Surgical implications of antithrombin III deficiency

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Antithrombin III is a potent coagulant inhibitor in plasma. Congenital deficiency of antithrombin III may predispose to thrombotic events and may complicate surgical management. We describe a patient with congenital antithrombin III deficiency who developed superior mesenteric vein thrombosis after the cessation of warfarin therapy which resulted in venous gangrene of the small intestine. Initial treatment of this deficiency with fresh frozen plasma and subsequent long-term management with warfarin therapy has been effective in avoiding further thrombotic events.

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Antithrombin III is a principal coagulant inhibitor of plasma that neutralizes thrombin and inhibits the serum proteases involved in the intrinsic clotting system.\(^1\)\(^-\)\(^9\) It is the only protein whose concentration has been directly correlated with thrombotic diseases.\(^9\)\(^-\)\(^13\) Diminished antithrombin III may occur as a congenital or acquired condition. Congenital antithrombin III deficiency was first described by Egeberg\(^7\) in 1965. Other reports have detailed families with diminished antithrombin III levels and the high incidence of thromboembolism.\(^7\)\(^-\)\(^11\)\(^-\)\(^14\) Congenital antithrombin III deficiency appears to be inherited as an autosomal dominant trait.

The patient described herein has a congenital deficiency of antithrombin III. He developed superior mesenteric vein thrombosis with subsequent loss of 90% of the small intestine after warfarin therapy had been stopped. Proper management of this patient could not be instituted until antithrombin III deficiency was documented. Pre-, intra-, and postoperative management of patients with antithrombin III deficiency must be designed carefully to prevent perioperative thrombosis and embolism without causing hemorrhage.

CASE REPORT

A 37-year-old white man was admitted to a community hospital after waking with severe generalized abdominal pain. Upon admission, gross bleeding from the rectum was noted. Past medical history revealed that 13 years earlier the patient had had deep vein thrombosis in the left leg with pulmonary embolism at the age of 24. At that time the patient was treated with heparin and placed on warfarin, 5 mg daily, for the next 12 years. Five months prior to admission, the patient was instructed by a different physician to discontinue warfarin therapy. He was asymptomatic until the present admission. The patient's family history included two healthy sisters, two nephews, and two nieces without evidence of thrombosis. Both parents were dead, and neither had had a history of thromboembolic disease.

Hospital course. A superior mesenteric artery arteriogram demonstrated a patent mesenteric artery with no filling of the mesenteric veins. A diagnosis of mesenteric venous infarction was made; the patient underwent an operation. Gangrenous intestine from 8 inches distal to the ligament of Treitz to 6 inches proximal to the iliocecral valve was found and resected with primary jejunoileal anastomosis. Shortly after the operation, the patient was placed on continuous intravenous heparin. Despite the administration of heparin, 3,000 U/hr (72,000 U/24 hr), there was only slight prolongation of the partial thromboplastin time (49 seconds, normal range: less than 45 seconds). The patient's postoperative course was complicated by the development of a fistula and obstruction at the jejunoileal anastomosis. This was managed by Cantor tube decompression and intravenous hyperalimentation. Two weeks after insertion of a left subclavian catheter for hyperalimentation, the patient developed swelling of the left arm and occlusion of the catheter. The diagnosis of left subclavian vein thrombosis was made on the basis of venography, the catheter was removed, and heparinization continued. Six weeks after the operation, the patient developed sudden loss of vision in the left eye, presumably
because of vascular occlusion. The patient was receiving 2,700 U heparin/hr with a partial thromboplastin time of 53 seconds (normal range: less than 45 seconds) at this time.

Two months after his initial operation the patient was transferred to the University of Chicago Hospitals for management of intestinal obstruction. On examination, the patient was obese, the abdomen was soft without masses, and the abdominal wound was well healed. The patient was blind in the left eye. There was no evidence of active thrombophlebitis. A barium meal examination revealed stenosis and extravasation of contrast material at the site of the previous jejunoileal anastomosis. Suprarenal thrombus in the inferior vena cava and ileofemoral thrombus were seen on venography. Laboratory tests indicated a partial thromboplastin time of 56 seconds (control = 24 to 27 seconds) on 2,000 U heparin/hr. The prothrombin time and platelet count were normal. An immunologic determination of antithrombin III levels was performed by radioimmunodiffusion with a monospecific antithrombin III antibody mixed with agar in plates. Antithrombin III levels in serum and plasma were 10 mg/100 ml (normal, 17 to 30 mg/100 ml) and 20 mg/100 ml (normal, 22 to 39 mg/100 ml), respectively (Fig. 1).

