Hereditary protein C deficiency presenting as venous mesenteric ischemia in three successive generations

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Citation

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Abstract

Mesenteric ischemia is an important cause of short bowel syndrome and death. This is a case report of a 48-year-old man who underwent surgery for suspected acute mesenteric ischemia. The intraoperative findings included acute mesenteric venous thrombosis with gangrene of a short segment of the small bowel. Family history revealed that his father and grandfather died of a similar disease. Laboratory findings showed protein C deficiency. In this situation acute thrombosis can be prevented effectively. Thus, Screening of the first-degree relatives of patients with definitive diagnosis of inherited thrombophilia is highly recommended.

INTRODUCTION

Inherited thrombophilia is a genetic tendency to venous thromboembolism. Factor V Leiden mutation is the most common cause of the syndrome, accounting for 40-50% of cases. The prothrombin gene mutation, deficiencies in protein S, protein C, and antithrombin account for most of the remaining cases, while rare causes include the dysfibrinogenemias [1,2] . Protein C is a vitamin K-dependent protein synthesized in the liver. Protein C circulates as a zymogen and exerts its anticoagulant function after activation to the serine protease, activated protein C (aPC) [3]. The primary effect of aPC is to inactivate coagulation factors Va and VIIIa, which are necessary for efficient thrombin generation and factor X activation [3]. Heterozygous protein C deficiency is inherited in an autosomal dominant fashion. The frequency of this abnormality ranges from 1 per 200 to 1 per 500 in a healthy general population [4, 5]. The absolute risk of thrombosis among patients with protein C deficiency was evaluated and the lifetime probability of developing thrombosis compared to those with no defect was 7.3. The most common sites of thrombosis are the deep veins of the legs, the iliofemoral veins, and the mesenteric veins [6].

Up to 75 percent of patients with mesenteric venous thrombosis have an inherited thrombotic disorder [7, 8]. The available data suggest that the most common disorder is the factor V Leiden mutation (causing resistance to activated protein C), which is present in 20-40% of patients [9].

Resistance to activated protein C also occurs from mutations other than the factor V Leiden mutation in approximately 10 % of patients [10, 11] , and is an independent risk factor for venous thromboembolism [11, 12]. We report a case of inherited protein C deficiency which presented as acute venous mesenteric ischemia having affected three first relatives in three successive generations.

CASE REPORT

In October 2007, a 48-year-old man was admitted to our Emergency Department with a 3 day history of abdominal pain. It first started as a vague abdominal discomfort in epigastrum followed by colicky pain in midabdomen. The pain significantly increased in intensity, and had extended through the whole abdomen. It finally became permanent. He also suffered from nausea, vomiting and anorexia. The patient’s last defecation was in semi liquid jelly- like form. His past medical history was unremarkable and he had had no previous abdominal surgery. The family history revealed that his father and grandfather respectively died at the age of 81 and 68 because of acute venous mesenteric ischemia with massive bowel gangrene and sever metabolic disorders. Unfortunately, they had not been evaluated for the cause of ischemia.

The patient's vital signs were blood pressure 140/80 mm Hg, pulse rate 120 beats/min, respiratory rate 18 breaths/min, and axillary body temperature 36.8°c.

Physical examination revealed mild symmetric abdominal

distention, generalized tenderness most prominent in midabdomen with equivocal rebound tenderness. Laboratory tests showed an increased leukocyte count of 12000 /μL with left shift (Neut: 87%). The patient's blood urea nitrogen, creatinine, and amylase levels were normal. Also, the urinary analysis interpreted as normal. Arterial blood gas revealed a mild metabolic acidosis. The history, physical examination and paraclinic studies led to the diagnosis of peritonitis, probably due to mesenteric ischemia. Other paraclinic evaluations such as computed tomographic (CT) scan were not indicated. Before Surgery, the patient was resuscitated and intravenous heparin (10/000 unit) in combination with broad-spectrum antibiotics (cefteriaxone and metronidazole) were administered.

Intraoperative findings revealed that a short segment (40 cm) of small bowel at 70 cm from Treitz ligament was significantly edematous and gangrenous. Other organs were normal. These findings confirmed the diagnosis of acute venous mesenteric ischemia. Thus, the infarcted bowel was resected. Then a primary anastomosis was performed. Treatment with heparin (5000 u/iv/Q4h) and antibiotics was continued in postoperative period. Warfarin was started on day 7 and the dosage was gradually increased until therapeutic anticoagulation is achieved (INR = 2-3).

Eleven days later he experienced complete clinical recovery and was discharged.

The laboratory tests to detect the presence of a hypercoagulable state were obtained. It revealed protein C deficiency (protein C activity 29% [normal range 70-130%] and protein C activated resistance: 240 [>120 sec: negative]), but protein S, antithrombin III and factor V Leiden all were normal.

To confirm the hereditary nature of the disorder, other family members were investigated with the same laboratory examination. The same disorder (protein C deficiency) was detected only in his uncle.

Now, the patient is on warfarin therapy with therapeutic dose anticoagulation.

DISCUSSION

Inherited thrombophilia represents about 30-40% of mesenteric vein thrombosis [13]. Some reports concluded that deficiency of protein C has a significant role in the pathogenesis of acute mesenteric ischemia [14].

Patients with a family history of thrombosis are at increased risk for a mutation who should be evaluated for inherited thrombophilia. In this situation thrombosis most commonly occurs in deep veins of legs, the iliofemoral and mesenteric veins.

Identification of an inherited thrombophilia via screening would permit the institution of prophylactic anticoagulation. Although in the asymptomatic patients it cannot be universally justified to use prophylactic anticoagulation for a long time, there are certain potential high-risk situations including surgery and pregnancy which may necessitate consideration of prophylactic treatment [15]. In addition, individuals can be educated about precautions and early symptoms of the serious thromboses. For example, women can be made aware of the risk/benefit ratio associated with oral contraceptives and hormone replacement therapy [16]. This applies particularly to individuals who are heterozygous for protein C, protein S, and antithrombin deficiency, conditions which appear to have a three to four fold higher thrombosis risk than heterozygous factor V Leiden [6].

The initial management of acute thromboembolic disease in patients with inherited risk factors for thrombosis is not different from that in other patients (heparin anticoagulation and resection of necrotic bowel) [17]. In addition, long term warfarin therapy is indicated to prevent recurrent venous thrombosis due to thrombophilic state [18, 19].

Our case – who had deficiency of protein C – as well as his two relatives presented with acute venous mesenteric ischemia. If this patient and his family members had been screened for detection of an inherited thrombophilia after father’s death, he and his medical team would be aware of alarm symptoms of mesenteric ischemia that consequently treated with heparin before infarction of the bowels.

CONCLUSION

Inherited hypercoagulable state is an important risk factor for development of acute mesenteric ischemia. Thus, Screening of the first-degree relatives of patients with definitive diagnosis of inherited thrombophilia is highly recommended.

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