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Original Research Article

A study on demographic and clinical profile of children with extra hepatic portal venous obstruction and with special reference to thrombophilic factors

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ABSTRACT

Background: Extra-hepatic portal vein obstruction (EHPVO) due to portal vein thrombosis is an important cause of portal hypertension in several region including India. The cause of thrombosis in these patients remains unclear. Objective of the study was to study the demographic features, etiology, clinical, laboratory findings with special reference to thrombophilic factors like protein C, protein S and antithrombin III deficiency in children with EHPVO.
Methods: The prospective analysis of 62 patients of EHPVO (<14 years of age) was done in the Department of Hepatology, SCB medical College, Cuttack. After detailed history, clinical examination, Ultrasound abdomen /color Doppler and Upper GI endoscopy, the subjects were analyzed for any deficiency of thrombophilic factors like protein C, protein S and antithrombin III.
Results: A total of 62 patients (37 Male, 25 Female) with mean age of 8.3+3.1 years were studied. Growth retardation was present in the form of wasting (alone) 20.9%, stunting (alone) 25.8% and both wasting and stunting was found in 9.8% cases. History of neonatal, umbilical sepsis and umbilical vein catheterization was found in 15.9% and 10.2% of cases respectively. Haemorrhage from oesophageal varices was prevalent symptoms in 85.9% patients. Splenomegaly was found in 91.9% patients and ascites in 9.4% patients. 47 patients studied for protein C, S and antithromibin III. 14 patients were found to have thrombophilia: protein C deficiency in 9, protein S deficiency in 8, Antithrombin III deficiency in 6.
Conclusions: The etiology of EHPVO in the majority of patients remain still unclear. It is commonly associated impaired somatic growth. The risk of EHPVO increases in the presence of thrombophilia, resulting from deficiency of naturally occurring anticoagulant proteins like Protein C, Protein S and Antithrombin III.

Keywords: Extrahepatic portal venous obstruction, Thrombophilia

INTRODUCTION

Extrahepatic portal veins obstruction (EHPVO) is a vascular disorder of the liver. It is defined by obstruction of the extra hepatic portal vein with or without involvement of the intrahepatic portal veins or splenic or superior mesenteric veins. Isolated occlusion of the splenic vein or superior mesenteric veins dose not constitue EHPVO.[1] The etiology of extrahepatic portal vein obstruction is highly diverse. Exchange transfusion, omphalitis, sepsis, umbilical catheterization, congenital abnormalities and hypercoagulable states are some of the suspected reasons. Prothrombotic disorders include deficiencies in the naturally occurring anticoagulants

(Protein C, Protein S and Antithrombin III) and factor V leiden and prothrombin gene mutations. EHPVO in childhood is most often chronic and presents with features of variceal bleeding and lump in the abdomen caused by splenomegaly. Imaging is the mainstay for the diagnosis of EHPVO. Ultrasound is a reliable non-invasive technique with a high degree of accuracy for the detection of portal cavernoma and is the investigation of choice.

The aims of this study were to assess demographic features, etiology, clinical laboratory findings with special reference to thrombophilic factors like Protein C, Protein S and Antithrombin III deficiency in children with EHPVO.

METHODS

A total of 62 children (upto 14 years) with features of EHPVO who attended GE OPD or hospitalized during January 2014 to June 2015 were included. The diagnosis of EHPVO was made on the basis of clinical features of portal hypertension, including gastrointestinal bleeding and splenomegaly, as well as ultrasonographic finding of portal cavernoma without evidence of chronic liver disease.

The anthrompometric data including weight was measured in light clothing without shoes to the nearest half kilogram on a calibrated digital scale. The height was measured in standing position and recumbent length was measured in younger children to the nearest half centimetre. Wasting was calculated as weight for height. Less than 80% of expected (Median (50^{th} percentile of CDC Standards)] weight for height taken as wasted. Stunting was calculated as height for age. Less than 90% of expected [Median (50^{th} percentile of CDC standard)]. Height for age taken as stunted. Routine investigations like complete blood count and liver function tests were done in all patients. Endoscopy was performed using video endoscope (Olympus GIF-V-70, Olympus Corporation, Tokyo, Japan) in all cases to look for esophageal varices, gastric varices and portal hypertensive gastropathy. Esophageal varices were graded (I-IV) according to the classification of Conn and Gastric varices were classified according to Sarin's classification.[2,3]

