Extrahepatic Portal Vein Obstruction in Children: Etiology, Treatment and Long-Term Outcome

Prapun Aanpreung, M.D.*, Niramol Tantemsapya, M.D., Monawat Ngerncham, M.D.**, Mongkol Laohapansang, M.D.****
**Department of Pediatrics, **Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

ABSTRACT

Objective: Extrahepatic portal vein obstruction (EHPVO) is a common cause of portal hypertension in children. Informative data about this disease in Thai children is still limited. The objective was to study etiology, clinical presentation, investigation, treatment, result and long-term outcome.
Methods: The medical records of patients aged less than 15 years with diagnosis of EHPVO at Siriraj Hospital from 1993 to 2013 were retrospectively analyzed.
Results: There were 22 children (13 males and 9 females) with median age at diagnosis 5.1 years. The etiology was idiopathic in more than 50%. The patients had umbilical vein catheterization at least 27.2%. The presenting symptoms were splenomegaly 54.5% and upper gastrointestinal bleeding 45.5%. Doppler ultrasonography showed positive results in 52.6%. Initial endoscopic finding showed esophageal varices (EV) grade I 27.3%, grade II 36.3%, grade III 31.8%, and gastric varices (GV) 4.6%. The indications for endoscopic interventions were primary prophylaxis 30%, secondary prophylaxis 40% and stopping GI bleeding 30%. The interventions included endoscopic sclerotherapy (EST) in 6 cases, esophageal variceal ligation (EVL) in 6 cases, both in 7 cases and glue injection in 1 case. Rebleeding occurred in 50% of secondary prophylaxis and bleeding groups, but none in the primary prophylaxis group. Patients were followed up for a median of 5.3 years. For long term follow-up, massive splenomegaly and hypersplenism were the major concerns. Surgical treatment included splenectomy (3 cases) and distal splenorenal shunt (1 case). None of the patients died from complications.
Conclusion: The etiology of EHPVO is unknown in the majority of patients. SCT and EVL had success to control and prevent variceal bleeding and eradicate varices. There is an unsettled issue about management of EHPVO after controlling acute bleeding. Currently, Meso-Rex bypass and distal splenorenal shunt are proposed to be the recommended treatment for suitable cases with reported success in both eradicating varices and controlling hypersplenism, albeit preserving the spleen.

Keywords: Portal hypertension, hypersplenism, sclerotherapy, esophageal banding

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INTRODUCTION

Extrahepatic portal vein obstruction (EHPVO) is the disease that has an obstruction of the extrahepatic portal vein with or without the involvement of the intrahepatic portal vein. It is not primarily associated with intrinsic liver disease and can be found in both adults and children with different etiology.[1] EHPVO results in prehepatic portal hypertension, which is a common cause of portal hypertension in children. The precise etiology in children is still unknown in more than 50% of cases,[2-4] but could be secondary to neonatal omphalitis, umbilical vein catheterization (UVC)[5] and thrombophilic diseases.[3,6] Upper gastrointestinal

Correspondence to: Prapun Aanpreung
E-mail: prapun.aan@mahidol.ac.th
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bleeding (UGIB) and splenomegaly are the most common presentations.[7] Radiographic studies are used to make a diagnosis. Esophagogastroduodenoscopy (EGD) has the major role to demonstrate esophagogastric varices. Endoscopic interventions have been the preferred method to stop and prevent bleeding from varices. This disease is not rare in Thai children, but informative data is still limited. The purpose of this study is to study etiology, clinical presentation, investigation, treatment, result and long-term outcome in children with diagnosis of EHPVO.

MATERIALS AND METHODS

The Siriraj Institutional Review Board approved this study. The diagnosis of EHPVO was made on the basis of signs and symptoms of portal hypertension as well as demonstrating obstruction of the extrahepatic portal vein by radiographic study without intrinsic liver disease. The medical records of patients aged less than 15 years with diagnosis of EHPVO at Siriraj Hospital from 1993 to 2013 were retrospectively analyzed. Data gathered for analysis included demographic information, hematologic and radiographic studies, treatments, results and long-term outcome. Cytopenia was defined as: hemoglobin <10 g/dL, total leukocyte count <4,000/mm^3 and platelet count <100,000 /mm^3. Protein C and S activity less than 50% was defined as abnormal study. EV were graded according to their size: grade I (small straight varices), grade II (enlarged tortuous varices occupying less than one third of the lumen) and grade III (large coil-shaped varices occupying more than one third of the lumen).[8] Primary and secondary prophylaxis were the treatments to prevent variceal bleeding in patients who did not have and had a history of hemorrhage, respectively.

