Original Research Article

Clinical presentation of pediatric extrahepatic portal vein obstruction: An observational and retrospective study in a tertiary care center in eastern India

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Abstract

Background: Extrahepatic portal vein obstruction (EHPVO) is an important cause of upper gastro intestinal bleeding in pediatric age group. In the majority of cases, the cause remains un-identified although it has diverse etiological factors. Objective of this study was to evaluate the clinical presentation, etiology, laboratory parameters, management and outcome of children admitted with EHPVO.**Materials and methods:** This was an observational and retrospective study done on thirty diagnosed cases of portal hypertension with EHPVO, selected by scrutinizing hospital data. Data items concerning patients' demographics, laboratory and radiological workup, endoscopic and surgical procedures, growth and development, were collected from the patients' clinical charts. Patients' clinical presentation and etiology of EHPVO with management and outcome were analyzed. Statistical analysis was performed using SPSS version 19.0.**Results:** Out of 30 patients, 21(70%) were males. Median age was 4year 8 months. History of umbilical catheterization was present in six cases and history of omphalitis was present in two patients. The predominant presenting symptom was hematemesis (15 patients, 50%). Twenty-two patients (73.3%) had splenomegaly. Of 16 patients who underwent liver biopsy 9 had histological activity index stage of 1/6. Twenty-seven (90%) had esophageal varices on endoscopy while ten patients had gastric varices. Only one case underwent splenectomy due to severe pancytopenia. Endoscopic variceal band ligation was done in twenty-six patients (96.3%) with no post -procedural complication. Endoscopic retrograde cholangiopancreatography was performed in four patients (14.3%) due to portal biliopathy. Common bile duct stenting was performed in all four patients. Of them, one patient underwent splenorenal shunt operation for indication of hemobilia. **Conclusion: -** EHPVO is a not so uncommon disease in Bihar. The etiological factors are still not known in most cases. However, endoscopic and surgical treatment options can ensure a good long-term prognosis.

Keywords: EHPVO, Esophageal varices, Gastric varices, Endoscopic retrograde cholangiopancreatography (ERCP), Endoscopic variceal band ligation, Splenectomy

Introduction

The extrahepatic portal vein obstruction (EHPVO) is an important cause of portal hypertension in both children and adults. Extra hepatic portal vein obstruction is defined as: (i) Extrahepatic occlusion of the portal vein, with or without involvement of the intrahepatic portal veins, splenic vein or superior mesenteric vein. (ii) It is frequently characterized by the presence of a portal cavernoma. (iii) Isolated occlusion of the splenic vein or superior mesenteric vein do not constitute EHPVO and may require distinct management approaches. (iv) Portal vein obstruction associated with chronic liver disease or neoplasia does not constitute EHPVO. [1,2]

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It is an important cause of upper gastro intestinal bleeding in pediatric age group. In the majority of cases, the cause remains un-identified although it has diverse etiological factors. Infections, toxins, and immunologic, prothrombotic and genetic disorders are possible causes in IPH, whereas prothrombotic and local factors around the portal vein led to EHPVO. [1]Although the mortality due to variceal bleeding has been decreased due to effective endotherapy, significant morbidity is seen due to hypersplenism, growth retardation, impaired quality-of-life and portal biliopathy. [3]There is scant information on the clinical presentation, etiology, management and outcome of patients with EHPVO in India. We aimed to evaluate the clinical presentation, possible etiological factors, management and outcome of patients presenting to our hospital with EHPVO.

Materials and methods

This was an observational and retrospective study on thirty (n=30) diagnosed cases of portal hypertension due to EHPVO. All the cases were selected by scrutinizing hospital data from Pediatrics and

Gastroenterology Department in IGIMS, Patna during the period from June 2018 January 2020.

Inclusion criteria

1. The hospital data was scrutinized for selection of cases based on one of the following diagnosis:EHPVO, portal biliopathy, splenectomy, gastrointestinal bleed, and splenomegaly and shunt surgery.
2. The patients of either gender and age less than 16 years were included.

Exclusion criteria

Patients with portal vein obstruction and portal hypertension associated with chronic liver disease and patients without portal vein obstruction were excluded from the analysis.

Data items concerning patients' demographics, laboratory and radiological workup, endoscopic and surgical procedures, growth and development, were collected from the patients' clinical charts. Patients' clinical presentation and etiology of EHPVO with management and outcome were analyzed.

Statistical analysis

Statistical analysis was performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). All continuous variables were represented by mean ± standard deviation and categorical variables by frequencies and percentages.

