Journal of Blood Research & Hematologic Diseases

Review Article A SCITECHNOL JOURNAL

EHPVO and Splanchnic Vein Thrombosis

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Abstract

Extrahepatic portal venous obstruction (EHPVO) is one of the vascular diseases of liver, characterized by obstruction, cavernomatous transformation of portal vein with thrombosis being the central event. It may or may not involve other splanchnic veins. Portal vein thrombosis with or without the cavernoma formation may occur secondary to cirrhosis, malignancies, surgeries etc. However, the term EHPVO is regarded a separate entity. It is mostly seen in younger generation, especially of Asian descent. Two issues regarding the EHPVO need special mention one the etiology and second the management. Management of EHPVO patients is still an evolving area with difference of opinion regarding many issues including the anticoagulation seen among the treating physicians. There are no concrete guidelines as to how best we can manage these patients. This review emphasizes on these evolving areas.

Keywords

Cirrhosis; Portal vein thrombosis; Thrombophilia

Introduction

It was in 1860s that portal vein thrombosis was first recognized by Stewart and Balfour in a patient who presented with splenomegaly and varices. The term cavernoma was coined by Kobrich to highlight the spongy appearance of portal vein [1]. Exact epidemiological figures regarding PVT have not been validated. An autopsy based study in USA and Japan reveals a prevalence of 0.05 to 0.5% of PVT. Prevalence of PVT studied by Ogran et al. seen on autopsy series is 1% [2]. In western world, 5-10% of portal hypertension is caused by PVT and in developing world the figure is 40%. In children 80% of portal hypertension cases are due to EHPVO [3]. Globally EHPVO is the second common reason for portal hypertension after cirrhosis. Incidence of PVT among cirrhotic patients ranges from 0.6% to 64.1% [4]. Latest imaging techniques detect symptomatic as well as asymptomatic cases of portal vein thrombosis and EHPVO with few recent retrospective studies showing an imaging prevalence of 1.7%. Digging its etiology especially in non-cirrhotic and non-malignant EHPVO cases and managing these patients is really a challenging task.

Pathophysiology

Consequent upon the initial thrombotic event in the portal vein, two types of rescue preserve the liver function viz, arterial rescue and venous rescue. Venous rescue gets formed in the form of collaterals. This neo-vascularization or neo-angiogenesis takes around four to six weeks [5,6]. The thrombosed portal vein transforms into a fibrotic cord with the collateral venous channels forming what is known as portal cavernoma. This structure surrounds structures like bile duct, gall bladder, pancreas, gastric antrum and duodenum [7,8]. As a result of this a hyperdynamic circulatory state with low resistance is established. On hepatic catheterization, HVPG is normal; however, direct portal pressure measurements and splenic pulp pressure measurements along with esophageal variceal pressures are increased. This gives a state of pre hepatic portal hypertension where liver functions usually remain normal whereas indocyanine green (ICG) clearance and galactose elimination capacity is slightly decreased.

Etiology with Etio Pathogenic Facts

Thrombophilic conditions account for 60% and local factors account for 30% of PVT cases with more than one factor usually responsible for thrombosis [9-16]. 30% of PVT cases remain idiopathic despite extensive workup. Once cirrhosis and malignancy is ruled out, evaluation regarding the thrombophillic states including primary myeloproliferative disorder should be initiated. One of the prospective studies showed that primary MPD accounts for over half of the cases of idiopathic group [17]. In these patients, occult or latent MPD is picked up by the presence of JAK2V617F mutation or Endogenous Erythroid Colonies (EEC) formation in the absence of typical features of full blown MPD [18,19]. Few of the drawbacks of EEC assay are lack of standardization, false positive and false negative results. JAK2V617F mutation analysis is done by PCR technology from peripheral blood. Morphological examination may show dysplastic megakaryocytes. Mutations in TAFI gene that is thrombin activitable fibrinolysis inhibitor, has recently been described as a risk factor for PVT [20]. Once occult MPD is ruled out, investigate for other thrombophillic states like antiphospholipid syndrome (IgG, IgM anticardiolipin antibodies, lupus anticoagulant), PNH (flow cytometry), Hyperhomocysteinemia (homocysteine levels, MTHFR gene mutation), Factor V Leiden mutation, Prothrombin gene mutation, Protein S (PS) and Protein C (PC) deficiency. Factor V Leiden mutation is the most common thrombophilia leading to PVT followed by PC deficiency [21]. Apart from the systemic risk factors, the local factors responsible are:- Abdominal cancers, Inflammatory lesions like diverticulitis, pancreatitis, Inflammatory bowel disease (IBD), Cytomegalovirus (CMV) infection, Surgery, Transplantation, Vascular Procedures/Tips.

