ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Management of Antithrombin Deficiency

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H&O What is antithrombin deficiency?

IP Antithrombin deficiency refers to a decrease in the natural clotting inhibitor, antithrombin. Antithrombin is important because it inhibits clotting factors, such as factor X and coagulation factor I. A decrease in antithrombin levels leads to an increase in the risk for thromboembolic events, primarily deep vein thrombosis and pulmonary embolism.

Nobody can survive with a complete deficiency of antithrombin because the risk of blood clots would be too high. People with congenital antithrombin deficiency usually have antithrombin levels between 40% and 75% of normal. In addition, we distinguish between type I and type II deficiency. Type I antithrombin deficiency occurs when the protein is normal but not enough is produced, representing a quantitative defect. Type II antithrombin deficiency occurs when the antithrombin protein concentration is normal or close to normal but its function is abnormal, representing a qualitative defect. Type II antithrombin deficiency can also present as a functional defect at the site where the heparin binds, which is called antithrombin heparin-binding site (HBS) deficiency. Heparin is a potent cofactor in the mechanism of action of antithrombin. Antithrombin deficiency may also be acquired.

H&O What are the causes of antithrombin deficiency?

IP Most congenital antithrombin deficiency is caused by a mutation in the serpin family C member 1 (*SERPINC1*) gene. The acquired form of antithrombin deficiency can be caused by health conditions such as liver cirrhosis or nephrotic syndrome. Additionally, the agent L-asparaginase, which is used in conditions such as acute lymphocytic leukemia, may lead to a decrease in fibrinogen and antithrombin levels.

H&O How common is antithrombin deficiency?

IP Although antithrombin deficiency is one of the rarest thrombophilias, it is the most important one in relation to the risk of thrombosis. Antithrombin deficiency is present in approximately 1% to 2% of people with a history of venous thromboembolism (VTE), and its occurrence is even lower in the general population. It was the first thrombophilia to be recognized, having been first described in a Swedish family by Egeberg in 1965.

H&O How is antithrombin deficiency diagnosed?

IP It is diagnosed quite easily using functional assays. Typically, a chromogenic assay is used to determine functional antithrombin levels based on the inhibitory activity of antithrombin on the production of thrombin or factor X. A clot-based assay also can be used, but chromogenic assays are established and easy to use. A research laboratory that is specifically focused on antithrombin will also be able to measure the concentration of antithrombin in the blood.

We proceed with testing in patients who have a family history of thrombosis and in those who develop thrombosis at a young age. The more severe and more pronounced the family history, the more suspicious we should be regarding antithrombin deficiency, especially in young women. In patients with VTE, we can more frequently identify factor V Leiden than antithrombin deficiency. People with factor V Leiden, however, have a lower risk of developing thrombosis and appear to have lower recurrence rates than those with antithrombin deficiency. Antithrombin deficiency is so rare that many practitioners never see a single case, but it is important to diagnose accurately because of the high recurrence rate of VTE and the high risk of VTE during pregnancy.

The use of direct oral anticoagulants (DOACs) before testing can lead to a deceptively high level of antithrombin, whereas the use of heparin before testing can lead to a deceptively low level of antithrombin. To get an accurate result on antithrombin testing, practitioners should consider interrupting DOACs for several days and heparin for several weeks before testing.

We want to keep patients on anticoagulation indefinitely in the case of a spontaneous thrombotic event.

H&O How is the condition managed?

IP If a person has a diagnosis of antithrombin deficiency but has not experienced thrombosis, we follow certain protocols. For example, combined oral contraceptives and hormone replacement therapy are contraindicated because estrogen causes a significant increase in thrombosis. Hormonal contraceptives that do not contain estrogen, such as progesterone-only contraceptives and hormonal intrauterine devices, are considered safe from a thrombosis standpoint. The use of vaginal estrogen is also considered safe for use in postmenopausal women.

If a person with antithrombin deficiency experiences thrombosis, anticoagulation is needed. One option for patients with extended thrombosis or pulmonary embolism is low-molecular-weight heparin (LMWH), although some patients with antithrombin deficiency exhibit resistance to heparin, including LMWH. In these cases, a higher dosage of heparin may be needed to reach either activated partial thromboplastin time prolongation or an anti-Xa level that is acceptable for the management of thrombosis.