The patient was prepared for operation by the administration of 2 U fresh frozen plasma 12 hours before operation and 2 U immediately preoperatively. The heparin infusion was decreased to a rate of 1,500 U/hr, which produced partial thromboplastin times in the range of 40 to 50 seconds (normal range, 24 to 27 sec). At operation, the suprarenal vena cava thrombus was removed and the vena cava was plicated below the renal veins. The necrotic terminal ileum was resected and a new jejuno-colic anastomosis was fashioned. The patient tolerated the procedure well. Postoperatively, the patient received 2 U fresh frozen plasma every other day and intravenous heparin at a rate (approximately 1,500 U/hr) sufficient to result in a partial thromboplastin time of 70 to 80 seconds (normal control, range 24 to 27 seconds). The patient recovered well from his operation and was administered warfarin on the seventh postoperative day. Thirty-six hours after receiving his first dose of warfarin by mouth (10 mg), the patient developed gastrointestinal hemorrhage that required 6 U of blood. Gastroscopy revealed hemorrhagic gastritis. Prior to administration of warfarin, the patient's prothrombin time was 12 seconds (control, 11 seconds) and his partial thromboplastin time was 86 seconds (control, 25 seconds) while receiving 1,500 U heparin/hr. Thirty-six hours later, at the time of upper gastrointestinal hemorrhage, his prothrombin time was 33 seconds (control, 11 seconds) and his partial thromboplastin time was 80 seconds (control, 26 seconds) on the same...
heparin regimen. After the administration of vitamin K (10 mg) and 2 U fresh frozen plasma, the hemorrhage ceased. Thirty-six hours later, the patient's prothrombin time was 11 seconds (control, 11 seconds) and his partial thromboplastin time was 86 seconds (control, 25 seconds) on 1,500 U heparin/hr. At the time of hemorrhage the patient had minimally impaired liver function as assessed by total bilirubin (1.1 mg/100 ml, normal range, 0.1 to 1.2 mg/100 ml), prothrombin time before warfarin therapy (12 seconds, control 11 seconds), alkaline phosphatase (78 mg/100 ml, normal range, 10 to 85 mg/100 ml), and transaminases (serum glutamic-oxaloacetic transaminase 44 mg/100 ml, normal range, 0 to 35 mg/100 ml) (serum glutamic-pyruvic transaminase 91 mg/100 ml, normal range, 0 to 35 mg/100 ml).

Heparin and fresh frozen plasma therapy were discontinued after the patient was stable on 7.5 mg of warfarin/day with a prothrombin time of two times normal and with a normal antithrombin III level (Fig. 1).

The patient has required permanent intravenous hyperalimentation for nutritional support at home. He is now well, his weight is stable at 197 pounds, and he has had no evidence of further thrombosis.

After the patient was discharged from the hospital, his immediate family was screened for antithrombin III deficiency. The patient's two sisters and three of their four children had immunologically determined antithrombin III levels below the normal range (Fig. 2).

**DISCUSSION**

The prevalence of antithrombin III deficiency in both Scandinavian and New England populations has been estimated to be one in 2,000. Antithrombin III deficiencies probably account for 2% of patients with venous thromboembolism. In families with inherited antithrombin III deficiencies, the incidence of thromboembolic events in patients with abnormally low levels of antithrombin III is between 40% to 70%.

Thrombotic manifestations of congenital antithrombin III deficiency usually develop between the ages of 15 and 40 and include (1) iliofemoral thrombosis; (2) superficial calf vein thrombosis; (3) pulmonary embolism; (4) inferior vena cava thrombosis; (5) mesenteric vein thrombosis; (6) thrombosis of the sagittal and transverse sinuses; (7) venous gangrene of the lower extremities; and (8) sudden death.