RESULTS

There were 22 children diagnosed as EHPVO (13 males and 9 females). The demographic data have been presented in Table 1.The median age of onset and at diagnosis was 4 and 5.1 years (range 0.6-13 years), respectively. Eleven patients were premature infants with a history of UVC in 6 cases. The other perinatal data, including neonatal sepsis, necrotizing enterocolitis, dehydration, and blood exchange transfusion in these patients could not be obtained due to limited parental recognition. Fifty percent were term infants without any perinatal illness. The presenting symptoms were splenomegaly (12 cases, 54.5%) and UGIB (10 cases, 45.5%). Physical examination showed splenomegaly (22 cases, 100%), massive splenomegaly: palpable >7 cm below left costal margin (6 cases, 27.3%) and anemia (6 cases, 27.3%).

TABLE 1. Demographic data and clinical presentations of patients with EHPVO

Total patient (case)	22
Sex ratio	M:F= 13:9
Age of diagnosis (y) median (range)	5.1 (0.6-13)
Age at onset (y) median (range)	4 (0.6-13)
Prematurity (case)	11
UVC	6 (27.3%)
Unknown history of UVC	5 (22.7%)
Term baby (case)	11 (50%)
Initial presenting symptoms: case /median age (y)	
Hematemesis	10 (45.5%)/4
Splenomegaly	12 (54.5%)/4
Physical examination (case) (%)	
Splenomegaly	22 (100%)
Massive splenomegaly	6 (27.2%)
Anemia	6 (27.2%)

UVC: umbilical vein catheterization

Initial complete blood count demonstrated thrombocytopenia in 16 cases (72.7%), leucopenia in 10 cases (45.5%) and anemia in 9 cases (40.9%). In addition, pancytopenia and bicytopenia were found in 9 and 5 cases, respectively. The further thrombophilic studies, including protein C and S activity were done in 10 patients and showed an abnormal protein C level in one case. The hematologic investigations have been presented in Table 2. Doppler ultrasonography demonstrated positive results in 10 of 19 cases (52.6%). The remainder of the studies were reported as patent portal vein (7 cases, 31.8%) and technique error (2 cases, 9.1%). The patients who needed further investigations to give or confirm a diagnosis have been presented in Table 3.

TABLE 2. Hematologic investigations

Initial hematologic findings (case)	
Thrombocytopenia	16 (72.7%)
Leucopenia	10 (45.5%)
Anemia	9 (40.9%)
Pancytopenia	9 (40.9%)
Bicytopenia	5 (22.7%)
Protein C activity < 50% (+ ve/ total)	1 /10
Protein S activity < 50% (+ ve/ total)	0/10

EGD was performed to diagnose varices or to control bleeding in all cases. First endoscopic finding showed EV grade I in 6 cases (27.3%), grade II in 8 cases (36.3%), grade III in 7 cases (31.8%) and GV in 1 case (4.6%). Initial endoscopic interventions were performed for primary prophylaxis treatment in 6 cases (30%), secondary prophylaxis treatment in 8 cases (40%) and stopping GI bleeding in 6 cases (30%). The endoscopic interventions were EST in 6 cases (median 8 sessions), and EVL in 6 cases (median 3.5 sessions). There were 7 cases receiving both EST and EVL sessions. There were rebleedings later on initiation of EST or EVL in 7 out of 14 cases in secondary prophylaxis and bleeding groups, but no rebleeding in the primary prophylaxis group. The summary of endoscopic intervention has been presented in Table 4.

Bleeding post endoscopic intervention was the most common complication from EST in 3 cases, EVL in 2 cases and glue injection in 1 case. A female patient with GV had glue injection to stop hemorrhage. One month later, she developed dyspnea and chest X- ray demonstrated glue embolism. The CT chest showed partial occlusion of main pulmonary artery and branches with pulmonary infarction at the posterior segment of right upper lobe. She was treated with antibiotics, oxygen therapy and supportive treatment with good improvement. The summary of complications have been shown in Table 5.