Grading of portal hypertensive gastropathy (PHG) was nil, mild, severe according to the description by Taor et al.[4] Either endoscopic sclerotherapy (EST) with sclerosant 3% phenol or Endoscopic varieceal ligation (EVL) with multiband ligator was done in patients presenting with variceal bleed. Repeated endoscopic procedure like EST, EVL done in every 7-14 days till eradication of varices. Thrombophilia testing was performed including Protein C, Protein S and Antithrombin III done in 47 cases. Protein C and Protein S was studied with ZYMUTEST Protein C & S kit (HYPHEN Bio Med, France), a complete ELISA kit for the assay of human Protein C and Protein S in citrated plasma. Antithrombin III was estimated by DIFFU-PLATE (Bio Cientifica SA, Argentian) a radial immunodiffusion for the determination of antithrombin III in serum.

Written informed consent was obtained from the patients or their parent/guardian as appropriate.

Statistical analysis

The statistical analysis was done by SPSS (version -21.0). Mean + SD was calculated for continuous data, frequency and percentage were calculated for qualitative data. The comparison between two groups (deficiency and non-deficiency of protein C, S and antithrombin III) done by independent 't' test for parameteric continuous data. The p-value <0.05 was considered as significant.

RESULTS

A total of 62 patients (37 M, 25 F, mean age 8.3+3.1 years (range 2-14 years)] included in this study. The clinical characteristics are summarized in Table 1.

The mean weight of male and female child was 18.7+7.0 KG and 20.8+6 KG respectively. The mean height of male and female child was 114.8+16.9 cm and 121.9+15.8 cm. respectively. Growth retardation was present in significant proportion of patients. Wasting (alone) was found in 20.9% cases, whereas stunting (alone) was found in 25.8% of cases. Both stunting and wasting were found in 9.8% cases. Normal growth was observed in 43.5% of our EHPVO children.

History of home delivery was found in 61.2% cases whereas hospital delivery was conducted in 38.8% cases. Among the etiological factors history of neonatal umbilical sepsis was found in 16.1% EHPVO children and umbilical vein catheterization was found in 9.6% cases. Upper GI bleeding was the most common clinical presentation, present in 85.5% patients followed by lump abdomen in left upper quadrant in 12.9% patients and abdominal distension in 9.6% children with EHPVO. At the time of diagnosis 91.9% patients were found to have Splenomegaly, 2-10 cm below left costal margin with mean size 5.1+2.3 cm. other physical findings included: hepatomegaly (14.5%), ascites (11.2%) and jaundice (3.2%).

At initial presentation, all patients were anemic, 90.3% of them having haemoglobin level below 10 gm/dl. 16.2% patients had signs of hypersplenism including leucopenia (TLC<4000/mm^3), thrombocytopenia (PLT<50000/mm^3). Normal liver function parameters were seen in most of our patients. Biochemical features of hepatic dysfunction in the form of low serum albumin (3.5 gm/dl.) (19.4%), prolonged prothrombin time (>3 seconds) (14.5%) and raised ALT (>40IU/L), AST (>40 IU/L) (9.6% each) were evident. The mean increased in serum bilirubin (>12

mg/dl) and alkaline phosphatise level (>112 IU/L) in 11.2% and 6.4% respectively.

Table 1: Clinical and laboratory characteristics of patients with EHPVO (n=62).

	No. of patient	Percentage
Age in (years)		
<5 years	15	24.2
5-9 years	25	41.5
10-14 years	22	35.9
Growth retardation		
Wasting alone (weight/height) (<80)	13	20.9
Stunting alone (height for age) (<90)	16	25.8
Both stunting and wasting	6	9.8
Normal	27	43.5
History of delivery		
Home delivery	38	61.2
Hospital delivery	24	38.8
Etiological factor		
Neonatal umbilical sepsis	10	16.1
Umbilical vein catheterization	6	9.6
Clinical presentation		
Upper GI endoscopy	53	85.5
Lump abdomen in left upper quadrant	8	12.9
Abdominal distension	6	9.6
Physical finding		
Splenomegaly	57	91.9
Hepatomegaly	9	14.5
Ascites	7	11.2
Jaundice	2	3.2
Laboratory findings		
Anemia (<10 gm%)	56	90.3
Leucopenia (<4000/mm^3)	25	40.3
Thrombocytopenia (1,50,000/mm^3)	28	45.2
Hypersplenism	10	16.2
USG (abdomen)/ color Doppler		
Portal cavernoma	54	87.2
Portal vein thrombosis (extrahepatic)	9	14.5
Ascites	7	11.2