Results

Thirty five children were included in the study but complete clinical data of five children were missing. Hence total of 30 patients were included in the analysis, out of which 21 (70%) were males while females were 9 (30%). The age at presentation was 4.8 ± 4.2 years (median 3 years; range: 1 month -14years). Majority of patients were below 14 years (80%).

Table 1: Clinical characteristics of patients with EHPVO at presentation

Patient Characterstics	Values
AGE	4.8 ± 4.3 Years
Gender (n %) Male Female	 21(70) 9(30)
Term (n %) Preterm	27(90) 3(10)
Perinatal Events: (n %) Umbilical Catheterisation Omphalitis SEPSIS, NEC	 6 (20) 2(6.6) 1(3.3)
Hematemesis, (n %)	15(50)
Malena, (n %)	2(6.7)
Jaundice, (n %)	3(9.9)
Splenomegaly, (n %)	22(73.3)
Liver Size, (n %)	12.3 ± 2.8cm
Spleen Size, (n %)	15.1 ± 2.8cm

Sd: Standard Deviation

Table 1 showed the clinical characteristics of patients. A review of the growth chart (for weight) was carried out in 30 eligible patients (<16 years of age). 10 (33.3%) were below the 25th percentile while rest showed normal growth development.All patients had undergone ultrasound (US) of the abdomen (conventional and Doppler) for the confirmation of diagnosis of EHPVO. Computed tomography (CT) was performed in 16 patients while magnetic resonance imaging (MRI) portogrphy was performed in two patients. In CT scan findings, along with cavernous transformation, portal vein thrombosis (PVT) was identified in four patients (20%) while in remaining portal vein was not visualized. In magnetic resonance (MR) portography, both the patients had cavernous transformation. The most common presenting symptoms were upper gastrointestinal bleed manifesting as hematemesis (15 patients, 50%) while two patients (6.7%) had melena only. In twenty-two patients (73.3%), splenomegaly was the only finding at presentation. Jaundice was presenting feature in three patients (9.9%) while diarrhea was present in one patient (3.3%).Liver biopsy was performed in 16 (53.3%) patients. There was no evidence of cirrhosis in any patient. Majority of patients had histological activity index stage of 1/6 (30%) as staged by pathologists.One patient had a history of omphalitis, and another one had been treated for pulmonary tuberculosis in the past. Detailed prothrombotic profiles were available in 24 patients, including one patient has low level of Protein C, S deficiency, none had Factor V Leiden mutation. In more than fifty percent of patients, no cause was identified.

Table 2: laboratory parameters of patients with EHPVO at presentation

Laboratory Parameters	Values
Haemoglobin(g/dl), mean±SD	8.5 ± 3
TLC, mean ± SD	5.1 ± 3.5
Platelet per mm3, mean ± SD	102 ± 91.7
PT , mean ± SD	13±2.1
INR, mean ± SD	1.2 ± 0.3
Total Bilirubin (mg/dl),mean ± SD	2.8 ±6.8
ALT(U/L), mean ±SD	60.1± 139.3
AST (U/L), mean ± SD	62.3± 11
GGT (U/L), mean ± SD	41.3 ± 12.4
Alkaline Phosphatase (U/L), mean ± SD	230.3± 270.1
Pancytopenia	6 (20)
Thrombotic profilen (%) Protein C, S deficiency Factor V Leiden mutation None	26(86.6) 1 0 25

Liver Biopsy:	
Stage, n (%)	
Stage 0/6	3(10)
Stage 1/6	9(30)
Stage 2/6	3(10)
Stage 3/6	1(3.3)
Not done	14(46.7)

Ishak modification of the Knodell HAI staging system
TLC: Total leukocyte count,PT:Prothrombin time, INR: International normalization ratio,ALT:Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma glutamyl transferase, SD: Standard deviation, HAI: Histological activity index

Table 2 shows laboratory investigations of patients with EHPVO at presentation. All patients had undergone upper gastrointestinal endoscopy.Three patients (10%) had no esophageal varices. Esophageal banding was done in 26 patients (76.7%) while in remaining one patient sclerotherapy was performed.No complications of sclerotherapy or banding were reported. Six patients (20%) had bleeding episode during follow-up. Along with esophageal varices ten patients (33%) had gastric varices and it was dealt with N-acetyl butyryl injection.

