual may therefore be required to protect against blood clots. Supplementation with intravenous antithrombin concentrates in risk situations (delivery, surgery) should be considered.

3. **Acquired antithrombin deficiency**
   Acquired causes are encountered more frequently than inherited deficiencies. Low levels of antithrombin can be seen in patients with:
   - acute clot or heparin therapy (see above);
   - nephrotic syndrome (a kidney problem in which high doses of protein, including antithrombin, are lost in the urine);
   - liver failure;
   - high-dose estrogen oral contraceptives decrease antithrombin levels (but low-dose OCPs do not. Also: postmenopausal hormone replacement does not influence levels);
   - 3rd trimester of pregnancy;
   - severe trauma, burns, DIC (= disseminated intravascular coagulation), widespread malignancies, high-dose chemotherapy for bone marrow transplantation.