In Doppler ultrasonography, portal cavermoma was found in 87.2% EHPVO children. Extrahepatic portal vein thrombosis found in 14.5% children. Ascites was present in 9.8% patients. The initial endoscopy findings showed presence of esophageal varices in all patients. EST was performed in 42 patients who presented with variceal bleeding and variceal obliteration was achieved in 85.7 % cases with 2-10 sessions (mean 5.2+2). EVL was done in 12 patients who also presented with variceal bleeding and variceal obliteration was achieved in 90% of children with 2-4 sessions (mean 2.8+0.9). 47 patients studied for protein C, S and antithrombin III which were thrombophilic marker, the naturally occurring anticoagulant proteins. Protein C deficiency was found in 19.1% patients with mean value of 43.4 +8.9% (p<0.05). The antithrombin III deficiency was found in 12.7% patients with mean value of 15.8+2.5 mg/dl (p<0.05) (Table 2).

Table 2: Thrombophilic factors in patients of EHPVO.

	Deficiency group	
	Number	Percentage
Protein C	9	19.1
Protein S	8	17
Anti-thrombin III	6	12.7

DISCUSSION

EHPVO is one of the important causes of portal hypertension. It constitutes 68-76% of portal hypertension in children from developing countries.[5]

Growth retardation was present in significant proportion of patients. Sarin et al had reported in a prospective study of 61 children with EHPVO, a reduction in incremental growth velocity and short stature was observed in about 50% of patients compared with healthy control.[6] Reduced portal blood supply to the liver and deprivation of hepatotrophic hormones regulating liver growth and function are probable responsible for it. They hypothesized that deprivation of portal blood leads to growth retardation is further supported by the fact that children who had more prolonged portal vein thrombosis had more marked growth retardation.

History of home delivery was found in 61.9% patients. Bhandarkar et al had reported history of home delivery in majority of patients in their study.[7] History of neonatal umbilical sepsis and umbilical vein catheterization was found in 16.1% and 9.6% patients respectively. Umbilical sepsis is the frequently incriminated predisposing condition for the development of EHPVO in children. The inflammatory process is believed to start in the umbilical stump before the normal obliteration of the vein and proceed proximally to involve the portal venous system. Several investigators believe that umbilical vein catheterization and umbilical sepsis are responsible for portal vein thrombosis (PVT) others disagree.[8-12] The discrepancies between the observations are probably because of the studies that have been retrospective and clinical. In an Indian prospective ultrasonographic study up to 24 months, none of the 11 patients with septicaemia or umbilical sepsis developed portal vein thrombosis.[13] It is possible that the untreated and probably more severe umbilical sepsis, which may result after deliveries conducted at home or unhygienic conditions, could result in portal vein thrombosis.

Usually patients come to attention with gastrointestinal bleeding as it was the case in 53 of our patients. 11 patients were diagnosed with splenomegaly when they sought medical help for lump abdomen in left upper quadrant. The most common physical finding was splenomegaly, found in 91.9% patients. Ascites was seen in 11.2% patients who had previous episodes of GI bleeding and on follow up, ascites completely resolved in all without administering diuretic therapy. A two case of jaundice (3.2%) was found in our study. It was not associated with ascites. The possible mechanism could contribute to jaundice is the development of "portal biliopathy" – the bid duct anomalies associated with portal hypertension.

All patients were anemic at presentation. Hemoglobin level below 10gm% was found in 90.3% of cases. Anemia was possibly due to frequent variceal bleeds before presentation and poor nutritional stutus. Leucopenia and thrombocytopenia (PLT <1,50,500/mm^3) observed in 40.3% and 45.2% of patient respectively. The significant drop in leukocyte and platelet count may be due to progressive hypersplenic state. Signs of hypersplenism including leucopenia and thrombocytopenia (PLT <50,000/mm^3) was found in 16.2% of patients. Normal liver function parameters were seen in most of our patients. Rangari et al postulated that the liver dysfunction in EHPVO could be due to a prolonged reduction in portal blood flow and /or development of portal biliopathy.[14]

Chronic obstruction of portal vein leads to numerous collateral formations and shows the characteristics formation of cavernous transformation. Doppler ultrasonography was performed in all patients in our study. Portal cavernoma (distinctive tangle of tortuous vessels in the porta hepatis) and echogenic thrombus within the portal vein lumen (extra hepatic) was seen in 87.2% and 14.5% respectively. Similar findings were reported by Sharma et at from India. Doppler ultrasonography may lead to early diagnosis of portal vein thrombosis.[15]