Table 3: Endoscopic and surgical procedures on patients with extrahepatic portal vein obstruction

Upper GI endoscopy,n (%)	
1. Oesophageal varices, n (%)	27 (90)
Grade 1	1 (6.7)
Grade 2	6 (20)
Grade 3	11 (36.6)
Grade 4	9 (30)
2. Gastric varices, n (%)	10 (33.3)
EVBL, n (%)	26 (96.3)
EST, n (%)	1 (3.7)
ERCP	4
CBD stone	1
CBD stricture	4

EVBL:Endoscopic variceal band ligation,EST:Endoscopic sclerotherapy,CBD:Common bile duct, ERCP: Endoscopic retrograde cholangiopancreatography

Table 3 shows the details of endoscopic and surgical procedures done on these patients.

Endoscopic retrograde cholangiopancreatography (ERCP) was performed in four patients (13.3%). In two patients, it was done at the time of presentation while in additional two patients, it was performed during follow-up. One patient had common bile duct (CBD) stone while all four had CBD stricture. CBD stenting was performed in all four patients.

In only one patient, spleno-renal shunt operation was performed for the indication of hemobilia. Three patients later underwent splenectomy due to severe pancytopenia. One patient died, due to sepsis by opportunistic organisms following splenectomy.

Discussion

Extrahepatic portal vein obstruction is one of the common causes of non-cirrhotic portal hypertension in developing countries. [3] Although 30% of variceal bleeders have EHPVO, [4]it does not account for patients' mortality.[5] Therefore, management of EHPVO is not limited to treatment of varices but it also involves treatment of significant morbidities like growth failure, portal biliopathy, hypersplenism and its complications, etc.There are various speculated etiologies of EHPVO including trauma, sepsis, umbilical vein catheterization, dehydration, myeloproli-ferative disorder, coagulation defects, congenital anomalies of portal vein, malignancy,and cirrhosis.[4,5]Hypercoagulable state due to deficiencies of protein C, protein S,antithrombin III, and prothrombin or excess production of procoagulants due to factor V Leiden or gene mutations have been associated as predisposing factors of venous thrombosis in adults. [3,6] While studies in children reported that anticoagulant deficiencies are common but not inherited. [6,7] Even with extensive workup, it is postulated that in patients with EHPVO, about 70% of cases remain idiopathic, [8] which is in accordance with our study.

In our study, in 50% of patients, no cause of PVT was identified, although Janus Kinase mutation was not performed due to un-availability of test, none of our patient had any evidence or history of trauma or malignancy at the time of presentation.One out of 24 patients were found to have anticoagulant deficiencies, in which Protein C deficiency was found in only one patient, which was consistent with the study of Sharma et al. [6] Anticoagulation analysis was not performed in their parents to determine the genetic origin as its role is not well-defined in pathogenesis of EHPVO. [5]

Keeping in view the debatable role of anticoagulation therapy in adults and no role in children, none of our patients was offered therapy. [5]EHPVO is between 35% to 78% of cases idiopathic, [9-16]so that a greater number of studies seeking to identify the etiology are required, especially those aimed at detecting prothrombotic states.Although most of the patients with EHPVO present with variceal bleed. [5] Bleeding from non-gastrointestinal sites has also been reported. [8] Other presentations include hypersplenism, abdominal pain due to splenic infarcts and jaundice due to portal biliopathy. Hemoperitoneum, hemobilia, bowel ischemia, and mesenteric vein thrombosis are rarely observed.In our study, patients mostly presented with hematemesis (50%) and splenomegaly was seen in twenty-two patients (73.3%). EHPVO should be suspected in all pediatric patients presenting with unexplained gastrointestinal bleeding and splenomegaly. Shneider[17] evaluated pediatric series with diagnosis of extrahepatic portal hypertension and reported that 46% to 90% of them presented with gastrointestinal hemorrhage and 25% presented with splenomegaly, and concluded that "the combination of gastrointestinal hemorrhage and splenomegaly should be suggestive of portal hypertension until proven otherwise".

Jaundice was present in three patients, out of which two had portal biliopathy while one had sepsis. In our study, only one patient developed hemophilia during the course of his illness and had undergone splenorenal shunt for its management.On clinical examination, patients with EHPVO usually have no stigmata of chronic liver disease. Ascites was present in 13–21% of cases[8] which was consistent with our study where ascites was present in

