Title: Splenectomy and Proximal Lieno-Renal Shunt in a Factor Five Deficient Patient with Extra-Hepatic Portal Vein Obstruction.

Article Type: Case Report

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Corresponding Author: Dr Srinivas Prabhu Chava, MS, MCh.

Corresponding Author's Institution: All India Institute of Medical Sciences, New Delhi, India.

Order of Authors: Srinivas Prabhu Chava, MS, MCh; Sujoy Pal, MS, DNB, MCh; Supriyo Ghatak, MS; Rajat Kumar, MD, DNB, FRCP; Peush Sahni, MS, Phd; Tushar K Chattopadhyay, MS
**Abstract**

A very rare case of factor five (V) deficiency with extra-hepatic portal venous obstruction and portal hypertension with hypersplenism is presented. A 16 year old boy presented with a history of gastro-esophageal variceal bleeding, splenomegaly and hypersplenism. During preoperative workup prolonged prothrombin time and activated partial thromboplastin time were detected, which on further evaluation turned out to be due to factor V deficiency. Proximal lienorenal shunt and splenectomy were successfully performed with transfusion of fresh frozen plasma during and after the surgical procedure. At surgery there was no excessive bleeding and the patient recovered well postoperatively.
Manuscript

Introduction:

Congenital deficiency of factor V (parahemophilia) is a rare inherited disorder of coagulation which appears to follow an autosomal recessive or partially dominant pattern (1, 2, 3, 4). Although the clinical features are rather mild compared with hemophilia, any surgical procedure undertaken without replacement therapy is uniformly complicated by excessive hemorrhage (1, 2, 5). As factor V concentrate is not available, fresh frozen plasma (FFP) is the only available source of factor V at the present time. We report a boy with extra-hepatic portal venous obstruction (EHPVO), portal hypertension and upper gastrointestinal (UGI) hemorrhage who also has factor V deficiency. Although many congenital anomalies such as cleft palate, mental retardation, short stature, syndactyly, atrial septal defect, ventricular septal defect, coarctation of aorta, duplication of the genitourinary collecting system have been associated with congenital deficiency of factor V (1, 2, 3, 4), the simultaneous occurrence of factor V deficiency with EHPVO has not been described till date. EHPVO is a relatively common cause of portal hypertension in India, especially in younger age group (6, 7). The etiology of EHPVO is unclear and most are idiopathic, although many causes have been postulated: congenital, umbilical sepsis, recurrent diarrhoea, dehydration, intra-abdominal infection, malnutrition and neonatal exchange transfusion (6, 8).