In study by El-Hamid et al on first endoscopy, esophageal varices were present in 85.3% patients.[16] According to Sarin et al esophageal varices were seen in 90-95% and gastric varices in about 35-40% patients with EHPVO.[17] Outcome of patients with EHPVO depends on the control of gastro-intestinal bleeding from varices. Recent advances in the non-surgical treatment of gastroesophageal varices have resulted in remarkable improvement in the clinical course of patients. EST has emerged as an effective treatment for bleeding esophageal varices.[18] According to Yaccha et al EST was helpful in eradication of esophageal varies in 88% with mean session of 8 per child.[19] A study by Poddar et al, EHPVO children with EST variceal eradication was achieved in 95% of cases with mean 5.0+2.4 sessions.[20] EVL has been shown to be superior to EST because varices are eradicated rapidly with fewer sessions and it has fewer associated complications.[18,21] Zargar et al compared EST and EVL. Although EVL achieved variceal eradication more quickly, there was no difference in terms of arresting active bleeding and variceal eradication.[22] The results of our study showed that both EST and EVL were effective, safe treatment for esophageal variceal bleeding in children and subsequently eradication of esophageal varices.

Sufficient evidence is now available to suggest that an underlying prothrombotic state exists in EHPVO patients that may initiate the venous thrombosis in the splenoportal axis. Primary deficiencies in natural coagulation inhibitors (protein C, protein E and antithrombin III), prothrombin gene mutation, methylene tetrahydrofolate reductase gene mutation, factor V Leiden mutation are described in causing thrombophilia in extrahepatic portal vein obstruction in children as high risk factors but low prevalence. Pinto et al studied 14 pediatric portal vein thrombosis patients prospectively.[23] They found protein C, protein S and antithrombin III deficiency in 42.9%, 21.4% and 7.1% respectively. 1 patient presented prothrombin gene mutation. Homozygous methylene tetrahydrofolate reductase genotype was observed in 3 of 14 PVT patients (21.4%). Gurakan et al found isolated protein C deficiency, isolated protein S deficiency, combined protein C/S/antithrombin III deficiency and factor V leiden mutation in 16.6%, 8.3%, 8.3% and 8.3% respectively in their series of EHPVO children.[24] EI-Hamid et al studied detailed prothrombotic profiles in 30 children with EHPVO. Protein C activity was low in 20% patients; protein S was low in 2 patients.[16] Antithrombin was normal factor V Leiden mutation were absent in all cases. According to study by Yaccha et al from India, out of 19 children with portal vein thrombosis they had studied alone Protein C deficiency was found in 5 children and combined protein C & elevated anticardiolipin antibody in 3 children.[25] Uttenreuther-Fischer et al identified 4.3% and Heller et al reported 4.2% pediatric portal vein thrombosis patients with hereditary protein C deficiency.[26-27] Seizes et al did not identify any patient with factor V leiden mutation out of total 20 EHPVO children they have studied.[28] According to Sharma et al factor V leiden and prothrombin gene mutations are infrequent in Indian patients with EHPVO.[16] Out study showed significant deficiency of protein C, protein S and antithrombin III 19.1%, 17% and 12.7% patients respectively out of total 47 patients studied for this.

Present study has some limitations. We did not assess other thrombophilic factors like factor V Leiden mutation, prothrombin gene mutation, methylene tetrahydrofolate reductase gene mutation and other acquired prothrombotic disorders due to financial constraints.

The overall prognosis of EHPVO was good. None of our children either required surgery for endoscopic therapy failure or died.

CONCLUSION

Study concluded that EHPVO may result in impaired somatic growth. The etiology was unknown in majority of the children. Umbilical sepsis and umbilical vein catheterization appears to be risk factors in the development of EHPVO. Normal liver function parameters were seen in most EHPVO patients. EHPVO is mostly manifested with gastrointestinal bleeding and death from these variceal bleeding were unusual. EST and EVL remains as useful, cost effective, non-surgical mode of therapy in controlling esophageal varices bleeding in children with EHPVO and subsequently eradication of esophageal varices. These observations raise the possibility that the risk of EHPVO increases in the presence of thrombophilia, resulting from deficiency of naturally occurring anticoagulant proteins like protein C, Protein S and antithrombin III.

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