four patients (13.3%) at the time of presentation.Laboratory parameters in our study revealed anemia in 85%, which could be explained by gastrointestinal bleeding or hypersplenism. The latter can account for leukopenia and thrombocytopenia found in our cases. These cytopenias warranted us in the early years of our experience to refer children with EHPVO for splenectomy. This policy was abandoned later; supplementation with folic acid and multivitamins (particularly vitamin B complex) and iron therapy, when required, is provided to all cases. Although patients with EHPVO may manifest thrombocytopenia secondary to hypersplenism, these platelets function almost normally. [18]Some derangement of liver functions in the form of mild elevation of transaminases or hypoalbuminemia was noted in a number of cases. This may be attributed to the prolonged reduction of portal flow. 19,20]Elevated alkaline phosphatase[21] and γ-glutamyl-transpeptidase will raise the suspension of portal biliopathy. One case had gall bladder stones, which is one of the findings related to portal biliopathy. [22]For the diagnosis of EHPVO, Doppler US is used as the first-line radiological investigation. CT abdomen or MR portography not only provide diagnosis but also delineate anatomical pathway for shunt surgery. In patients with EHPVO, esophageal varices are reported to be found in 80–90% of cases. [5]and gastric varices in 31–44%. As compared to cirrhotic cases, the esophageal varices are often larger [8] the results of our study are consistent with the above-mentioned findings. Esophageal varices were found in 90% of the study population, and the majority of patients (20 patients, 66.6%) had varices of grade III and IV. Gastric varices were also present in 33% of patients.Conventional management of EHPVO is focused on control of variceal bleed followed by secondary prophylaxis. However, the prognosis is better compared to patients with chronic liver disease due to better liver reserve. Although endoscopic sclerotherapy (EST) and endoscopic variceal band ligation (EVBL) have comparable efficacy in variceal eradication [8] the data on EVBL in children are sparse [24] Therefore, EST is considered a conventional modality in children for treatment of esophageal varices. [24]In our study, due to available expertise, varices in children were dealt with EVBL and EST was performed in one patient only and no post procedure complications were observed.Portal biliopathy refers to abnormalities in biliary ductal walls due to portal hypertension. [25]Its frequency in adults is 80–100% while it is symptomatic in only 5–38% patients. [5,25] Poddar et al [26]reported 13 cases of portal biliopathy in children with only one patient being symptomatic.The suggested mechanisms of the high incidence of portal biliopathy in patients with EHPVO are prolonged continuous external compressions by portal collaterals, ischemic injury to biliary wall leading to stricture or both. [5, 8]In our study, cavernous transformation was present in all patients but only 2 presented with jaundice at the time of presentation while two patients developed jaundice later in the follow-up period.Biliary changes due to portal biliopathy lead to various ominous consequences such as cholangitis, choledocholithiasis, and secondary biliary cirrhosis. [27] Even with vigorous management, 4–10% of patients die due to these complications. [27,28] Likewise in our study, only one unfortunate patient died due to cholangitis secondary to portal biliopathy at the time of presentation.Endoscopic retrograde cholangio pancreato-graphy is a useful modality for the diagnosis of portal biliopathy, but as the majority of patients are asymptomatic at the time of presentation, it is reserved for cases where intervention is needed. [25] Depending on the requirement, patients can undergo endoscopic sphincterotomy, stent or nasobiliary placement, stone extraction, mechanical lithotripsy, or stricture dilatation. [27] Although MR cholangiopancreatography coupled with portography allows visualization of the biliary tree similar to ERCP, but in some cases, it gives false diagnosis of obstruction. [25] Of 30, four of our patients underwent ERCP, and all had stricture dilatation and stent placement, but only two of them had stone extraction.

Extrahepatic portal vein obstruction leads to growth retardation in children, and it has been reported to be about 51–54.5%. [29,30] The postulated mechanisms include portal enteropathy induced malabsorption and/or impaired growth-factor synthesis from liver due to shunting of blood away from it.In our study, only 10 patients (33.3%) were below 25th percentile for growth development. The low prevalence can possibly be due to the fact that in 8 (26.7%) patients, growth chart was not available.Shunt surgery is chiefly indicated when endotherapy fails to control variceal bleeding or in cases of delayed complications of portal biliopathy. Other indications include growth failure, massive splenomegaly, impaired quality-of-life and ahead of bilioenteric anastomosis. [8,27] Although in the era of endoscopic management, emergency shunt surgery is infrequent, but in this study, one patient underwent splenorenal shunt surgery due to the development of hemobilia. In this case, hemostasis was temporarily achieved with covered self-expandable metallic stent deployed in the CBD.

Overall, the prognosis of patients with EHPVO after control of variceal bleeding is almost 100% for the long-term survival [31] Even, the mortality rate with uncontrolled variceal bleeding is <5%. [5]

Conclusion

Extra-hepatic portal vein obstruction is the common cause of non-cirrhotic portal hypertension. Due to effective endoscopic and surgical management, the mortality from variceal bleeding has diminished markedly. Early and accurate diagnosis and appropriate treatment are the key factors for the improved prognosis.

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