Case report

A 16 year old boy was admitted to the Department of Gastrointestinal Surgery, All India Institute of Medical Sciences (AIIMS), for the management of recurrent
UGI bleeding. He had first episode of hematemesis and melena at the age of 11 years. He was managed elsewhere with 3 units of blood transfusion and underwent endoscopic sclerotherapy for esophageal varices. He had his esophageal varices obliterated with 10 sessions of endoscopic sclerotherapy. He had recurrent UGI bleeding 9 months ago with hemodynamic instability, for which he received 4 units of blood transfusion and was referred to AIIMS. Also, he complained of a progressively growing lump in the left upper abdomen since the age of 3 years. He never had jaundice, ascites or encephalopathy. There was no history of any gum bleed, epistaxis, ecchymosis or prolonged bleeding from minor cuts. His general physical examination was normal; abdominal examination revealed a 6 cm nontender smooth splenomegaly and a normal liver span. UGI endoscopy at AIIMS revealed 3 columns of grade II esophageal varices and fundal varices. Duplex ultrasound scan of the abdomen showed a normal liver, splenomegaly and obliterated portal vein with multiple collaterals (portal cavernoma) in the hilum of the liver. Splenic vein measured 12 mm. His haemogram revealed features of hypersplenism (hemoglobin- 13 gm/dl, total leucocyte count- 2300/mm$^3$, platelets- 70,000/mm$^3$). Liver function tests, other than prothrombin time (PT), were within normal limits (Serum Bilirubin- 0.7 mg/dl, S. Alkaline Phosphatase- 190 U/dl, S. Aspartate transaminase- 32 U/dl, S. Alanine transaminase- 28 U/dl). PT, activated partial thromboplastin time (APTT), and thromboelastogram (TEG) were significantly deranged (table 1). Assay for clotting factors revealed factor V deficiency (less than 20% of normal); rest of the clotting factor concentrations were normal and the screening for factor inhibitors
was negative. The possible problems during surgery with regard to excessive bleeding were explained to the parents and an informed written consent was obtained. The patient was seen by a clinical hematologist and a plan for pre and peri-operative FFP infusions with coagulation monitoring was decided upon. The patient was transfused 1500 ml of FFP the day before operation. Post transfusion the PT, APTT and TEG significantly improved (table 1), although they did not normalize. He was transfused 900 ml of FFP over 3 hours just before the start of the operation. He underwent splenectomy and proximal lienorenal shunt (PLRS) through a left thoraco-abdominal incision (8th intercostal space) using a standardized surgical technique described by us previously (7). The intra-operative blood loss was 1000 ml. During the operation he received two units of packed cells and 750ml of FFP. The operative time was 4 hours and the patient remained hemodynamically stable throughout the procedure. Postoperatively he received 600ml of FFP every 12 hours for the first 48 hours followed by 450 ml of FFP every 12 hours for the next 48 hours. There was no bleeding from the drain sites and the wounds healed well without haematoma formation. Abdominal drain and chest tube were removed on 3rd and 8th postoperative days, respectively. Patient had high spiking fever ranging between 39º and 40º Centigrade in the initial postoperative period. Although initially started on i.v. amoxicillin with clavulinic acid and amikacin as per our protocol, antibiotics were changed to teicoplanin and piperacillin-tazobactam on the 3rd postoperative day. He became afebrile on the 6th postoperative day and i.v. antibiotics were continued till 10th postoperative day. Cultures from blood, urine and drain fluids were repeatedly
sterile. An ultrasound evaluation did not reveal any subphrenic or intra-abdominal collection. He was discharged on the 12th postoperative day. At 4 months follow up the patient has had no recurrence of variceal bleeding, no evidence of hypersplenism (hemoglobin- 11 gm/dl, total leucocyte count- 6600/mm³, platelets- 325,000/mm³) and a Doppler ultrasound study showed a patent lienorenal shunt.

Discussion

Factor V (labile factor or proaccelerin) is a large single chain glycoprotein (2196 amino acids) and the gene for factor V is located on chromosome 1 q21-q25. The average plasma concentration of factor V is 6.6 µg/ml (20 nmol/L). Platelets contain approximately 18-25% of the factor V in whole blood, within α granules. Liver appears to be the primary site of factor V biosynthesis. Procofactor V does not bind factor Xa and is essentially completely inactive. The primary catalyst of factor V activation in-vivo is α-thrombin. Activation of procofactor V yields the functional form of factor Va which acts as a cofactor for the serine protease factor Xa in the prothrombinase complex and leads to rate enhancement of almost 300,000 fold in the process of factor Xa activation of prothrombin (4).