Heparin resistance is common in patients with antithrombin III deficiency. This observation can be explained by recent evidence which indicates that antithrombin III and heparin cofactor are identical molecules. In vitro experiments have shown that antithrombin and thrombin form a one-to-one stoichiometric complex and that heparin greatly accelerates the formation of this complex without affecting the molar ratio or dissociability. It is likely that the interaction of heparin with antithrombin induces a conformational change in the antithrombin molecule that allows more rapid interaction with thrombin. Patients with low levels of antithrombin III are deficient of this cofactor necessary for heparin anticoagulation and therefore display “heparin resistance.”

Administration of warfarin has been demonstrated to increase antithrombin III levels in deficient patients. The mechanism for this increase is not clear. Liver disease, active thrombosis, pregnancy, oral contraceptive agents, and menopause are all associated with a decrease in antithrombin III levels.

Antithrombin III levels can be measured biologically or by immunodiffusion techniques. In the clinical setting described, the immunologic technique is preferred because heparin therapy (such as this patient received) has been reported to decrease the biologically measured activity of antithrombin III.
Congenital antithrombin III deficiency was established in the patient described by the following criteria: (1) the patient had multiple radioimmunologic determinations of antithrombin III and all were below the normal range until the patient began to receive warfarin; (2) administration of fresh frozen plasma did seem to decrease the amount of heparin required to produce partial thromboplastin time in the range of 2½ times control; (3) the clinical history of an episode of thrombosis at the age of 24 is characteristic of the presentation of congenital antithrombin III deficiency, i.e., a thrombotic episode in the third decade; (4) the patient had several relatives who had multiple determinations of antithrombin III below the normal range; (5) for 12 years after being placed on warfarin therapy the patient experienced no thrombotic episodes and five months after cessation of warfarin therapy, the patient presented with catastrophic superior mesenteric vein thrombosis; and (6) subsequent administration of warfarin to this patient during his recovery produced increases in antithrombin III levels to within the normal range (Fig. 1).

This patient was managed acutely with administration of fresh frozen plasma. This management was selected because absorption of warfarin given by mouth was thought to be uncertain because of the patient’s short intestinal tract and bowel obstruction. Fresh frozen plasma contains normal amounts of antithrombin III. Although this patient experienced a complicated clinical course, administration of fresh frozen plasma was associated with the decrease in amount of heparin required to produce partial thromboplastin times of 80 seconds (compare December 6 with January 20 in Fig. 1). We did not demonstrate any increases in measurable antithrombin III levels by the administration of 2 U fresh frozen plasma every other day during the perioperative period. This may be explained by the following: (1) the half-life of antithrombin is 72 hours and (2) the patient’s plasma volume was estimated to be 3,500 cc. Therefore, the administration of 400 cc of fresh frozen plasma containing normal amounts of antithrombin III would be diluted one to nine and result, at most, in a 12% change in antithrombin III levels. This small difference may not be detected by our assay or may be obscured by consumption. After fresh frozen therapy was begun, the patient did not experience any additional thrombotic episodes.

It is likely that the 10 mg of warfarin induced an episode of upper gastrointestinal hemorrhage in this patient because (1) his prothrombin time rose from 12 to 33 seconds coincident with the onset of bleeding; (2) neither the patient’s partial thromboplastin time nor his heparin requirement changed over the same period of time; and (3) bleeding stopped when the patient was given vitamin K. In patients subjected to prolonged fasting, an alteration in bowel flora, or liver disease, there may be a relative vitamin K deficiency. These patients may have an exaggerated response to the administration of warfarin. Some of these factors may explain the exaggerated response to a single dose of warfarin which occurred in this patient.

The diagnosis of antithrombin III deficiency should be ruled out in patients with thromboembolic disease who do not have an obvious predisposing cause, in patients who display heparin resistance, and in women who develop thrombosis early in pregnancy or while taking oral contraceptives. Because active thrombosis may cause decreased antithrombin III levels, evaluation of these patients must be continued after the acute episode has resolved. A family history and measurement of antithrombin III levels in family members may be useful in patients suspected of defects in antithrombin III activity. Many patients with this disorder have relatives who have suffered multiple episodes of calf vein thrombosis, pulmonary emboli, or who have died suddenly.

When cessation of warfarin therapy is contemplated in patients who have had previous thromboembolic disease, the measurement of antithrombin III levels before termination of warfarin therapy and 1 week later are helpful. Any fall in antithrombin III levels below the normal range indicates a need for continued warfarin therapy in that patient.

REFERENCES
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