In the case of a life-threatening thrombotic event, antithrombin replacement may be needed during the acute event. After any heparin resistance is normalized, normal doses of heparin can be used to treat the patient like someone without antithrombin deficiency who has experienced a thrombotic event. We typically continue antithrombin replacement for approximately 5 to 7 days, although there are no comparative studies to establish the optimal timeline. We traditionally have used coumarin derivatives such as warfarin, phenprocoumon, and acenocoumarol. Most experts now think that we can also use a DOAC such as apixaban (Eliquis, BMS/Pfizer) or rivaroxaban (Xarelto, Janssen), although there is no evidence proving the effectiveness of DOACs in these patients. It is unclear how long we should administer these agents before lowering the dose in patients with antithrombin deficiency. The label for apixaban specifies lowering the dose after 6 months to 2.5 mg twice daily.

H&O How long should patients continue with treatment?

IP We want to keep patients on anticoagulation indefinitely in the case of a spontaneous thrombotic event, because recurrence rates are very high in these patients. The answer is more complicated in patients who experience a triggered thrombotic event. I would argue in favor of long-term anticoagulation in patients with a triggered thrombotic event who have a type I antithrombin deficiency or a type II antithrombin deficiency with a positive family history. I would also recommend long-term anticoagulation in patients with a homozygous type II deficiency, whose antithrombin activity is only 15% to 25% of normal.

H&O How does pregnancy affect treatment?

IP Women with antithrombin deficiency have an elevated risk of developing thrombosis during pregnancy. In some cases, the thrombosis is the first sign of pregnancy. Women with antithrombin deficiency who are pregnant should receive LMWH, as coumarins are contraindicated during pregnancy. Although this is not evidence-based, I recommend increasing the dosage of LMWH in pregnant women who have antithrombin deficiency and a personal history of thrombosis as well as a family history of thrombosis and antithrombin deficiency. Even women without thrombophilia experience a small decrease in

antithrombin levels during pregnancy, although we do not know whether this contributes to a meaningful increase in clotting.

Because delivery is always a high-risk situation, I recommend giving antithrombin replacement immediately before and after delivery. Patients should also receive a prophylactic dosage of LMWH for at least 5 to 7 days. Women who are breastfeeding may stay on LMWH, whereas those who are not breastfeeding have the option of warfarin, phenprocoumon, acenocoumarol, or DOACs.

A very specific group of patients are those with homozygous, type II-HBS antithrombin deficiency. In a study that I published in 2017 with Kraft and colleagues, we found that only 7 out of 22 pregnancies that we analyzed among women with homozygous, type II antithrombin deficiency resulted in a live birth, and all the infants were born preterm.

H&O What types of research that you would like to see conducted?

IP It would be wonderful if in 10 years we could use a tool such as CRISPR to repair the *SERPINC1* mutation.

Fitusiran is an investigational, subcutaneously administered small interference RNA therapy that leads to a decrease of antithrombin plasma levels. It is in development for the prophylactic treatment of people with hemophilia A or B. Interestingly, this therapeutically induced antithrombin deficiency has been demonstrated in phase 2 and 3 trials by Kenet and colleagues to decrease the bleeding tendency in patients with severe hemophilia. Thus, the delicate balance of the hemostatic system is impressively demonstrated by the increased thrombotic risk in patients with isolated antithrombin deficiency, whereas antithrombin deficiency leads to a decrease in bleeding in those with a congenital bleeding disorder.

H&O What is the prognosis for people with antithrombin deficiency?

IP Interestingly, the lifespan seems to be normal in these patients. In the European Prospective Cohort on Thrombophilia (EPCOT) study, a group of us examined the mortality rate among a cohort of people with thrombophilia vs individuals in a control group. We were unable to identify a decreased life expectancy in this cohort, which is an encouraging finding for people with thrombophilia.

Disclosures

Dr Pabinger-Fasching has received honoraria for lectures and advisory board meetings from CSL Behring, Takeda, Sanofi, Roche, Pfizer, BMS, and Bayer; and has received research support to her institution from CSL Behring and Roche.

Suggested Readings

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