Congenital deficiency of factor five or parahemophilia is an extremely rare disorder with an estimated prevalence of 1 in 1 million (9). Less than 200 cases of inherited factor five deficiency have been reported since first described by Owren in 1947 in a woman with menorrhagia (10). It is an autosomal recessive trait (1, 2, 4), manifests clinically only in patients who inherit defective genes from both the parents. Other modes of inheritance have been implicated in certain
kindreds (2, 3). In heterozygotes, the level of factor five in plasma is approximately half of the normal and the carriers are easily identifiable by routine laboratory studies (4). Combined factor V and VIII deficiency has also been described and probably occurs more commonly than factor V deficiency alone. Factor V is an extremely labile protein and is rapidly degraded in stored blood or plasma. As no factor V concentrate or recombinant factor V is available, treatment consists of FFP. The half life of factor V is probably about 12 to 15 hours although a range from 4.5 to 36 hours has been described (1, 2, 3, 4, 5, 11). More rapid disappearance is expected during surgery due to bleeding. The clinical features are rather mild compared with hemophilia and they experience few bleeding problems in daily life but experience bleeding complications following dental extraction, severe trauma or surgery. The goal of hematologic management in the perioperative period is to maintain sufficient levels of clotting factors for a sufficient period of time to prevent bleeding complications. Conventional regimen for patients with congenital clotting factor deficiency undergoing major elective surgery is to bring patient’s plasma level to 100% just prior to surgery, maintain a level greater than 60% for 4 days and a level greater than 40% for 4 days (12). However, the safe plasma factor V level for major surgery is thought to be 25% to 33% and there are case reports where elective surgery has been successfully performed above that level. In one of the reports bleeding occurred 54 and 78 hours following dental extraction and factor V levels at these times were 24% and 18% of normal, respectively (5). Hence, it is
important to maintain adequate levels of factor V in the postoperative period. Recommended dosage of FFP replenishment in these patients undergoing major surgery is 20 ml/kg of body weight as loading dose over 3-4 h to prevent the adverse effects of volume overload followed by 10 ml/kg every 12-24 hours (9), as has been used by us. The simultaneous occurrence of factor V deficiency with EHPVO has not been described till date. We have not encountered a single case of factor V deficiency in 808 cases of EHPVO we have operated on since 1976 (unpublished data). EHPVO is a relatively common cause of portal hypertension in India, especially in younger age group (6, 7). Splenectomy and PLRS is an effective treatment (secondary prophylaxis) for this condition and is successful in preventing rebleeding in almost 90% of cases (7). This operation also takes care of the large splenomegaly and associated hypersplenism seen in these patients. As the liver function is normal in these patients, PLRS is not associated with encephalopathy. PLRS is considered a major undertaking with potential for significant morbidity and mortality, and many prefer endoscopic sclerotherapy (EST) for the control of esophageal varices. These patients usually have multiple collateral vessels in the lienorenal and gastrosplenic ligaments, splenic attachments to the diaphragm and in the retroperitoneum around splenic and renal vessels. As mobilization of the spleen and splenic vein may cause significant hemorrhage, painstaking ligation of these collaterals during splenectomy and meticulous dissection of often thin walled, distended and friable splenic vein from pancreatic tail is required. However, in centers with substantial
experience the complication rate is low; our own elective mortality rate for PLRS is 0.7%, rebleed rate is 11% and encephalopathy rate is zero (7). Moreover, PLRS is a one time procedure for EHPVO which treats the painfully enlarged spleen, hypersplenism and portal hypertension at the same time. It eliminates the risk of variceal bleeding immediately whereas EST takes an average of 8 sittings to obliterate varices over many months (13). The patient remains at risk of rebleed until the varices are obliterated. Also, with EST the portal system is not decompressed and these patients are at 16% risk of variceal recurrence in esophagus (13) and 11% develop new varices in stomach (14), with consequent high rebleed rates, as has happened in our patient following EST. These patients are also at risk of development of ectopic varices and bile duct varices with portal biliopathy following EST. Hence there is a strong case for decompressive shunt surgery in these EHPVO patients particularly in Indian conditions where access to tertiary medical care and safe blood banks is limited. A patient with coagulation disorder is more likely to be at risk of recurrent life threatening gastrointestinal bleed and blood borne viral diseases and consequently more likely to benefit from an effective portal decompressive procedure. Our experience with this case suggests that this surgical procedure can be safely undertaken in clotting factor deficient patients with non cirrhotic portal hypertension if meticulous surgical hemostasis is achieved at operation and the deficient factor is adequately replaced in the perioperative period until wound healing has sufficiently progressed to prevent further bleeding.
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