In children, Sarin et al. attempted to assess the etiology for PVT. They showed that in majority of the children cause could not be identified, however, in children where they could the major cause was the injury to umbilical vascular system (oomphalites, umbilical vein catheterisation) or intrabdominal and umbilical sepsis. However, a coexistent prothrombotic state could not be ruled out [22].

Clinical Features

In a large Indian series by Sarin et al. over 500 patients of EHPVO were studied [23] (Table 1).

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Table 1: The clinical features are summarized as.

	%
Mean age (yrs.)	19.4
Sex (M/F)	1:0.5
Hematemesis/malena	77%
Mass Left upper quadrant	20%
Transient Ascites	23%
Jaundice	23%
Esophageal varices	93%
Portal gastropathy	60%
Portal biliopathy	90%

Clinical Features of EHPVO Patients

EHPVO can present in children as early as 6 weeks after birth or in adulthood. Clinical features depend on age of presentation and whether the onset is acute or chronic. It commonly presents as hemetemesis usually massive or malena. Most of the times, GI bleed is recurrent and can occur from esophageal gastric varices, ectopic varices or may present with obscure GI bleed or bleeding from the biliary tract [24]. Other common features include anemia and splenomegaly with or without hypersplenism (5 to 10 %). Sometimes the splenomegaly becomes massive. 10 to 20 % of children can have transient ascites post-surgery or GI bleed [25]. Ascites can also be seen in adults especially if the disease is long standing and associated with decline in liver functions. Portal biliopathy is a common manifestation of EHPVO resulting predominantly from the compression of paracholedochal collaterals on bile ducts, causing their strictures and focal narrowing. It can present with jaundice, gall stones, CBD stones cholangitis, secondary biliary cirrhosis and hemobilia [26,27]. Due to the decrease in hepatotropic growth factors, IGF-I and IGF-BP3, EHPVO patients can come with growth retardation and short stature [28,29]. Immune defects occur due to decreased cell mediated immunity because of T cell sequestration by spleen and from some unknown factors regulating lymphocytosis.

As mentioned earlier that PVT can present in acute or chronic form. The development of symptomatology depends on extent of portal vein thrombosis, rapidity of its development and concomitant factors. Acute PVT may present with sudden onset of abdominal pain, fever and other nonspecific abdominal symptoms including nausea, vomiting, and diarrhea [30]. Signs of portal hypertension are typically lacking in non-cirrhotic patients. In chronic PVT patients there is portal cavernoma formation with features of portal hypertension like splenomegaly, varices with or without bleeding.

EHPVO Diagnosis

The main diagnostic modality for EHPVO is imaging which include a Doppler USG or CT portovenography. Liver function tests and liver biopsy are usually normal. Endoscopy reveals esophageal, gastric or anorectal varices. In recent thrombosis, Colour Doppler Ultrasound shows no color flow or doppler signal within portal vein, and absence of cavernoma and in chronic there is no color flow in portal vein and hepatopetal signal within the cavernoma or varices. Doppler ultrasound has a sensitivity of about 90% for recognizing PVT cases [31,32]. However, due to lack of expertise, low clinical suspicion, different patient characteristics, it may at times fail to detect these cases.

Computed tomography and magnetic resonance imaging have better accuracy than Doppler ultrasound for diagnosing PVT, and in addition it looks out for concomitant diseases and also rules out alternative diagnoses.

Site of PVT

Type 1: only trunk

Type2: only branch 2a(one), 2b(both branches)

Type3: Trunk and branches

Prognosis

The natural history of EHPVO depends upon the presence or absence of cirrhosis or malignancy. In non-cirrhotic and non-malignant EHPVO, the course is relatively benign. Morbidity is related to GI bleed, thrombosis extension, biliopathy and hypersplenism. In a large single center study of 832 patients with splanchnic thrombosis at any site, the 10 year overall survival rates were 60% [30]. In another study, the 10 year survival of non-cirrhotic non-malignant EHPVO was 81% [33]. In a retrospective study of 173 patients of PVT, the overall survival was 69% at 1 year and 54% at 5 years and after the exclusion of cirrhosis and malignancy these rates raised upto 92% and 76% respectively [34]. In another retrospective study of 136 non cirrhotic non-malignant EHPVO patients, 84 of whom had received anticoagulation the incidence of thrombosis was 5.5/100 patient-years and incidence of GI bleed was 12.5/100 patient-years [35]. In one of the prospective study, 38% recanalization rates were achieved with anticoagulation [36], while as in a retrospective study of 120 patients half of whom had received anticoagulation, the risk of recurrent thrombosis was 3% at 1 year, 8% at 5 years and 24% at 10 years [37].