The long-term outcome has been shown in Table 6. Patients were followed up for a median of 5.3 years (range 0.3-13 years). None of the

TABLE 3. Radiologic abdominal investigations

Investigation	Positive/ Total
Ultrasound	3/3
Doppler ultrasound : Thrombosis	10/19
Patent portal vein	7/19
Technique error	2/19
Celiac angiography	6/6
Splenoportography	1/1
CT scan	2/2
CTA	4/4
MRV	7/7

CT scan: computed tomography scan
CTA : computed tomography angiography
MRV: magnetic resonance venography

TABLE 4. Endoscopy and interventions

Initial upper endoscopy finding (case)	
Esophageal varices grade I	6 (27.3%)
Esophageal varices grade II	8 (36.3%)
Esophageal varices grade III	7 (31.8%)
Gastric varices	1 (4.6%)
Indication for endoscopic intervention (case)	
Secondary prophylaxis	8 (40%)
Primary prophylaxis	6 (30%)
Acute bleeding	6 (30%)
Endoscopic intervention	
No intervention: case	2 (9%)
Sclerotherapy : case/ session (median)	6 (27.3%)/8
Esophageal banding : case/ session (median)	6 (27.3%)/3.5
Both : case/ session (median)	7 (31.8%)/7
Glue injection : case	1 (4.6%)
Recurrent bleeding (case)/total	
Post primary prophylaxis	0/6
Post bleeding and secondary prophylaxis	7/14

TABLE 5. Complications of endoscopic interventions

Complication	Case
Bleeding	6
Post sclerotherapy	3
Post banding	2
Post glue injection	1
Sepsis	1
Pulmonary embolism	1
Mild esophageal stricture	1

TABLE 6. Long term follow-up

Duration of follow- up (median)	5.3 (y)
Varices grade I (last endoscopy)	5 (22.7%)
Hypertensive gastropathy	8 (36.4%)
Hypersplenism	19 (72.7%)
Massive splenomegaly	12 (40.9%)
Post splenectomy	3 (13.6%)
Post splenorenal shunt	1 (4.6%)
Post ligation small bowel varices	1 (4.6%)
Propranolol : duration of treatment (median)	4 (y)
Continued	6 (40%)
Discontinued	9 (60%)

patients died due to gastrointestinal bleeding or sepsis. The last EGD demonstrated EV grade I in 5 cases (22.7%), GV in 1 case (4.5%) and portal hypertensive gastropathy (PHG) in 8 cases (36.4%). Hypersplenism (19 cases, 72.7%) and massive splenomegaly (12 cases, 40.9%) were the major concerns during follow-up. Surgical treatment, including splenectomy (3 cases) and distal splenorenal shunt (1 case) were performed due to those problems. Fifteen patients received oral propranolol for decreasing portal pressure with median duration of 4 years of treatment. There was no side effect reported. This was being administered and discontinued in 6 and 9 cases, respectively.

DISCUSSION

EHPVO is not an uncommon disease in Thai children. Early diagnosis, acute and long-term care are necessary in these patients. Unlike patients with chronic liver disease, they have good prognosis due to preserved liver functions. While mortality is low, there is significant morbidity, including variceal bleeding, hypersplenism, limitation of quality of life, growth retardation and neurocognitive impairment commonly occurs. Our study presented 22 cases of EHPVO during a 20-year period with the idiopathic etiology in more than 50%. The possible etiology in this study was UVC. The real number of UVC and other data in our premature baby group were not obtained. UVC has been implicated as a cause for EHPVO, but there is variable reported incidence in infant and children from zero to 43%.[9] The development of thrombosis is common in the newborn period, although the majority of thrombi resolve spontaneously. Thrombophilic disorders are the other possible causes such as protein C and protein S deficiency. There were reports of hereditary and acquired thrombophilia in 35% of children with EHPVO.[3,6] Mildly low values of protein C and S may result from an impaired liver function or portosystemic shunting rather than genetic deficiency, for which there is no role for anticoagulant therapy. Etiologies in our study were idiopathic in more than 50% and may be related to UVC in at least 27.2% of cases.

The majority of our patients were diagnosed at age of 5.1 years with presenting symptoms of UGIB and splenomegaly. Some patients with splenomegaly had hematologic investigations for a longer period before transferring the patients to the pediatric gastroenterologist. In our study, initial presentation of UGIB was found in 45.5% and endoscopic finding showed EV grade II and III in the majority of cases suggesting moderate to severe portal hypertension. Early diagnosis of EHPVO should be recognized in all cases of isolated splenomegaly with history of perinatal illness, especially UVC in order to decrease morbidity from UGIB.

Radiographic studies are the mainstay to make a diagnosis of EHPVO. During the early period of this study, Doppler ultrasonography was a new technique to demonstrate obstruction of the portal vein, but accuracy depended on radiologist experience, patient age and cooperation of the patient. In this study, it showed positive results in 52.6%. Nevertheless, it is still the initially suggestive investigation. Splenoportography and celiac angiography were the next investigations at that time. These methods were more invasive, but had positive results in all cases in this study. Splenoportography is almost never used today. Computed tomography angiography (CTA) and magnetic resonance venography (MRV) are useful for giving more detail of the portal system in both extra and intrahepatic vessels.[10] Radiation side effects, timing, anesthesia risk and cost are the major concerns for their use as routine investigation. Thus, they are reserved for evaluation in cases suitable for surgical shunts.