Treatment

The management of PVT/EHPVO needs a multidisciplinary approach which involves a hematologist, a hepatologist/gastroenterologist, surgeon and interventional radiologist.

The management of these patients is divided into following sections.

Anticoagulation

Because of the paucicity of prospective trials, there are no concrete anticoagulation guidelines regarding the management of these patients, especially the asymptomatic chronic EHPVO group. In recent EHPVO patients who are symptomatic, low molecular weight heparin followed by oral anticoagulation should be started immediately. In recently detected asymptomatic patients, anticoagulation may also be considered. In chronic EHPVO patients the role of anticoagulation is still not clear. However, in patients with prothrombotic state, therapy may be considered. Before starting anticoagulation one has to be cautious of coexisting coagulopathy, thrombocytopenia and variceal status. Ageno W et al. suggested following guidelines for anticoagulation [38].

¬ In non-cirrhotic symptomatic SVT patients, consider full therapeutic dose LMW heparin followed by oral anticoagulation.

¬ In cirrhotic symptomatic patients, consider full therapeutic dose LMW heparin after carefully assessing the associated bleeding risk points like varices, thrombocytopenia etc. In these high risk situations one may consider decreasing the dose of LMW heparin to half and delay oral anticoagulation.

¬ In malignancy associated SVT, use full therapeutic dose LMW heparin for 1 month and then reduce it to 75% of the original dose for 3-6 months

¬ If platelet count is between 30000-50000/cu.mm, reduce the dose of LMW heparin by 50%. If platelets are <30000/cu.mm, abstain from using anticoagulation.

¬ If there is associated renal failure, use unfractionated heparin or reduce the LMW heparin dose by 50% with anti Xa monitoring. If creatinine clearance is <15 ml/min, abstain from using anticoagulation.

¬ If SVT is detected incidentally, then apply same guidelines as proposed for symptomatic patients except if the thrombosis is nonocclusive, not recent and limited to single vein segment, absence of permanent risk factors like major prothrombotic states.

¬ The use of thrombolytic agents may be restricted to few selected patients with severe presentation and less risk of bleeding e.g in associated mesenteric vein thrombosis with intestinal ischemia.

The potential benefits of anticoagulation may be improved survival, reduced recurrence rates, improved recanalization, and decrease in portal pressures with reduction in variceal bleeding. Because of the heterogeneity of patients, the risk and benefits should be weighed on individual basis.

Portal biliopathy

MRCP is the best investigation to identify portal biliopathy. No treatment is required if asymptomatic. For choledocholithiasis, endoscopic procedures like ERCP are performed. For CBD stricture, treatment includes endoscopic stenting, portosystemic shunting or hepaticojejunostomy [39].

Control of bleeding

For non-bleeding varices, data is insufficient as to which is the best modality of primary prophylactic treatment, beta blockers or endoscopic therapy. Endoscopic treatment remains the best choice for control of acute variceal bleeds as well as for the secondary prophylaxis. In pediatric EHPVO patients, Mesenteric left portal vein bypass (REX Shunt) may be performed if bleeding becomes difficult to control [39].

Shunt surgeries

Mesenteric left portal vein bypass (REX shunt) may be an option for patients with complications of EHPVO especially in children. The indications are recurrent variceal bleeding despite endoscopic therapy, presence of ectopic varices not amenable to endoscopic treatment, symptomatic hypersplenism, massive splenomegaly, growth failure and portal biliopathy [39].

Conclusion

In the absence of robust prospective studies, management of chronic PVT/EHPVO patients remains a challenge. Further large scale studies are needed to elucidate the mechanisms operating for non-cirrhotic, non-malignant EHPVO patients and newer evidence based guidelines on treatment of such patients particularly the asymptomatic ones needs to be established.

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