UGIB is a serious condition that needs proper managements including stabilization, somatostatin, antibiotics, acid suppressor and endoscopic intervention. EST and EVL have been the standard procedures for treatment of variceal bleeding in portal hypertension in children with high effectiveness.[11,12] In the early period of this study, EVL was not available, so all patients had EST performed to control bleeding or prophylaxis. Subsequently, all cases had EVL performed, except in younger children. EVL is mainly replacing EST with comparable effectiveness in controlling bleeding. Our patient had less number of sessions of EVL compared with EST. Regarding complications, post intervention bleeding occurred in both interventions. Gastric varices were not common in this study, which was different from others.[3,7] Our patient with GV had pulmonary embolism and infarction from glue injection. Careful intervention and close monitoring are advised for this procedure in children to prevent and diagnose this serious complication.

Nonselective beta- blocker has been suggested to use to decrease portal pressure in adults in preventing variceal bleeding with promising efficacy,[13] but in children, it is not recommended owing to limited information as to efficacy and appropriate dosing regimen.[1] Our patient received propranolol with endoscopic intervention for primary and secondary prophylaxis. Efficacy was difficult to evaluate due to a small number of cases and no definite protocol.

Primary and secondary prophylaxis intervention have been suggested for preventing rebleeding in adults with portal hypertension.[14] In children with EHPVO, these are still debated.[15] For the current recommendation of primary prophylaxis, there is insufficient evidence to support a clear recommendation for endoscopic therapy.[1] In this study, 6 patients had primary prophylaxis intervention without rebleeding result. This may be from less severity of portal hypertension. For secondary prophylaxis, there were more rebleeding later on following the initiation of EST or EVL. There is an unsettled issue about management of EHPVO after control of acute bleeding. These patients should have shunt surgery or endotherapy for variceal eradication.[15] Conventionally, endoscopic intervention was considered as a substitute for surgical therapy in children, because in most patients' collaterals outside the gastrointestinal tract or cavernous transformation of the portal vein will develop without later need for portosystemic shunt procedures.[16] Recently, the treatment for children with EHPVO who have experienced variceal bleeding, which should be considered, is a surgical shunt between the mesenteric vein and the left portal vein (Meso-Rex bypass surgery) or alternative distal splenorenal shunt.[1] Meso-Rex bypass represents a more effective surgical procedure in cases of recurrent bleeding, severe hypersplenism, or encephalopathy. However, there are large studies from India showing a good long-term outcome in children treated with EST and EVL for eradication of varices.[11,12,17-19] The majority of our patients had endoscopic intervention performed to eradicate varices rather than performing surgery the as same as the previous reports. For our long-term outcome, endoscopic intervention was able to effectively eradicate esophageal varices and prevent rebleeding. PHG commonly occurs in patients who have undergone variceal obliteration,[20] which was found in 36.4% of our patients.

For long-term follow-up, the other main concerns in the majority of our patients were massive splenomegaly, hypersplenism and limited physical activity. Besides that, our definite protocol of treatment was not settled. Three patients had splenectomy performed with improvement of hypersplenism and physical activity. Current concept for treatment of hypersplenism is Meso-Rex bypass surgery, which allows splenic preservation.[1] Splenectomy will not diminish the probability of variceal hemorrhage and may remove the option of a distal splenorenal shunt as a future intervention. The Meso-Rex bypass also reconstitutes portal blood flow to the liver, which is more effective in resolving hepatic encephalopathy caused by spontaneous portosystemic shunting in cases after a splenorenal shunt. Unfortunately, this highly selective shunt can only be carried out in cases with patent intrahepatic portal veins.

In conclusion, EHPVO is still a common cause of portal hypertension in Thai children. Early diagnosis is necessary to prevent morbidity

from UGIB. Endoscopic intervention, including EST and EVL are useful to control and prevent variceal rebleeding. Massive splenomegaly, hypersplenism and rebleeding are the principal concerns in long-term follow-up. Currently, Meso-Rex bypass and distal splenorenal shunt are proposed to be the recommended treatment in the children with EHPVO. Because this study was retrospective, there were some limited data such as thrombophilic studies and definite protocol for endoscopic intervention. The prospective study should be conducted in the future.

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